Chapter 4

Cancer-preventive effects

Human studies

The groupings used to evaluate epidemiological studies were:

- Total fruit consumption
- Total vegetable consumption
- Total fruit and vegetable consumption

Where possible, potatoes, pulses and mushrooms were excluded from the evaluations (see also Chapter 1).

The Working Group was concerned that reporting of associations between specific cancers and specific individual foods or subgroups of fruit and vegetables might be subject to publication bias. Few of the studies identified had examined the effects of total intake of fruit and vegetables combined. Therefore the Working Group decided to evaluate the evidence in relation to total fruit and to total vegetables. This approach is conservative in that an effect of any specific fruit or vegetable, or subgroup of them, would be diluted, but would not be conservative if relationships between cancer and fruits and vegetables were due to composite effects of multiple bioactive components.

General issues

In assessing the evidence on the relation between cancer and intake of fruit and vegetables, sources of heterogeneity between studies include:

- differences in study design, with different potential opportunities for bias and confounding to influence results;
- differences in reference period;
- differences in definition of exposure (see Chapter 1);
- differences in dietary assessment instrument and its method of administration (see Chapter 2);
- differences in the extent and control of measurement error;
- differences in the extent to which potentially confounding factors were investigated, and in the adequacy of adjustment for these;
- effect modification;
- differences in methods of statistical analysis;
- chance (and multiple testing);
- differences in study context.

In appraising individual studies, it is important to consider their design, as this affects the biases that may occur and their generalizability. Problems associated with specific designs are addressed in the next section. Problems that affect more than one type of design are discussed in subsequent sections.

Study design

Randomized controlled trials

The definitive method of investigating the efficacy of a potentially preventive intervention is the randomized controlled trial. The particular strength of this design is that, provided the trial is sufficiently large, the distribution of potential confounders, known (measured) and unknown (unmeasured), will differ between the group assigned to receive the intervention and the control group no more than would be expected by chance. In addition, the exposure potentially can be precisely defined, although in the context of fruit and vegetables this would probably apply to the advice (and any measures taken to support this) rather than intake. Blinding (masking) can exclude the possibility that knowledge of the exposure status of the subjects could bias the assessment of outcome. However, subjects cannot be blinded to their intake of foods. For various reasons, such as non-compliance, it is possible that subjects may not receive the exposure to which they have been assigned. The reasons for this may be associated with the outcome of interest. For example, in a randomized trial of the cancer-preventive effect of advice to increase fruit and vegetable intake, there could be a high proportion of non- or poor compliers in the intervention group. In one randomized controlled trial of individualized advice to increase vegetable and fruit intake, drop-outs were more likely to be smokers and of lower socioeconomic status than those who did not drop out (Smith-Warner *et al.*, 2000). As smoking and socioeconomic status are related to cancer outcome, so also is drop-out. It is therefore crucially important that the data are analysed according to the principle of "intention-to-treat", otherwise the effect of randomization in minimizing potential confounding is lost (Peto *et al.*, 1976; Fergusson *et al.*, 2002).

In trials of interventions designed to assess the effects of increasing

intakes of fruit and vegetables, randomization should result in similar baseline intakes of fruit and vegetables between the arms of the trial. In theory, the intervention group will augment its intake of fruit and vegetables above the baseline level by a certain amount. However, especially if the intervention is intended to result in increased intake over a prolonged period, measurement of adherence to the intervention is a crucial issue. In addition, changes in intake of fruit and vegetables may bring about other changes such as reduction in meat intake or weight gain, which may have their own effects on cancer incidence, and so complicate interpretation of the effect of the intervention.

In specifying criteria for assessing evidence on which health policies and guidelines are based, several national organizations accord the highest level of evidence to randomized controlled trials (NHMRC, 1999; Briss *et al.*, 2000; SIGN, 2001). Comparisons between such trials and observational evidence have been made for certain topics, but not for consumption of fruit and vegetables (Ioannidis *et al.*, 2001), because few randomized controlled trials of the effects of fruit and vegetables have been conducted. Differences in the estimated magnitude of effect between trials and observational studies are very common and the directions of the differences are difficult to predict (Britton *et al.*, 1998; MacLehose *et al.*, 2000). There are many potential reasons for such differences, including a short period of observation in the trials, trials conducted during an inappropriate period of the natural history of the disease or using end-points with unknown predictive value (especially intermediate end-points, see below), use of a different quantity of fruits and/or vegetables in the trial, or bias or measurement error in the observational studies.

The only randomized controlled trials of the effects of fruit and vegetables in the area of cancer and precancerous lesions have examined the effects of a recommendation to consume a specified amount and/or dietary counselling. Such counselling tends not to be limited to fruit and vegetable intake (there may be, for example, advice to reduce fat intake) and may influence other health-related behaviour. Although trial results can be especially compelling and have widespread implications, caution is needed in generalizing from the results of trials on specially selected groups to the population as a whole.

Cohort studies

In a cohort study, individuals who are disease-free are recruited to participate in the study and are then followed over time to identify those who develop the disease. Information on, for example, socio-demographic factors, medical history and lifestyle factors such as diet is collected at the beginning of the study, before the onset of disease. The cohort design could be regarded as similar to the randomized controlled trial, except that the assignment of exposure is subject-selected rather than randomized. Consequently, (a) it is necessary to measure potential confounders and adjust for them; (b) the distribution of unknown and unmeasured confounders may differ between the groups being compared; (c) it may not be meaningful to analyse the study according to "intention to treat", as any change in exposure (diet) may be highly context-dependent and unlikely to be reproducible in other populations and periods, (d) changes in exposure as a consequence of early symptoms of disease and biases in loss to follow-up that are directly or indirectly related to exposure are potential issues affecting interpretation; and (e) the subjects are not blinded to their exposure status – this may compromise the extent to which assessment of outcome is independent of exposure status.

Large numbers of subjects have to be enrolled in a cohort study in order to have adequate statistical power to determine associations with specific types of cancer. Gains in efficiency, over numbers of subjects analysed or numbers of tests performed on collected specimens, are possible in cohort studies with nested case–control and case–cohort designs, but the requirement for a large cohort size overall is unchanged. Therefore, the methods used for assessment of dietary intake and potentially confounding factors need to be suitable for application to large numbers of subjects. This has implications for the extent of potential measurement error (see Chapter 2). A potential advantage of the cohort design compared with the case–control design is that concurrent measurement of current diet is likely to be better correlated with the true current diet than is retrospective measurement of past diet with the true past diet. Another advantage is that repeated measurements can be obtained, if resources are available. Repeated measurement allows changes in diet and other relevant exposures to be monitored, and also permits development of a summary measure of exposure less subject to random misclassification than a single measure. This gives the investigator a choice of measure of 'diet', including diet at the beginning of the study, more recent intake or a summary measure of repeated exposures.

A strategy for dealing with the possibility that pre-diagnostic changes in diet may bias the observed association between diet and disease is to exclude cases diagnosed in the initial period of follow-up. Investigators often assess whether results are altered by

the exclusion of cases identified in the initial period of follow-up, such as the first two years.

Participation bias in a cohort study affects the generalizability of the results, but does not compromise their internal validity. However, it has been suggested that the tendency for the most health-conscious to participate may reduce the variability of dietary intake, making it difficult to detect associations with disease risk (Steinmetz *et al.*, 1994). Over-representation of health-conscious active persons interested in their diet has been noted in dietary surveys (Harris *et al.*, 1989; van't Hof & Burema, 1996; Sidenvall *et al.*, 2002). There is also a possibility that subjects in a cohort study who are knowledgeable concerning effects of diet on health may report their diet in a manner that represents what they believe they should eat, not what they actually eat. This could be a problem of some studies of health professionals.

Bias resulting from differential loss to follow-up by exposure could occur if, for example, both loss to follow-up and fruit or vegetable consumption vary by socioeconomic status. Limited data on loss to follow-up tend to be presented for cohort studies. In a case–control study of lung cancer nested within a cohort study in New York State, USA, although there were some differences in diet between those lost to follow-up (19 of 525 controls, 3.6%) and those whose outcome was known, the results of analyses relating to diet and alcohol were similar including and excluding losses to follow-up (Bandera *et al.*, 2002). In a longitudinal study of cognitive ageing, those who did not return for follow-up had lower educational levels than those who did return (Van Beijsterveldt *et al.*, 2002). In studies in the USA, members of minority groups have tended to have higher drop-out rates than whites (Vernon *et al.*, 1984; Bowen *et al.*, 2000). In a study of black women in the USA, those who were lost to follow-up tended to be less well educated than those who remained in the study (Russell *et al.*, 2001). A related issue concerns the return of incomplete information during follow-up, i.e., item non-response. This has been shown to be associated with subsequent loss to follow-up (Deeg *et al.*, 2002).

In cohort studies, disease rates during follow-up are typically analysed with respect to the values of factors measured at enrolment. Enrolment diet may accurately reflect typical lifetime intake. However, because of the combined effects of measurement errors and changes in the exposure of participating subjects over time, this approach may underestimate the strength of association between habitual level of exposure during the period of follow-up and disease risk. Repeated measurements of baseline exposure in a representative sample of participants in a cohort study can be used to estimate the magnitude of measurement error and correct for it. Repeated measurements taken later in the exposure period can be used to correct for changes in exposure. Using a food frequency questionnaire (FFQ), Goldbohm *et al.* (1995) observed a high degree of consistency of within-subject dietary patterns relating to fruit and vegetable consumption between five successive annual assessments.

Limited participation at enrolment affects the generalizability of the findings from the study cohort. It does not affect the validity of the study findings.

Case–control studies

In a case–control study, individuals who have recently developed a disease and a sample of individuals without the disease being investigated are recruited and information is then collected on potential risk factors during a specified reference period before the onset of disease. One of the main advantages of the case–control design compared with the cohort design is that the total number of subjects whose diet has to be assessed is much smaller. In theory, this gives more flexibility in the choice of methods for determining diet and potentially confounding exposures than with cohort studies. Thus, for example, data can be collected by in-person interview using a detailed quantitative dietary instrument rather than by self-completed questionnaire.

As in cohort studies, the assignment of exposure is subject-selected rather than randomized, and this raises similar issues with regard to potential bias and confounding. The main potential biases of the case–control design are (a) inappropriate choice of cases or controls, leading to selection bias and (b) misreporting of past diet.

Selection bias

In a number of studies of cancer in relation to fruit and vegetable intake, controls comprised subjects hospitalized with other types of cancer or with a range of other disorders. Hospital-based studies may be attractive for investigations of diseases when it is difficult to characterize the underlying study base (Wacholder *et al.*, 2002). Another possible attraction is that, provided that the diseases of control subjects are of similar severity to that of the cases, recall bias may be minimized (see discussion of recall bias). However, if the conditions for which a subject is hospitalized are themselves related to fruit and vegetable consumption, the measure of association would be distorted (Wacholder *et al.*, 1992).

Selection bias also may occur as a result of differential non-participation between cases and controls. There has been concern about a decline in participation rates (Olson, 2001), especially in population-based studies.

This could result in people selected as population controls being largely those most likely to be at home when contacted. Therefore in studies using population controls, it is critical to ensure as high a response as possible from those eligible in the base population. Information on the potential effects of low participation rates is limited (Madigan *et al.*, 2000).

Differential misclassification of diet – recall bias

Retrospective measurement of diet is likely to be less well correlated with the true diet during the reference period than is the case for concurrent measurement of diet and the true current diet (see Chapter 2). If cases and controls differ in their accuracy of dietary recall, the comparison of the reported diet will be biased.

It has been suggested that the likelihood of recall bias may be greater when recall is poor in general (Coughlin, 1990). However, this was not apparent in a systematic review of empirical studies of recall bias published between 1966 and 1990 (Chouinard & Walter, 1995).

Dietary information obtained from cases and controls by questionnaire or interview was compared with information on the index subject obtained from the next of kin or spouse in two studies in the USA. In one, the responses of 67 men with cancer to a dietary interview were compared with those of their spouses to the same instrument regarding intake of the index subject; a similar comparison was made for 91 male neighbourhood controls and their spouses (Marshall *et al.*, 1980). The study instrument included 27 items to assess vegetable consumption and 11 to assess fruit consumption. The proportion of case–spouse pairs reporting exact agreement regarding vegetable consumption was 59%, compared with 65% for control–spouse pairs, while for fruit consumption the proportions were 49% and 56% respectively. The proportion of case–spouse pairs reporting agreement of vegetable consumption within one category (out of 11 possible categories) was 88% compared with 94% for control–spouse pairs. The corresponding proportions for fruit were 76% and 88%. In the other US study (Herrmann, 1985), the response to a diet interview of 94 cases with colon cancer and their next of kin, and 93 controls selected using an area probability sampling scheme and their next of kin, were compared. The instrument had 31 items relating to consumption of vegetables and 12 relating to fruit. The agreement, over five categories of frequency of consumption, was higher for case–next of kin than control–next of kin pairs both for vegetables (agreement 70% for case–next of kin pairs and 66% for control–next of kin pairs; kappa 0.45 and 0.40 respectively) and fruit (agreement 66% for case–next of kin pairs and 63% for control–next of kin pairs; kappa 0.42 and 0.41 respectively). Although these studies indicate reasonable agreement between the reports of index subjects and proxy subjects, concern has persisted about the quality of data from proxy respondents (Nelson *et al.*, 1990; Lyon *et al.*, 1992).

In other studies, data from self-completed questionnaires or from interviews carried out as part of a survey or enrolment into a cohort study were compared with data obtained from subjects after diagnosis of cancer and from control subjects identified at that time (Table 9). All but one of the studies relating to food groups used FFQs in both assessments. In most of these studies, the data were interpreted as showing little evidence of recall bias (Friedenreich *et al.*, 1991; Holmberg *et al.*, 1996; Lindsted & Kuzma, 1990). Hammar and Norell (1991) noted that there was good agreement between retrospective and original information among subjects who reported that they had not changed their diet between 1967 and 1987. However, this was not the case for those who had changed their diet, and this was a particular issue for those who had changed their diet because of disease. [The ability of some of these studies to detect recall bias may have been limited because of misclassification likely to have resulted from the instruments used, the small size of some of the studies, and correlated errors between the dietary assessments.]

Two studies presented data only on nutrients. Wilkens *et al.* (1992), in a study in which both assessments of diet were made by interview, found that although there were no marked differences overall between cases and non-cases in the ability to recall past diet, this did not apply in certain subgroups, such as subjects with the longest recall interval (8–10 years), and cases with colorectal cancer or any cases diagnosed with distant stage disease, compared with non-cases. Giovannucci *et al.* (1993) reported finding no association between breast cancer and intake of total or saturated fat when prospectively collected data were analysed, but a positive association when retrospectively collected data were analysed. However, the prospective analysis related to 392 cases and 786 controls, while the retrospective analysis related to 300 cases and 602 controls. Thus, the difference in results may not be entirely attributable to recall bias; response bias might have contributed. In a study in Finland, Männistö *et al.* (1999) compared data obtained by FFQ from cases of breast cancer with data from (*a*) population-based controls and (*b*) subjects who were referred for the same examinations as cases but who were later diagnosed to be healthy. There was evidence that group (*b*) differed from group (*a*) in reporting of milk products,

Table 9. Summary of studies of recall bias in relation to fruit and vegetables and cancer: comparison of data obtained prospectively with those obtained after diagnosis of cancer for cases, and at a similar time for controls

Study	Cases		Controls		Prospective method		Retrospective method		Number of items		Results
	Type	*N*	Type	*N*	Type	Timing	Type	Timing	Veg.	Fruit	
Lindsted & Kuzma, 1989	Incident, ns	117	Survivors aged <82 years, ns	99	FFQ	1960	FFQ, subset of 1960 instrument	1984	1	1	Spearman rank-order correlation for veg. 0.21 for cases, 0.25 for controls; for fruit 0.26 for cases, 0.23 for controls. Exact and close agreement greater for controls than cases for both veg. and fruit
Lindsted & Kuzma, 1990	Mainly breast, female genito-urinary or colorectal	181	Controls selected randomly from cohort of survivors aged <82 years	225	FFQ	1976	FFQ, subset of 1976 instrument	1984	7 (included 2 categories relating to rice)	7	Spearman rank-order correlation for veg. in range 0.35–0.61 for cases, 0.27–0.65 for controls; for fruit 0.29–0.51 for cases and 0.31–0.46 for controls. % agreement greater for cases than controls for 4/7 veg. categories and 4/7 fruit categories. Over all 35 food groups, case–control difference in recall error was not significant in multivariate analysis that conditioned on dietary changes.
Friedenreich *et al.*, 1991	Breast	325	Selected from participants in mammography screening trial (same study base as cases)	628	FFQ	1982–85	Self-administered FFQ identical to first except reference period specified as diet at time of first FFQ	1988	17	10	Pearson correlation for veg. 0.50 (95% CI 0.41–0.58) for cases and 0.48 (95% CI 0.42–0.54) for controls; for fruit 0.55 (0.47–0.62) for cases and 0.58 (95% CI 0.53– 0.63) for controls
Hammar & Norell, 1991	Colorectal	45	Random sample of original cohort	135	FFQ	1967	FFQ identical to first except reference period specified as diet at time of first FFQ	1987	1		Among subjects with high consumption according to the original report, controls tended to under-estimate their previous consumption of fruit/veg. more than cases. Among those with low consumption according to the original report, cases tended to over-estimate their previous consumption more than controls.
Holmberg *et al.*, 1996	Breast	265	Selected from participants in mammography screening (same study base as cases)	431	FFQ	1987–90, sent out with invitation to participate in screening	Interview	6 mo after screening	9	4	Veg.: 31.3% agreement for cases, 37.3% for controls; kappa 0.16 and 0.08 respectively (0.12 and 0.18 when analysis restricted to subjects who returned complete questionnaires). Fruit: 38.5% agreement for cases, 41.9% for controls; kappa 0.23 and 0.18 respectively

and for premenopausal women a difference was apparent also for reporting of tea, sugar, fats and vitamins. Thus the OR of breast cancer in premenopausal women for the highest quintile of vegetable consumption versus the lowest in comparison with group (*a*) was 1.3 (95% CI 0.5–3.1) and with group (b) 0.6 (95% CI 0.3–1.4).

Investigations of the theoretical impact of recall bias for dichotomous exposures shows that even severe recall bias causes only weak to moderate spurious associations (Drews & Greenland, 1990; Swan *et al.*, 1992; Khoury *et al.,* 1994). However, in a simulation analysis, differential underreporting of fat and energy intake by cases but not controls substantially altered the association between fat intake and disease risk (Bellach & Kohlmeier, 1998). The direction and magnitude of the effect depended on the type of error structure.

Differences in reference period between types of study

An implicit difference between trials and cohort studies on the one hand and case–control studies on the other lies in the reference period about which data on intake of vegetables and fruit are sought. In trials and cohort studies, the reference period is typically at enrolment, although in some studies data on diet at later timepoints in follow-up have been obtained. In case–control studies, data are typically sought for a reference period before diagnosis for cases and for a corresponding period before recruitment for controls. Although investigators recognize that there may be a long latent period in cancer development, they have also noted that reporting of past diet is influenced by current diet. It has been assumed that while total intake declines with age, the relative intake of different nutrients varies little in adult life (Willett, 1998d). However, increasing diversity in the foods available for consumption and the increasing consumption of convenience foods may mean that this assumption is no longer tenable in a number of countries (see Chapter 3).

Differences in the length of the reference period are a potential source of variability between studies in populations where availability of fruit and vegetables varies by season.

It is possible that early life exposure to fruit and vegetables is important in the etiology of cancer. The food frequency approach taken in cohort studies (of older individuals) to date provides little to no information on early-life exposure. To the extent that self-reported adult intake is a poor measure of early-life diet, additional exposure error is introduced into studies.

Differences in definition of exposure between types of study

Standard methods for classifying exposure to vegetables and fruit in epidemiological studies have not been established (Smith *et al.*, 1995) (see Chapter 2). The instruments used in most studies have been designed to assess variation in nutrient intake, rather than variation in intake of fruit and vegetables *per se*. As an example of the lack of standardization, studies differ in whether fruit juice consumption is included in fruit consumption, vegetable juice intake with vegetable consumption, and whether potatoes or mature beans are included in vegetable intake (Slattery, 2001; Smith-Warner *et al.*, 2001a).

The number of fruit and vegetable questions has varied considerably across studies, which may influence the specific fruit and vegetable groups examined and the intake estimates obtained. The contrast in intake estimates for the high versus low categories for relative risk estimation also has been highly variable across studies.

Differences in study instrument and its method of administration between types of study

The methods of dietary assessment used in epidemiological studies to estimate individual dietary exposure include FFQs, diet history interviews, 24-hour dietary recalls and food record methods (see Chapter 2). Most studies have used FFQs. Key factors that differ include the number and formulation of questions, inclusion of data on portion size and the method of administration. For example, in studies of colorectal cancer in which the number of items used to assess dietary intake was reported, this varied between 35 and 276 items for cohort studies, and 10 to 300 items for case–control studies (see below). Direct interviewing has been used in many case–control studies, whereas this is seldom used in cohort studies.

Measurement error

Issues in assessing evidence from different studies include (*a*) whether a validation study has been done; (*b*) if one has been done, its adequacy (see Chapter 2); and (*c*) whether information for the validation study was used in the analyses based on the primary study instrument. Little is known about the measurement error structure for reported fruit and vegetable intake in FFQs. Errors in the instrument being validated and in the reference method tend to be correlated (Plummer & Clayton, 1993; Goldbohm *et al.*, 1995; Day *et al.,* 2001; Kipnis *et al.*, 2001), while the extent of error varies with characteristics of the subject (Prentice, 1996; Horner *et al.*, 2002). In consequence, both the attenuation of the dietary effect and the loss of statistical power may be greater than previously estimated, making modest (but important) reductions in relative risk

difficult to detect (Kipnis *et al.*, 2003). Potential solutions to this problem include the development and use of FFQs with far more detailed questions about fruit and vegetable intake; use of more intensive instruments (recalls, diaries) as the primary dietary assessment tool, and development of unbiased biomarkers of fruit and vegetable intake, analogous to urinary nitrogen as a biomarker of protein intake. At present, such fruit and vegetable biomarkers do not exist.

Adjustment for misclassification (calibration) may not deal with possible heterogeneity between studies because of differences in the design and administration of the primary study instrument.

End-points

In most studies, the primary end-point has been newly incident cancers. However, in some studies, mortality due to specific types of cancer has been the primary end-point and these would be biased if fruit or vegetable intake were associated with survival.

In randomized trials, and some observational studies, intermediate effect markers have been used as end-points. An intermediate effect biomarker is a detectable lesion or biological parameter with some of the histological or biological features of preneoplasia or neoplasia but without evidence of invasion, which is known either to be on the direct pathway from the initiation of the neoplastic process to the occurrence of invasive cancer, has a high probability of resulting in the development of cancer, or is a detectable biochemical abnormality which is highly correlated with the presence of such a lesion. Thus intermediate effect markers include (*a*) detectable precancerous changes in an organ (confirmed by histology), (*b*) alteration of a gene that is considered to play a causative role, (*c*) DNA damage, (*d*) other indicators of carcinogenesis, such as the expression of a marker of an exposure known to be a cause of a cancer (e.g., positivity for human papillomavirus (HPV) DNA), and (*e*) effects on metabolic factors thought to be involved in etiology, e.g., effects on phase I and phase II enzymes, antioxidant pathways and steroid hormone metabolism. Causation is not a requirement for inclusion in this group, but the expectation is that the relevant biomarkers can eventually be connected in a biologically mechanistic manner to the cancer (Miller *et al.*, 2001).

There is likely to be a hierarchy of intermediate biomarkers. Those that are known to be on the causal pathway to cancer are at the top and can be truly called intermediate effect markers. Then there are markers where present knowledge indicates only a probability of cancer association, but it is uncertain as to whether they are on the causal pathway – they can only be called intermediate markers. A subset of intermediate effect markers, which can be modulated, have been called surrogate end-point biomarkers (Kelloff *et al.*, 2000).

It has not been convincingly shown that the use of fruits and vegetables, or derivatives from them, in men and women with any type of preneoplastic lesion can substantially reduce the subsequent development of truly invasive cancer (see subsequent sections of this chapter). In general, not enough is known on the natural history of precancerous lesions to identify those that will progress to invasive cancer if allowed to do so, nor to define the time point in the natural history of progression of intermediate end-points to cancer where an intervention will prevent the development of the cancer. If an intervention, such as fruit and vegetables, acts at the later stages of carcinogenesis, a randomized trial with an intermediate end-point will fail to demonstrate any effect. It would only be if the intervention was administered after the occurrence of the intermediate end-point, and was shown not to prevent the development of subsequent cancer, that a benefit from the intervention could be excluded. Such studies are, however, likely to be precluded for ethical reasons, and therefore it may be impossible to use randomized trials to evaluate the effect of inhibition of the later stages of carcinogenesis.

Confounding

An association between intake of fruit and vegetables and cancer could be due to confounding. This may be because a high intake of fruit and vegetables is associated with other behaviours related to health (Serdula *et al.*, 1996; Williams *et al.*, 2000). In particular, smokers consume lower quantities of vegetables and fruit than non-smokers; some studies (Serdula *et al.*, 1996, Agudo *et al.*, 1999; Voorrips *et al.*, 2000a; Sauvaget *et al.*, 2003) but not all (Nuttens *et al.*, 1992; McPhillips *et al.*, 1994; Wallstrom *et al.*, 2000) have shown that differences in consumption are greater for fruit than for vegetables. Mean intake of fruit and vegetables of past smokers may be higher than those of current smokers (Miller *et al.*, 2003).

In most studies, data on smoking behaviour have been self-reported and the accuracy of these data may vary between studies (e.g., Lindqvist *et al.*, 2002). In some studies, higher levels of alcohol consumption have been associated with lower intake of fruit and vegetables (Serdula *et al.*, 1996; Wallstrom *et al.*, 2000). In addition, high intakes of fruit and vegetables are associated with reduced intake of potentially harmful foods such as red meat. Thus intervention studies aimed at increasing intake of vegetables and fruit may also result in reduced fat intake (Smith-Warner *et al.*, 2000). Physical inactivity is a consistent risk factor for colon and breast cancer and may be associated with other types of

cancer (e.g., endometrium, prostate) (IARC, 2002) and fruit and vegetable consumption is likely to be correlated with physical activity. Even though many studies adjust for physical activity, this characteristic is not measured with great accuracy and residual confounding remains a possibility. In addition, consumption of fruit and vegetables varies by age, gender, socioeconomic status and ethnicity. In most countries where the relationship between fruit and vegetable intake and measures of socioeconomic status has been investigated, the general pattern has been that intake was higher among people of higher socioeconomic status (Subar *et al.*, 1990; Murphy *et al.*, 1992; Potter, 1997) (see Chapter 3).

When confounders are measured inaccurately, it follows that the analysis cannot properly control for confounding. If both the primary exposure of interest and the confounder are measured inaccurately, it is possible that the two sets of errors may be interrelated, so the apparent relationship between exposure and confounder may be quite different from that between the underlying variables (Clayton & Hills, 1993).

Due to the association between intake of fruit and vegetables and important risk factors for cancer like smoking and cancer on one side, and the possible errors in measuring these factors on the other side (e.g., Marshall *et al.*, 1996; Lindqvist *et al.*, 2002; Stram *et al.*, 2002), it is difficult to exclude residual confounding completely. For example, Stram *et al.* (2002) illustrated with a simulation that even a modest correlation between smoking and serum β-carotene, combined with errors in smoking assessment, might plausibly explain the observed inverse association of serum β-carotene levels with lung cancer risk in terms of residual confounding.

Effect modification

Components of fruit and vegetables can interact with biological targets by modifying the risk associated with carcinogenic exposures. For example, DNA damage related to tobacco smoking could be inhibited by fruit and vegetable components. Such effect modification needs to be clearly distinguished from confounding, because it represents a genuine protective effect that occurs only in those exposed to the carcinogens. For this reason, it is important to analyse epidemiological data not only with an approach based on adjustment for potential confounders (e.g., smoking), but also stratifying by carcinogenic exposures (e.g., never-smokers, ex-smokers, current smokers).

If fruit and vegetable intake is protective only for persons with a specific genetically determined metabolic profile, the incorporation of appropriate genetic information into epidemiological studies could 'sharpen' the relative risks observed in the 'susceptible' group. Work on such nutrition–gene interactions presents considerable difficulties, however, given that there are many bioactive constituents of fruits and vegetables and many enzymes involved in their absorption and metabolism, with functionally important allelic variants for at least some of these enzymes.

Statistical analysis

Categorization of exposure

An issue in statistical analysis is whether to consider reported dietary intake as a continuous or a categorical variable. When the objective of dietary assessments is to rank subjects according to their intake rather than to provide a precise quantitative measure of absolute intake, analysis by ordered categories such as tertiles, quartiles or quintiles is less sensitive to the effects of outliers than analysis of continuous variables (Willett, 1998e). The measure of the effect of the nutrient on disease can be interpreted as the effect of changing intake between quantiles of intake, e.g. from the lowest to the highest. Categorization by quantiles can be based on the distribution of (*a*) cases, (*b*) non-cases and (*c*) all subjects. These three methods have been found to give the same statistical power to detect a trend across quantiles over a wide range of study situations (Hsieh *et al.*, 1991). The choice of method may be influenced by consideration of how the quantiles relate to the source population and by ease of implementation.

Adjustment for energy intake

Total energy intake requires attention in the analysis and interpretation of nutritional epidemiology studies for several reasons. (1) It may be a primary cause of disease. Low energy intakes have reduced the incidence of tumours in experimental animals. Thus, adjustment for energy intake may be performed in human observational studies to mimic the isocaloric conditions in animal experiments. (2) It may be associated with disease in a non-causal manner and, since reported intakes of many specific food groups or nutrients tend to be correlated with total reported intake, total energy intake may confound associations with many food groups or nutrients. (3) Factors such as physical activity, body size and metabolic variation influence energy intake and may influence the risk of disease; variation in nutrient intake secondary to the influence of these factors on total energy intake is extraneous when investigating the effect of variation in nutrient intake on disease (Willett, 1990).

Methods of adjustment have been discussed by Willett (1990) and Kushi *et al.* (1992). More recently, it has been noted that the impact of measurement error on energy-adjustment models is

uncertain (Kipnis *et al.*, 1997), and there is renewed debate about energy adjustment (Block, 2001; Day *et al.*, 2001; Day, 2002; Willett, 2001a, b, c). There is some doubt as to whether energy adjustment is required for assessment of fruit and vegetable intake. Fruits and vegetables are sources of non-fat energy. It has been suggested that adjustment for body weight may be a better approach to adjust for the overall effects of energy (Day & Ferrari, 2002).

Low intake or missing values

Treatment of data from subjects reporting very low total intake or with a high proportion of missing values can lead to (*a*) selection bias from excluding such subjects or (*b*) misclassification introduced by imputation of values to avoid this (Vach & Blettner, 1991; Greenland & Finkle, 1995; Demissie *et al.*, 2003; Lyles & Allen, 2003). It is important to consider what method has been used, and whether the investigators reported any impact on the study results from different methods of dealing with this problem.

Study context

Heterogeneity between studies could arise from differences in many aspects of study context, including the types of fruit and vegetables available for consumption, their growing conditions, typical methods of preparation (storage, cooking), variability of exposure in the study population and of genetic background.

In cohort studies, few participants consume more than 4–5 servings of vegetables (or fruits) per day. This simply reflects the ranges of fruit and vegetable intake common in the USA and Europe, where these studies were conducted. The cohort studies to date could not evaluate whether substantial cancer protection is associated with higher levels of intake.

Integration of evidence

In reviewing the evidence in the rest of this chapter, the Working Group used inclusion criteria. Case reports were not considered, and ecological studies were not used in the evaluation. Cohort and case–control studies were always considered unless in the judgement of the Working Group they were inadequate in conception, design, conduct or analysis.

There have been several instances of sequential or multiple publications of analyses of the same or overlapping data-sets. When the reports clearly related to the same or overlapping data-sets, only data from the largest or most recent publication were included.

Meta-analyses and pooled analyses that were available are described at the end of the relevant section.

The data considered are presented in detail in the tables. In general, the tables include only data for total fruit, total vegetables, and total fruit and vegetables combined, unless for a specific study, the subgroups for which data were presented appeared to comprise a substantial proportion of fruit or vegetable intake, e.g. fresh fruits for fruits, or raw and cooked vegetables for vegetables. However, the data on sub-groups do not contribute to the evaluations, and no data are presented on cruciferous vegetables, as they will be the subject of a future evaluation. The odds ratios (ORs) or relative risks (RRs) presented are always those reported relating the highest quantile of consumption (of total fruit or total vegetables) to the lowest. Confidence intervals for these ORs are included when reported by the authors. When the authors reported ORs for the lowest to the highest consumption, the Working Group computed the inverse, and the result of these computations (and of the inverse of the confidence intervals if available) appears in square brackets in the tables.

The data used in the evaluations also appear as plots (Figures 16–51). Only those studies on total fruit or vegetables which reported confidence intervals and adjusted for the main confounders for the relevant sites are included in the plots. Meta-analyses and pooled analyses reported in the tables or discussed in the text have not been included in the plots. An estimate of the overall effect across all the evaluable studies, calculated as explained below, is presented, taking the size of the study (as reflected in the confidence interval) into account when weighting the individual study findings. The result of applying a test for heterogeneity is given with each plot. The reader is cautioned that these summary estimates do not constitute the result of a formal meta-analysis, and they should not be interpreted as such.

The summary estimates in the plots were calculated as follows. Using the log of the relative risks for the highest versus lowest exposure categories in the individual studies, designated as β_i, the pooled estimate (summary value, β_p) was obtained, separately for cohort and case–control studies, as

$$\beta_p = [\Sigma_i\, \beta_i/\mathrm{var}(\beta_i)]/[\Sigma_i\, 1/\mathrm{var}(\beta_i)]$$

with estimated standard error

$$\mathrm{SE}(\beta_p) = [\Sigma_i\, 1/\mathrm{var}(\beta_i)]^{-1/2}$$

The χ^2 for heterogeneity was calculated as

$$\chi^2 = \Sigma_i\, (\beta_i - \beta_p)^2/\mathrm{var}(\beta_i)$$

with (N–1) degrees of freedom, where N is the total number of studies.

The analyses and generation of the plots were performed using the R software (Ihaka & Gentleman, 1996). Individual studies are presented in the plot in chronological order, with the 'box size' proportional to the inverse of their variance.

For some studies, results are reported for subcategories of the population under study, for example, males and females, pre- and postmenopausal women, colon and rectal cancer. In the calculation of the overall effect and in the final plot, the subgroups counted as individual studies; however, when counting the number of evaluable studies for different cancer sites, subgroups were considered as coming from a single study.

In reviewing the evidence on each cancer site, the Working Group considered the following criteria:

- Overall quality of design
- Comparability of source population of cases and controls
- Adequacy of control for potential confounding
- Evidence of dose–response effect
- Evidence of effect modification
- Evidence for difference in effect by age, gender and subsite of cancer
- Evidence of publication bias
- Evidence of heterogeneity of effect between studies

Effects by site

The tables summarizing epidemiological studies and their results by site (Tables 10–112 are grouped on pages 103–245).

Grouped sites of the upper gastrointestinal tract

The most important factors responsible for the occurrence of cancers of the upper gastrointestinal tract (oral, pharyngeal and oesophageal cancers), as well as cancer of the larynx, are tobacco smoking and alcohol drinking, which interact in a multiplicative way (WCRF/AICR, 1997). There are therefore serious risks of residual confounding in observational studies of cancers at all these sites.

Combined fruit and vegetables

Cohort studies

Three cohort studies have reported upon fruit and vegetable consumption in relation to grouped sites of the upper gastrointestinal tract, two conducted in Europe and one in the USA. One included all incident cancers from mouth to oesophagus (Boeing, 2002); another also included larynx (Kjaerheim *et al.*, 1998) and a third additionally included nasopharynx and stomach (Kasum *et al.*, 2002). Boeing (2002) reported a significantly decreased risk associated with consumption of fruit and vegetables combined; the other studies reported data only on subcategories (Table 10).

Oral cavity and pharynx

Fruit

Cohort studies

No cohort study on fruit consumption and risk of oral or oropharyngeal cancer was identified by the Working Group.

Case–control studies

Five studies in the USA and Australia have been reported (Table 11). Wynder *et al.* (1957) used a hospital-based case–control design and included 543 males and 116 females with cancer in their analysis. Neither vegetable nor fruit consumption was significantly different in males, but women with tongue cancer ($n = 57$) had lower citrus fruit consumption than controls (the findings are not tabulated). One study, which included deceased subjects, found an inverse association (Winn *et al.*, 1984). Three analyses of data from a large study in the USA (McLaughlin *et al.*, 1988; Gridley *et al.*, 1990; Day *et al.*, 1993) found inverse associations for fruit consumption except among blacks in total and black females.

In four South American hospital-based studies, inverse associations for fruit or citrus fruit consumption were significant in three.

In Europe, most of the case–control studies were conducted in northern Italy and nearby areas. Case recruitment was hospital-based and controls were hospital patients. In addition to reports from single study centres (Franceschi *et al.*, 1991a; La Vecchia *et al.*, 1991), combined analyses have been conducted using the various data sources in different combinations (Bosetti *et al.*, 2000b). The publications of Negri *et al.* (1991) and La Vecchia *et al.* (1991) seem to have used overlapping data-sets. The results of Negri *et al.* (1991) were used for the Working Group's evaluation because of the larger number of subjects reported. Except for the first, the studies revealed inverse associations, one of which was non-significant. A sub-analysis for never-smokers showed a non-significant risk reduction in those having more than a low intake of fresh fruit (Fioretti *et al.*, 1999). Franceschi *et al.* (1999) reported on a multicentre study conducted between 1992 and 1997, using an expanded validated questionnaire. More recent studies elsewhere in Europe have shown a consistent inverse relationship with fruit consumption.

Fruit consumption was inversely related to oropharyngeal cancer in one of the two older studies in southern Asia. However, this study reported only raw data without adjustment. A recent hospital-based case–control study in India showed a protective effect of fruit consumption in the whole study population, as well as among male smokers and non-smokers and alcohol drinkers and non-drinkers (Rajkumar *et al.*, 2003b).

In most studies that addressed the issue (Winn *et al.*, 1984; Oreggia *et al.*, 1991; Tavani *et al.*, 2001; Sánchez *et al.*, 2003), an inverse association with fruit consumption was found across all strata of smoking and alcohol-drinking status.

Vegetables

Cohort studies

In the large cohort study of Hirayama (1990) in Japan, the frequency of intake of green-yellow vegetables was

inversely associated with risk of oropharyngeal cancer non-significantly in men and significantly in women.

Case–control studies

Three analyses of data from a large study in the USA (McLaughlin *et al.*, 1988; Gridley *et al.*, 1990, Day *et al.*, 1993) found a significantly reduced risk associated with vegetable consumption only in black men (Table 12).

In four studies in South or Central America, there was no significant effect of vegetable consumption except for a study in Uruguay involving 57 cases of squamous-cell carcinoma of the tongue.

The European case–control studies on diet and risk of oral and oropharyngeal cancer used hospital-based case recruitment and hospital patients as controls. The studies in northern Italy, except that of Franceschi *et al.* (1991a), show a consistent significant inverse relationship between vegetable intake and risk of oral and pharyngeal cancer. A sub-analysis on never-smokers revealed no protection by vegetables (Fioretti *et al.* 1999).

In a recent study in southern India, vegetable intake was inversely related to risk (Rajkumar *et al.*, 2003b). This was true for current smokers and non-smokers as well as for alcohol drinkers and non-drinkers. Neither of two studies from northern Asia presented data on total vegetable consumption.

Most other studies that addressed the issue suggest that the inverse association with vegetable consumption persists across all strata of smoking and alcohol-drinking status.

Combined fruit and vegetables

Results on total fruit and vegetable consumption from three case–control studies in North America have been reported. Graham *et al.* (1977) reported no difference between 584 cases of oral cavity cancer and 1222 hospital controls in intake of various fruit and vegetables, but no numerical data were presented. Gridley *et al.* (1992) reported that fruit and vegetable intake was associated with reduced risk (presented as a point estimate) for oral and pharyngeal cancer, independent of supplement use (Table 13). Winn *et al.* (1984) also reported a significant inverse relationship for combined fruit and vegetable consumption.

Precancerous lesions

Three case–control studies investigated precancerous lesions with respect to fruit and vegetables (Table 14). In two studies of submucous fibrosis and leukoplakia in male tobacco users in different states of India, cases and controls were selected by medical examination of household members. Only in the study of Gupta *et al.* (1999) was total fruit and vegetable consumption evaluated, and no inverse association was reported. Similarly, the study of Morse *et al.* (2000) did not show a significant inverse association with fruit and vegetable consumption.

Salivary gland

Zheng *et al.* (1996) (Table 15) did not find an association of either fruit or vegetable consumption with salivary gland cancer.

Nasopharynx

In the two case–control studies (Table 16), significant inverse associations were reported only for orange and tangerine consumption.

Discussion

The data available for evaluation are almost entirely from case–control studies, of varying design. Fruit consumption was evaluable in 10 studies: the mean odds ratio (OR) was 0.45 (95% confidence interval (CI), 0.38–0.53), range 0.10–0.70 (Figure 16). Vegetable consumption was evaluable in seven studies: mean OR = 0.49 (95% CI 0.39–0.62), range 0.19–0.80 (Figure 17).

Most of these studies adjusted for the potential confounding effects of tobacco and alcohol consumption, though many, especially the earlier studies, did so rather crudely. Therefore it is not possible to exclude an effect of residual confounding. Further, many of the case–control studies were hospital-based, and even in those that were population-based, full comparability of the data from cases and controls may not have been achieved, nor can the inherent biases associated with this design be eliminated.

Only three case–control studies considered the effect of fruit and vegetable consumption on presumed precursor lesions of the mouth. No significant inverse association was found. Similarly, no effect of these exposures on salivary gland cancer (one study) was found, while for nasopharyngeal cancer (two studies), only subcategories of exposure were considered.

Oesophagus

Fruit

Cohort study

Only one cohort study considered total fruit consumption (Table 17). This was conducted in the Life Span Study in Japan that included 120 321 atomic bombing survivors and non-exposed controls. A borderline significant inverse association was found (Sauvaget *et al.*, 2003).

Case–control studies

Three of the five studies in the USA found significant inverse associations for fruit consumption (Table 18). Four out of six studies in South America also found significant inverse associations, while two that did not report an effect were on citrus and non-citrus fruit, and not all fruits combined. The findings from four studies in South America were also included in a

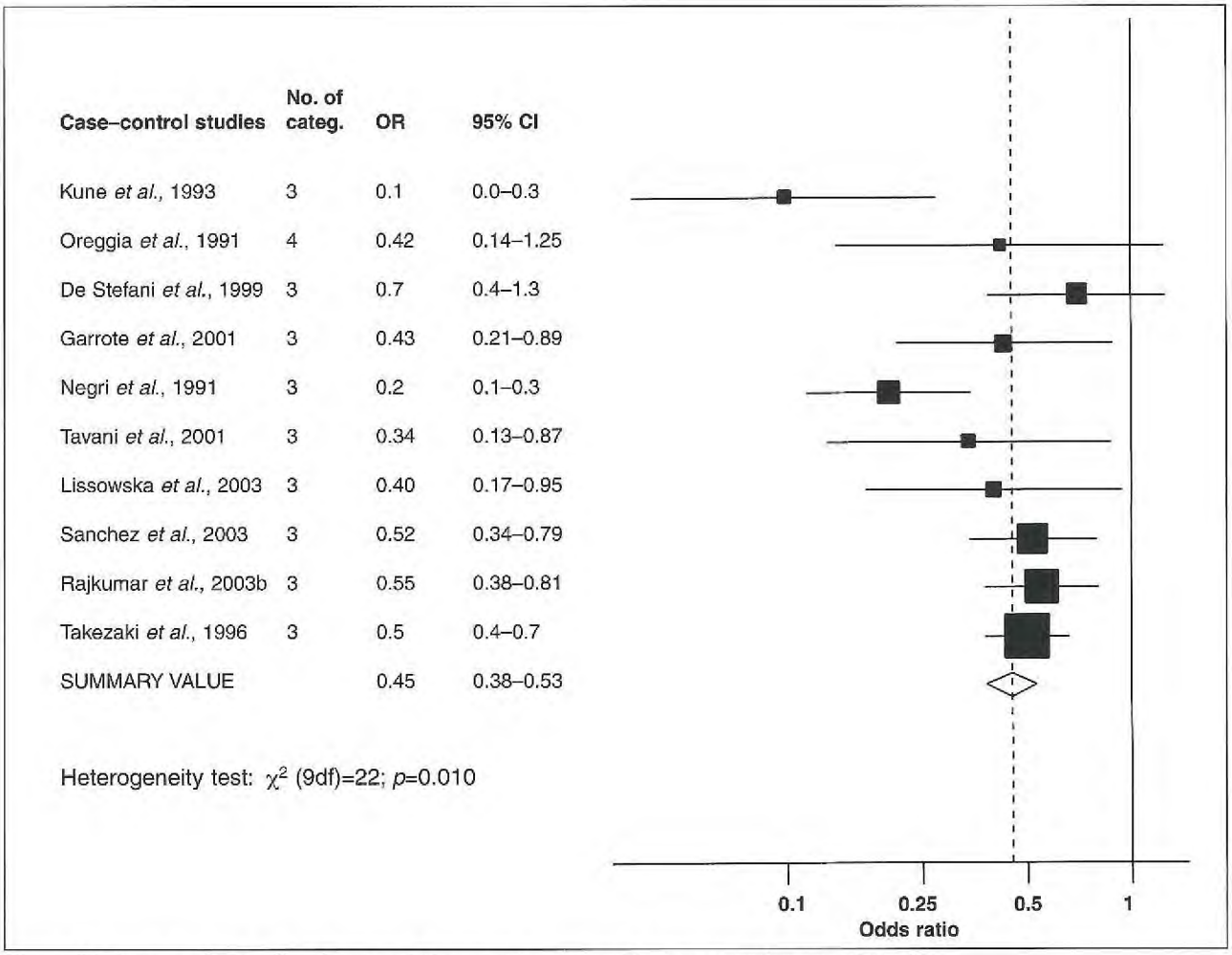

Figure 16 Case–control studies of oral and pharyngeal cancer and fruit consumption (see Table 11)

pooled analysis (Castellsague *et al.*, 2000) which found a significant inverse association.

The studies in Europe also generally found fruit consumption to be inversely related to risk, except for a small study in Greece. The large study of Tuyns *et al.* (1987) evaluated citrus fruit and other fresh fruit but not total fruit. Many hospital-based case–control studies were conducted in northern Italy. Following an early report (Decarli *et al.*, 1987), Negri *et al.* (1991) (294 cases in June 1990) summarized the results of the studies so far conducted. The reports of Tavani *et al.* (1993) for women, Tavani *et al.* (1994) for non-smokers and Tavani *et al.* (1996) for non-drinkers were based on the same data-set extended to 316 cases until December 1992. Most of the cases were already covered by the report of Negri *et al.* (1991). Bosetti *et al.* (2000a) used an expanded validated questionnaire in a multi-centre study on citrus and other fruits conducted between 1992 and 1997. In nearly all these studies, significant inverse associations were found.

Several studies in southern Asia have been reported. Cook-Mozaffari *et al.* (1979) conducted a population-based study between 1974 and 1976 with 344 incident cancers of the oesophagus and twice the number of controls. When they considered recent diet, they found relative risk estimates below 1.0, most of them significant for nearly all fruit items considered, but they did not present relative risk estimates for total fruit. The hospital-based case–control study of Prasad *et al.* (1992) in Hyderabad, India, included only 35 cases and did not present relative risk estimates for food items. The hospital-based study of de Jong *et al.* (1974) among Singapore

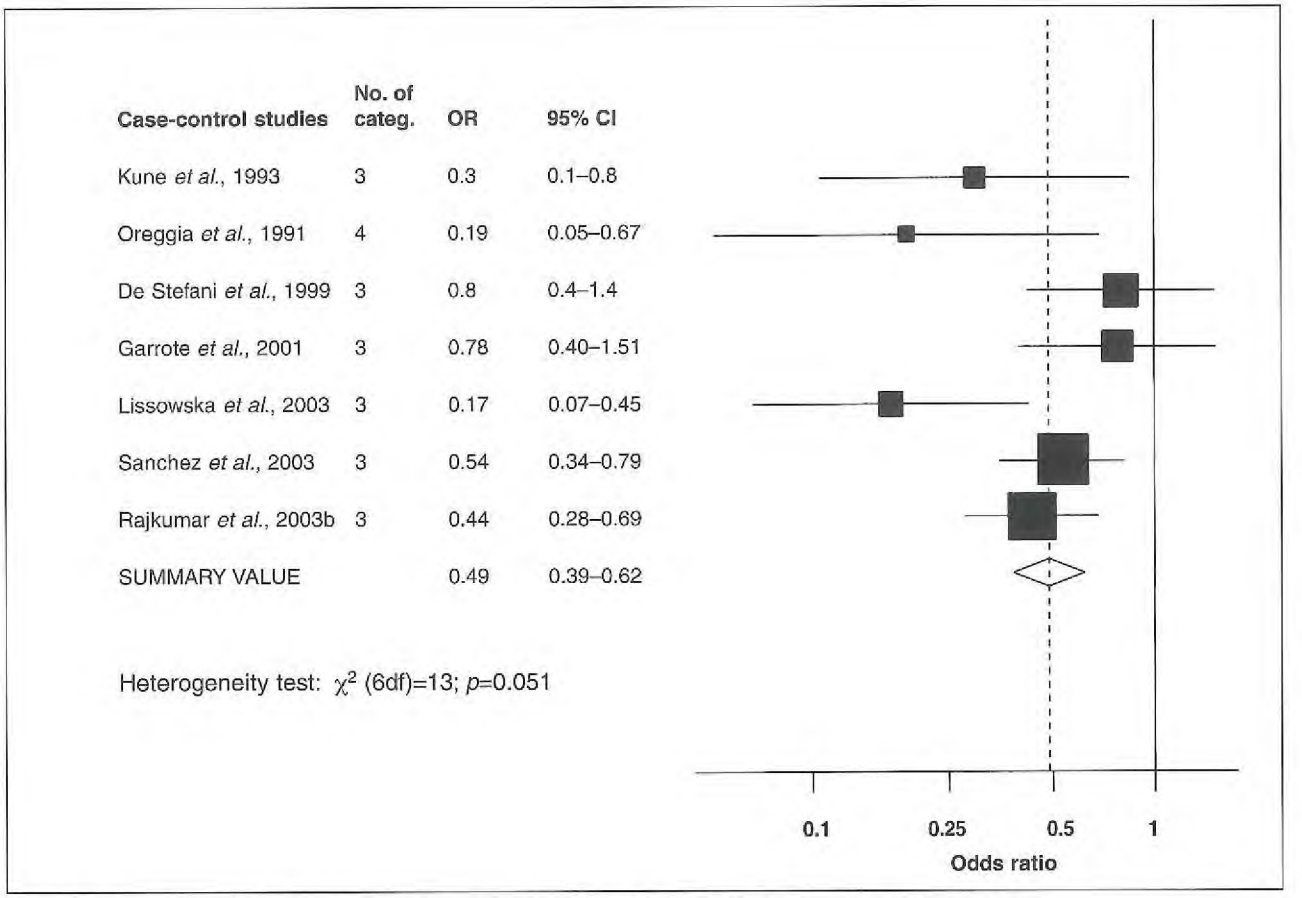

Figure 17 Case–control studies of oral and pharyngeal cancer and vegetable consumption (see Table 12)

Chinese with 131 squamous-cell oesophageal cancer cases and 345 hospital controls also did not analyse total fruit, but only banana consumption. Of the four studies from India and Turkey included in Table 18, risk estimates were below 1.0 in one of the Indian studies and both in Turkey.

Of the nine studies in northern Asia included in Table 18, five considered total fruit, one finding a significant inverse association only for men. Of the remainder, one was based on oesophagitis diagnosed by oesophagoscopy in relatives in households.

Tavani *et al.* (1994, 1996) found that fruit intake was significantly inversely related to risk in the low-exposure groups of alcohol drinkers and smokers. Cheng *et al.* (1995) also reported that among never-smokers and non-drinkers, selected from a previously analysed study population, consumption of citrus fruit was inversely related to risk.

Vegetables

Cohort studies

All four cohort studies were conducted in China or Japan, but none considered the effect of total vegetable consumption (Table 19).

Case–control studies

All five studies in the USA showed an inverse association between vegetable consumption and risk of oesophageal cancer (Table 20). Wynder & Bross (1961) also reported lower intake of vegetables among 150 squamous-cell oesophageal cancer patients compared with 150 other tumour patients used as controls. Similarly, of the five studies in South America, all but one showed an inverse association between vegetable consumption and risk of oesophageal cancer. This was confirmed in the overview analysis of data from four of the studies (Castellsague *et al.*, 2000). Further, except for squamous-cell carcinoma in one small study in Greece, all the studies in Europe showed inverse associations, though only four assessed total

vegetable intake. The studies conducted in northern Italy are best represented by the reports of Negri *et al.* (1991) and Bosetti *et al.* (2000a).

In the study in Iran by Cook-Mozaffari *et al.* (1979), relative risk estimates below 1.0, most of them not significant, were found for nearly all vegetable items, though total vegetable intake was not considered. The two studies in India and the two in Turkey all found inverse associations with vegetable consumption, although one of those in India did not assess total vegetable consumption.

Similarly, all but one of the nine cancer studies conducted in northern Asia found inverse associations between various groupings of vegetables and oesophageal cancer, though only one considered total vegetable consumption. This was supported for women but not men by the study of Chang-Claude *et al.* (1990) of oesophagitis among relatives.

The study of Tavani *et al.* (1994) in never-smokers revealed that vegetable consumption measured as total green vegetable consumption or carotene index is inversely related to risk of cancer of the oesophagus and in both low and high alcohol drinkers. Cheng *et al.* (1995) reported that among never-smokers and non-drinkers, selected from a previously analysed study population, consumption of green leafy vegetables was inversely related to risk.

Combined fruit and vegetables

Cohort studies

No studies were identified by the Working Group.

Case–control studies

The hospital-based case–control study by Mettlin *et al.* (1981) of male patients with 147 cases and 264 controls was one of the first to investigate fruit and vegetable consumption with respect to risk of oesophageal cancer. However, the only comparison was between case consumption and the consumption by the total study population. The findings indicated that fruit and vegetable consumption was significantly inversely related to case status.

All six studies with published estimates on combined fruit and vegetable intake found an inverse relationship with oesophageal cancer risk (Table 21).

Discussion

For oesophageal cancer, fruit consumption was evaluable in 16 case–control studies: the mean OR was 0.54 (95% CI 0.48–0.61), range 0.14–1.50 (Figure 18). Vegetable consumption was evaluable in 10 case–control studies, giving a mean OR = 0.64 (95% CI 0.57–0.72), range 0.10–0.97 (Figure 19).

The observation of an inverse association with fruit and vegetable intake in most of the studies was confirmed by a recent meta-analysis by Riboli & Norat (2003). For both dietary factors, the combined relative risk estimate was significantly below 1.0.

The data indicate that cancer cases have usually eaten less fruit and vegetables over their lifetime and that those eating more fruit and vegetables than the rest of the study population usually experience less oesophageal cancer. However, it remains uncertain whether this results from a true protective effect or is due to residual confounding by tobacco smoking, alcohol drinking and social factors. Studies that looked at effects of fruit and vegetables in particular subgroups of never-smokers and non-drinkers and those that looked at effects of these food items across strata of smoking habits and alcohol drinking indicate similar associations of fruit and vegetable consumption across all the subgroups considered, but the power of these studies was low.

Stomach

Despite reductions in incidence and mortality rates in most countries, stomach cancer is still one of the most common malignant neoplasms worldwide. The reasons for the decline and for geographical differences are not fully understood, but domestic refrigeration, increased year-round availability of fruits and vegetables, and reduced use of salt are believed to be relevant factors.

Fruit

Cohort studies

The association between intake of fruit and the risk of stomach cancer has been examined in 11 cohort studies (Table 22), most of which reported an inverse, although often non-significant, association.

Guo *et al.* (1994) found no association for either cardia or non-cardia cancer.

Case–control studies

Most of the 37 case–control studies of the association between intake of fruit and risk of stomach cancer included in Table 23 showed an OR below 1.0.

Two studies reported associations according to anatomical subsite; these showed significant inverse associations for both cardia and non-cardia cancer (Palli *et al.*, 1992; Ekström *et al.*, 2000). Six case–control studies reported upon the association according to histological subtype. In three, there was a significant inverse association for each histological type (Correa *et al.*, 1985; Harrison *et al.*, 1997; Ekström *et al.*, 2000), in one a significant inverse association for the intestinal type in females only (Kato *et al.*, 1990), in one a significant inverse association for the differentiated histological type (Ito *et al.*, 2003) and in one no association for any subtype (Ward & Lopez-Carrillo, 1999).

Vegetables

Cohort studies

The association between intake of vegetables and risk of stomach cancer

Case–control studies	No. of categ.	OR	95% CI
Brown *et al.*, 1988	3	0.5	0.3–0.9
Castellsagué *et al.*, 2000 (S)	3	0.37	0.27–0.51
De Stefani *et al.*, 1999	3	0.4	0.3–0.6
De Stefani *et al.*, 2000b (S)	4	0.18	0.09–0.39
Negri *et al.*, 1991	3	0.3	0.2–0.4
Tzonou *et al.*, 1996a (S)	5	0.9	0.67–1.21
Tzonou *et al.*, 1996a (A)	5	0.84	0.65–1.08
Cheng *et al.*, 2000 (A)	4	0.18	0.05–0.57
Sharp *et al.*, 2001 (A)	4	0.64	0.25–1.67
Terry *et al.*, 2001b (A)	4	0.7	0.4–1.1
Terry *et al.*, 2001b (S)	4	0.6	0.4–1.1
Wolfgarten *et al.*, 2001 (A)	2	0.16	0.04–0.53
Wolfgarten *et al.*, 2001 (S)	2	0.33	0.12–0.91
Phukan *et al.*, 2001	2	0.3	0.08–4.2
Onuk *et al.*, 2002	2	0.14	0.06–0.31
Hu *et al.*, 1994	4	1.5	0.8–2.9
Hanaoka *et al.*, 1994	4	0.50	0.18–1.39
Gao *et al.*, 1999	3	0.75	0.36–1.55
Yokoyama *et al.*, 2002	5	0.78	0.28–2.17
SUMMARY VALUE		0.54	0.48–0.61

Heterogeneity test: χ^2 (18df)=82; p<0.001

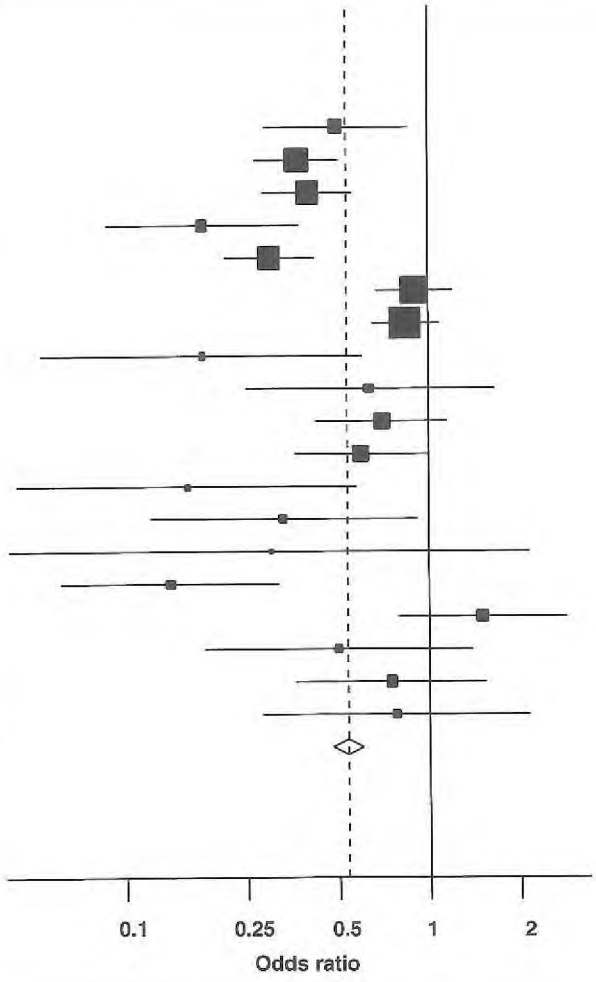

Figure 18 Case-control studies of oesophageal cancer and fruit consumption (see Table 18)
S = squamous cell carcinoma, A = adenocarcinoma

was examined in 11 cohort studies (Table 24). Although all studies except two showed relative risks below 1.0, the association was generally not significant.

One study showed a significant inverse association for cases with differentiated histological type, but none for those with undifferentiated type (Kobayashi *et al.*, 2002). In two studies, the association between total intake of vegetables and the risk of stomach cancer was examined according to anatomical subsite; in each there was no significant association for either cardia or non-cardia cancer (Inoue *et al.*, 1994; Kobayashi *et al.*, 2002).

Case–control studies

Most of 39 case–control studies reported in Table 25 showed an OR below 1.0.

In two studies, the association between intake of total vegetables and the risk of stomach cancer was examined according to anatomical subsite; in one there were significant inverse associations for both cardia and non-cardia cancer for raw vegetables (Palli *et al.*, 1992), while in the other the association was not significant (Ekström *et al.*, 2000). Five studies reported upon the association between intake of vegetables and the risk of stomach cancer according to histological subtype; in three there was a significant inverse association for both histological types (Ward & Lopez-Carrillo, 1999; Ekström *et al.*, 2000;

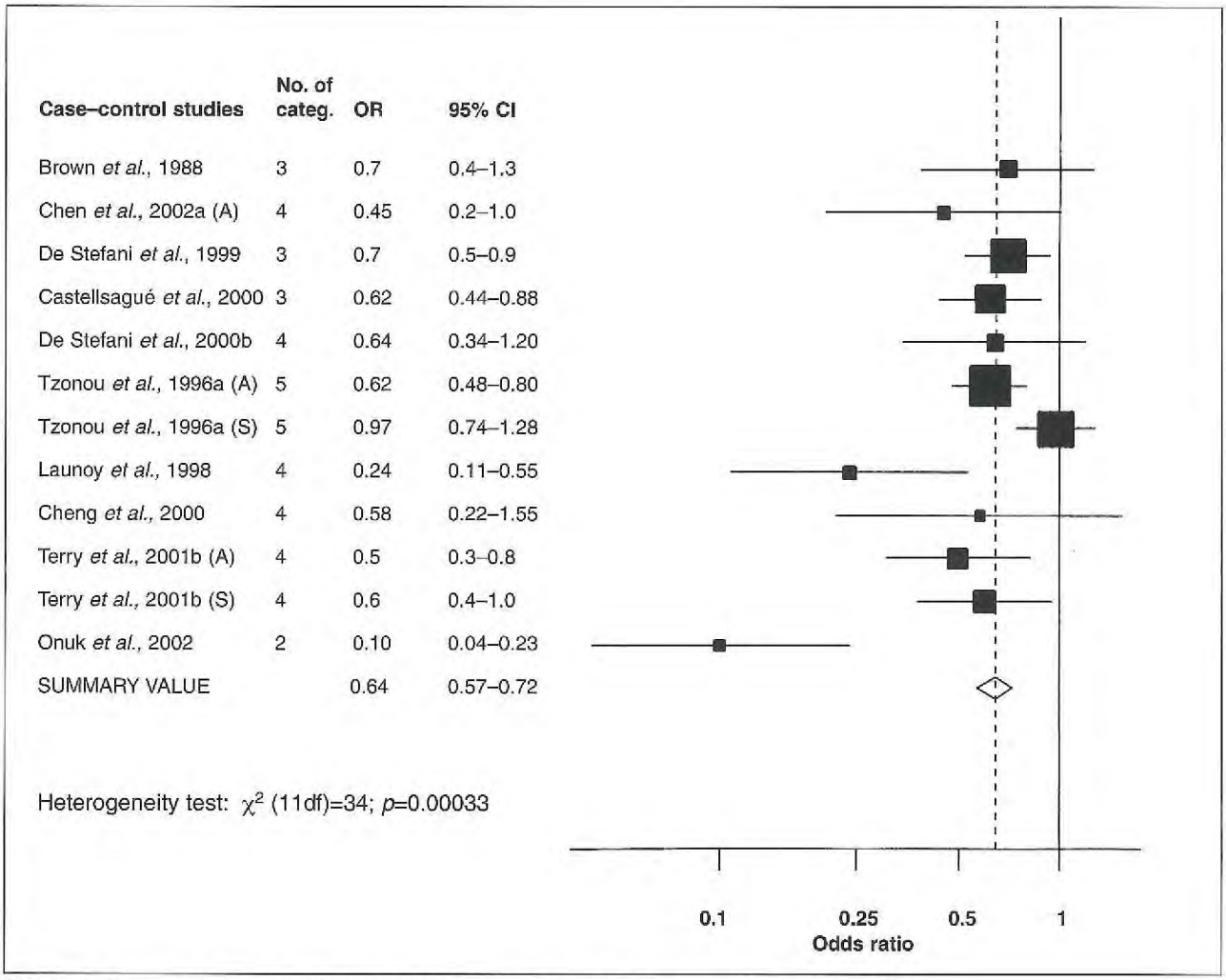

Figure 19 Case–control studies of oesophageal cancer and vegetable consumption (see Table 20)
A = adenocarcinoma; S = squamous-cell carcinoma

Ito *et al.*, 2003), in one for the intestinal type only in males (Kato *et al.*, 1990) and in one a non-significant inverse association (Harrison *et al.*, 1997).

Combined fruit and vegetables

Cohort studies

Three cohort studies examined the association between combined intake of total fruit and vegetables and the risk of stomach cancer (Table 26). In two of these, there was a significant inverse association, although one study considered only fresh fruit and raw vegetables.

Case–control studies

In all three of the case–control studies that evaluated the combination of fruit and vegetables, there was a significant inverse association (Table 27).

Discussion

Fruit consumption was evaluable in 10 cohort studies of stomach cancer. The mean relative risk (RR) was 0.85 (95% CI 0.77–0.95), range 0.55–1.92 (Figure 20). In the 28 evaluable case–control studies, the mean OR was 0.63 (95% CI 0.58–0.69), range 0.31–1.39 (Figure 21).

Vegetable consumption was evaluable in five cohort studies. The mean RR was 0.94 (95% CI 0.84–1.06), range 0.70–1.25 (Figure 22). Twenty case–control studies were evaluable and the mean OR was 0.66 (95% CI 0.61–0.71), range 0.30–1.70 (Figure 23).

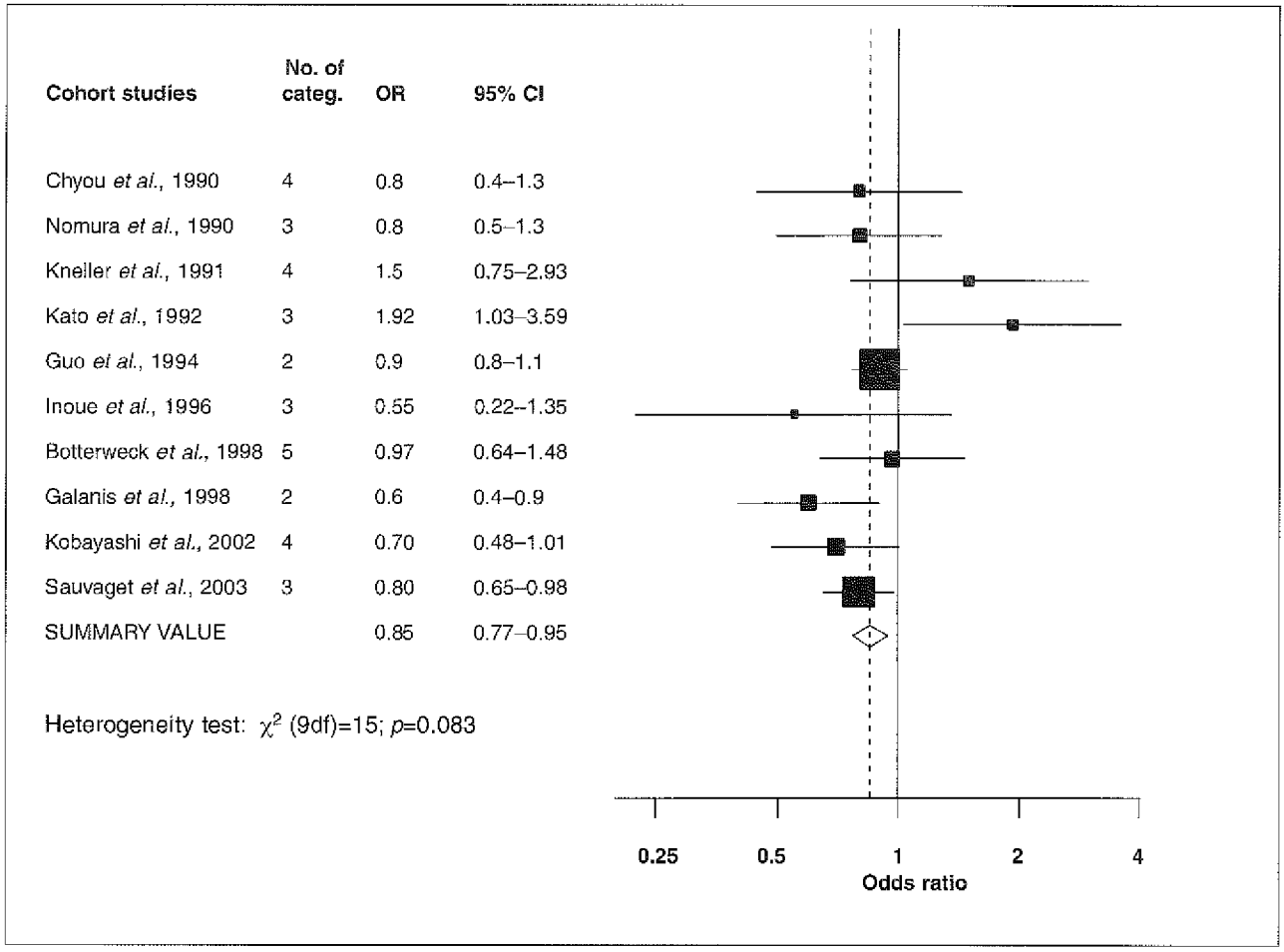

Figure 20 Cohort studies of stomach cancer and fruit consumption (see Table 22)

The results of the cohort studies are not consistent. Besides differences in population and the types of fruit and vegetables consumed, other factors that could explain the heterogeneity are the quality of design, food intake assessment, uncontrolled confounding and effect modification. In most cohort studies, there were inverse associations, but these were statistically significant in only two studies for fruit and one for vegetables. In two cohort studies, a positive association was reported between fruit intake and stomach cancer risk, one in a high-risk male American population and the second in Japanese. However, the numbers of cases in both studies were low. In all except two of the cohort studies, the dietary questionnaire was not validated and the numbers of total items in the questionnaire were low.

Stomach cancer is a disease of complex etiology involving multiple risk factors including dietary, infectious, occupational, genetic and preneoplastic factors. It is possible that unmeasured or unidentified risk factors may have affected some study results. While all the studies adjusted for sex and age, adjustment for *Helicobacter pylori* infection was rarely possible. Only three cohort studies adjusted for history of stomach disease and family history of stomach cancer. Two studies did not adjust for tobacco or alcohol intake and one of these reported a significant risk increase associated with high intake of fruit.

The relationship between stomach cancer risk and diet has been extensively investigated in case–control studies, mainly in European and Asian populations. The case–control studies showed more consistent and stronger effects of fruit and vegetables on stomach cancer risk than the cohort studies. Most of the case–control

Case–control studies	No. of categ.	OR	95% CI
Correa *et al.*, 1985 (B)	4	0.33	0.16–0.66
Correa *et al.*, 1985 (W)	4	0.47	0.24–0.92
Jedrychowski *et al.*, 1986	3	0.31	0.15–0.64
Kono *et al.*, 1988 (H)	2	0.7	0.4–1.0
Kono *et al.*, 1988 (P)	2	0.5	0.3–0.8
De Stefani *et al.*, 1990a	3	0.36	0.23–0.56
Kato *et al.*, 1990 (M)	3	0.83	0.51–1.33
Kato *et al.*, 1990 (F)	3	0.77	0.33–1.78
Wu-Williams *et al.*, 1990	3	0.67	0.29–1.67
Boeing *et al.*, 1991a	3	0.56	0.35–0.91
Yu & Hsieh, 1991	2	0.5	0.3–0.8
Hoshiyama & Sasaba, 1992	3	0.8	0.5–1.3
Jedrychowski *et al.*, 1992	3	0.72	0.56–0.94
Sanchez-Diez *et al.*, 1992	2	0.31	0.11–0.87
Ramon *et al.*, 1993	4	0.85	0.21–1.11
Inoue *et al.*, 1994	2	0.86	0.70–1.10
Cornée *et al.*, 1995	3	0.50	0.25–1.03
Muñoz *et al.*, 1997	3	0.47	0.21–1.05
Xu *et al.*, 1996	4	0.5	0.4–0.8
Harrison *et al.*, 1997 (I)	*	0.5	0.3–0.9
Harrison *et al.*, 1997 (D)	*	0.5	0.2–1.0
La Vecchia *et al.*, 1997	3	0.6	0.5–0.8
Gao *et al.*, 1999	3	0.88	0.47–1.67
Ward & Lopez-Carrillo, 1999	4	1.0	0.5–2.2
Ekström *et al.*, 2000 (C)	4	0.5	0.2–1.0
Ekström *et al.*, 2000 (N)	4	0.6	0.4–0.8
Huang *et al.*, 2000 (FH +)	*	1.39	0.69–2.82
Huang *et al.*, 2000 (FH -)	*	1.11	0.74–1.67
Mathew *et al.*, 2000	4	0.7	0.2–3.6
De Stefani *et al.*, 2001	3	0.35	0.21–0.59
Hamada *et al.*, 2002	2	0.4	0.2–0.9
Kim *et al.*, 2002	3	0.67	0.33–1.39
Nishimoto *et al.*, 2002	4	0.6	0.3–1.2
Ito *et al.*, 2003	4	0.68	0.40–1.16
SUMMARY VALUE		0.63	0.58–0.69

Heterogeneity test: χ^2 (33df)=54.4; p=0.0108

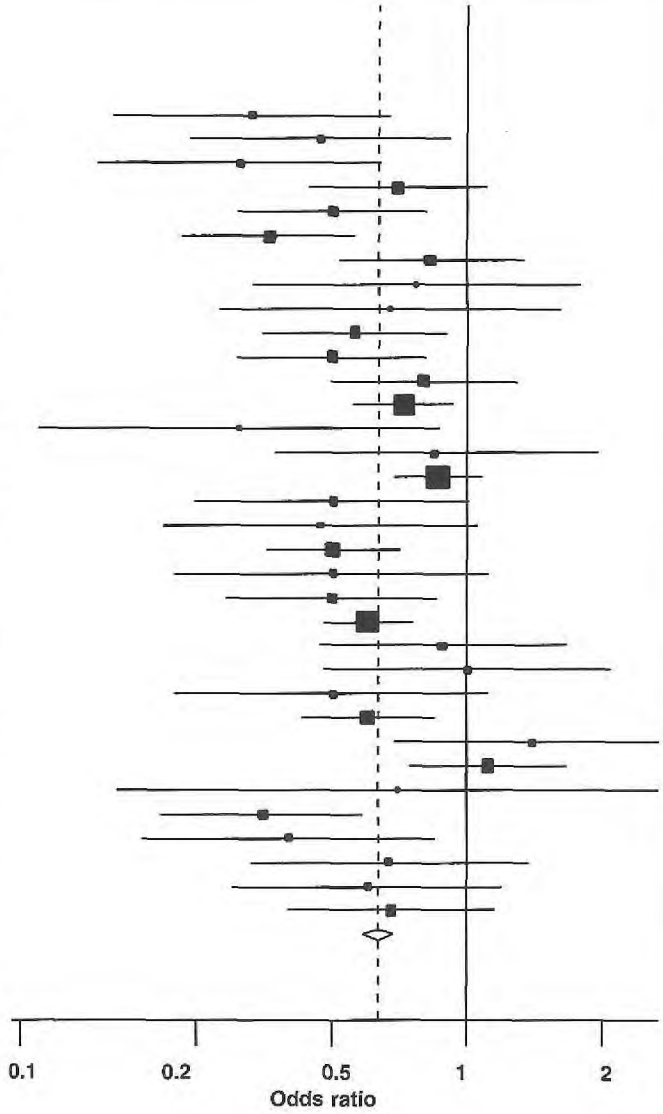

Figure 21 Case–control studies of stomach cancer and fruit consumption (see Table 23)
B = blacks; W = whites, H = hospital controls; P = population controls; M = males, F = females; I = intestinal type; D = diffuse type; C = cardia; N = non-cardia; FH+ = gastric cancer family history positive; FH– = gastric cancer family history negative; * = *not applicable*

Cohort studies	No. of categ.	OR	95% CI
Chyou *et al.*, 1990	4	0.7	0.4–1.1
Kneller *et al.*, 1991	4	0.9	0.48–1.78
Botterweck *et al.*, 1998	5	0.86	0.58–1.26
McCullough *et al.*, 2001 (M)	3	0.89	0.76–1.05
McCullough *et al.*, 2001 (F)	3	1.25	0.99–1.58
Kobayashi *et al.*, 2002	5	0.75	0.54–1.04
SUMMARY VALUE		0.94	0.84–1.06

Heterogeneity test: χ^2 (5df)=9.5; p=0.09

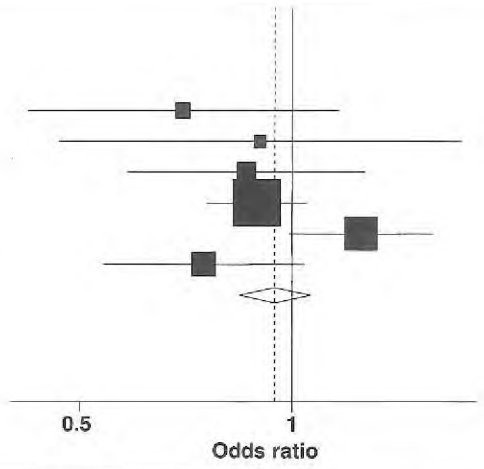

Figure 22 Cohort studies of stomach cancer and vegetable consumption (see Table 24)
M = males; F = females

Case-control studies	No. of categ.	OR	95% CI
Correa *et al.*, 1985	4	0.50	0.25–1.00
Risch *et al.*, 1985	*	0.84	0.72–0.96
Jedrychowski *et al.*, 1986	3	0.61	0.25–1.49
De Stefani *et al.*, 1990a	3	0.37	0.23–0.59
Boeing *et al.*, 1991a	3	0.86	0.54–1.36
Jedrychowski *et al.*, 1992	3	0.60	0.46–0.78
Memik *et al.*, 1992	3	0.6	0.31–1.23
Sanchez-Diez *et al.*, 1992	2	0.70	0.41–1.08
Hansson *et al.*, 1993	4	0.50	0.32–0.78
Cornée *et al.*, 1995	3	0.77	0.37–1.60
Xu *et al.*, 1996	3	0.5	0.4–0.8
Harrison *et al.*, 1997 (I)	*	0.8	0.5–1.3
Harrison *et al.*, 1997 (D)	*	0.7	0.4–1.2
Muñoz *et al.*, 1997	3	0.47	0.22–1.03
Ji *et al.*, 1998 (M)	4	0.4	0.3–0.5
Ji *et al.*, 1998 (F)	4	0.7	0.5–1.1
Ward & Lopez-Carrillo, 1999	4	0.3	0.1–0.6
Ekström *et al.*, 2000 (C)	4	0.5	0.3–1.1
Ekström *et al.*, 2000 (N)	4	0.7	0.5–1.0
Mathew *et al.*, 2000	3	1.1	0.2–5.0
De Stefani *et al.*, 2001	3	0.83	0.49–1.43
Chen *et al.*, 2002	4	1.7	0.77–3.7
Kim *et al.*, 2002	3	0.64	0.31–1.32
SUMMARY VALUE		0.66	0.61–0.71

Heterogeneity test: χ^2 (22df)=50; p=0.00059

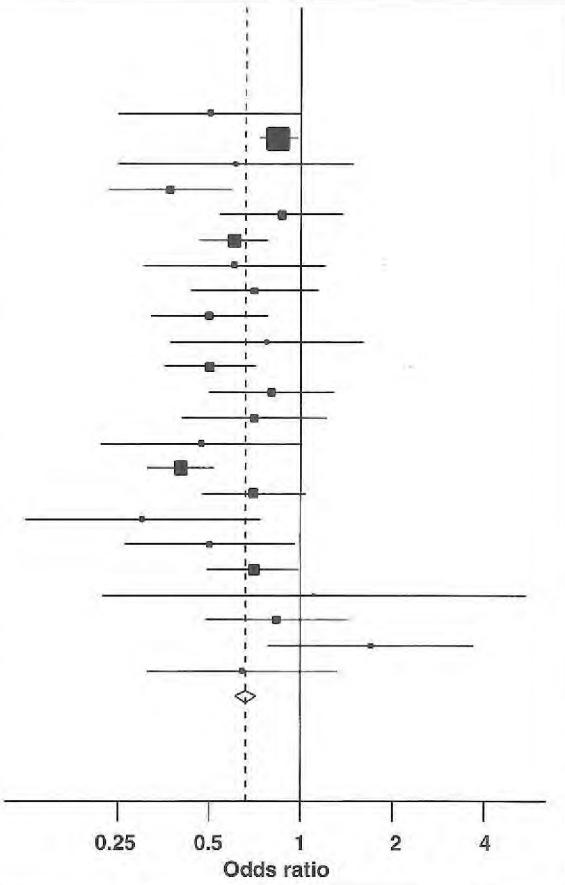

Figure 23 Case–control studies of stomach cancer and vegetable consumption (see Table 25)
I = intestinal type; D = diffuse type; M = males; F = females; C = cardia; N = non-cardia; * = not applicable

studies adjusted for more potential confounders than the cohort studies, particularly for other dietary factors, family antecedents of stomach cancer and socioeconomic status. The use of hospital-based or population-based controls was not a clear indicator of any difference in results. Only a few studies analysed the results by gender and there is very limited information about associations according to histology or tumour subsite.

The reason why case–control studies were more likely to show inverse associations is not clear. One explanation could be recall bias. Further, people with preclinical symptoms of stomach carcinoma or stomach disorders may change their dietary habits months or years before the diagnosis. In the Netherlands Cohort Study, analyses limited to cases occurring in the first year of follow-up revealed a strong inverse association with high combined fruit and vegetable consumption. With these cases excluded, the associations were much closer to the null value. Also stratified analyses (on stomach cancer and vegetable and fruit consumption combined) for subjects with and without stomach disorders revealed a stronger inverse association in subjects with stomach disorders (Botterweck *et al.*, 1998).

Three cohort studies and three case–control studies evaluated combined intake of fruit and vegetables, and in all except one cohort study there were significant inverse associations. The absence of such estimates in other reports could be because the hypotheses were related to particular sub-groups of fruits and vegetables, or perhaps due to publication bias.

Colon and rectum

Because of potential end-point misclassification between specific colorectal subsites, this section focuses on colorectal cancer *in toto*. Where reports include separate risk estimates for colon and rectal cancer, these site-specific findings are noted in the accompanying tables.

Fruit

Cohort studies

Table 28 summarizes data from 12 cohort studies of fruit consumption and colorectal cancer. Results from these studies, conducted in Europe, in the USA and one in Japan, were published within the last ten years. In only one of these studies (Terry *et al.*, 2001a) is there evidence of a significant inverse association with fruit consumption.

A pooled analysis of data from 10 cohort studies (many included in Table 28) has so far been reported only in an abstract (Smith-Warner *et al.*, 2002a). The analysis included 4966 cases of colorectal cancer from a total of 533 753 men and women followed for 6–16 years. The pooled multivariate relative risks for the highest versus lowest quartile of intake of total fruit were 0.94 (95% CI 0.84–1.04) for colon and 0.96 (0.78–1.17) for rectal cancer.

Case–control studies

Table 29 presents data from 21 case–control studies of fruit consumption and colorectal cancer, some published nearly two decades ago. These investigations were nearly evenly split between population-based and hospital-based case–control studies. The geographical diversity is somewhat greater than for the cohort studies, some studies having been conducted in Asia, South America and Australia.

The findings are also diverse; only five studies reported significant inverse associations and then often for only one gender, five showed non-significant inverse associations and for the remainder, the ORs tended to centre around 1.0.

Vegetables

Cohort studies

Table 30 presents data from 13 cohort studies of vegetable consumption in relation to colorectal cancer. Again, these studies were conducted only within Europe and the USA. For none was a significant inverse association reported between vegetable consumption and colorectal cancer (or colon and rectum cancer separately).

A pooled analysis of data from 10 cohort studies (many included data in Table 30) has so far been reported only in an abstract (Smith-Warner *et al.*, 2002a). The analysis included 4966 cases of colorectal cancer from a total of 533 753 men and women followed for 6–16 years. The pooled multivariate relative risks for the highest versus lowest quartile of intake of total vegetables were 0.95 (95% CI 0.85–1.05) for colon and 0.93 (0.79–1.10) for rectal cancer.

Case–control studies

Data from 27 hospital-based and population-based case–control studies of colorectal cancer, published over the last 25 years, are summarized in Table 31. These studies were conducted in Asia, Australia and South America, as well as Europe and North America. Significant inverse associations for vegetable consumption were reported in 15 studies, though for some of these the associations were in only one gender, or for colon or rectal cancer. In addition non-significant inverse associations were noted in eight studies.

Combined fruit and vegetables

Cohort studies

Table 32 presents data from six cohort studies that considered combined fruit and vegetable consumption in relation to colorectal cancer, all conducted within Europe and the USA. In one there were significant inverse associations with colorectal cancer as a whole

and with rectal cancer (Terry *et al.*, 2001a), in another with colon cancer in females (Shibata *et al.*, 1992).

Case–control studies

Five case–control studies of colorectal cancer have evaluated total fruit and vegetable consumption (Table 33). One found a significant inverse association for females (Shannon *et al.*, 1996) and another for both sexes combined (Deneo-Pellegrini *et al.*, 2002).

Adenomatous polyps

Fruit

Cohort study. One cohort study has reported upon fruit consumption and the detection of polyps on endoscopy (Table 34). A significant inverse association was reported.

Case–control studies. Six case–control studies have considered adenomatous polyps (Table 35); three reported inverse associations with fruit intake. In one small study, there was a significant positive association with hospital controls, but not with population controls (Almendingen *et al.*, 2001). [The Working Group was uncertain that the controls in this study were comparable to the cases, in view of the disparity between numbers of cases and controls and the much smaller number of controls.]

Vegetables

Cohort study. One cohort study reported no association between vegetable consumption and the detection of polyps on endoscopy (Table 36).

Case–control studies. Six case–control studies of adenomas have evaluated vegetable consumption (Table 37). There were inverse associations in males in one (Smith-Warner *et al.*, 2002b) and in females in another (Sandler *et al.*, 1993), but no clear association was noted in other studies that evaluated risk in both genders together. In a small study, there was a suggestion of an inverse association in comparison with hospital controls, but not with healthy controls (Almendingen *et al.*, 2001).

Combined fruit and vegetables

Randomized trial. The Polyp Prevention Trial (PPT) was a randomized intervention study of the effect of a low-fat, high-fibre, high-fruit and vegetable diet on the recurrence of colorectal adenomatous polyps in individuals older than 35 years (Schatzkin *et al.*, 2000). Intervention participants increased their intake of fruit and vegetables from 2.05 to 3.41 servings per 1000 kcal energy intake; control participants increased only from 2.00 to 2.23 servings per 1000 kcal. Intervention participants, compared with controls, lowered their fat intake by approximately one third and increased total fibre intake by about 75%. The primary trial result, however, was null: adenoma recurrence rates were virtually identical in the intervention and control groups over a four-year follow-up period (RR = 1.00; 0.90–1.12).

Cohort study. No cohort study has reported upon combined fruit and vegetable consumption and adenomas.

Case–control studies. One case–control study of adenomas reported non-significant inverse associations (Table 38).

Discussion

Colorectal cancer

The evidence for an inverse association between fruit intake and colorectal cancer is weaker in the cohort studies than in the case–control studies. The small reduction in risk observed in cohort studies is restricted to women. Over the 11 evaluable cohort studies, the mean RR was 1.00 (95% CI 0.96–1.05), range 0.50–1.60 (Figure 24) and for the nine evaluable case–control studies, the mean OR was 0.87 (95% CI 0.78–0.97), range 0.30–1.74 (Figure 25). A meta-analysis (Riboli & Norat, 2003) has shown a small statistically significant reduction in risk (per 100 gram increase in daily consumption) for the case–control studies (0.93; 95% CI 0.87–0.99) and a small non-significant reduction for cohort studies (0.96; 95% CI 0.90–1.01).

Similarly, the evidence for an inverse association between vegetable consumption and colorectal cancer is considerably weaker in the cohort studies than in the case–control studies. The mean RR for the 10 evaluable cohort studies was 0.9 (95% CI 0.85–1.05), range 0.72–1.78 (Figure 26) and for the 13 evaluable case– control studies the mean OR was 0.63 (95% CI 0.56–0.70), range 0.18–1.29 (Figure 27). The meta-analysis showed a substantial reduction in risk (per 100 grams) for the case–control studies (0.87; 95% CI 0.80–0.95) but only a small non-significant reduction in risk (0.96; 95% CI 0.90–1.05) for the cohort studies (Riboli & Norat, 2003). [If the relationship between vegetable consumption and colorectal cancer were linear, the OR of 0.87 per 100 grams of vegetable intake would translate into a risk reduction of approximately 40% for five servings versus one serving of vegetables daily.]

Adenomatous polyps

Adenomatous polyps are considered necessary precursor lesions for most large-bowel malignancies (Schatzkin *et al.*, 1994). Both observational and experimental studies of adenomas can thus be informative with respect to etiological factors operating in the earlier stages of colorectal carcinogenesis.

The one randomized intervention trial showed no apparent protective effect from an intervention for adeno-

Cohort studies	No. of categ.	OR	95% CI
Shibata *et al.*, 1992 (M)	3	1.12	0.69–1.81
Shibata *et al.*, 1992 (F)	3	0.50	0.31–0.80
Steinmetz *et al.*, 1994	4	0.86	0.58–1.29
Kato *et al.*, 1997	4	1.49	0.82–2.70
Hsing *et al.*, 1998a (CR)	4	1.6	0.9–2.8
Pietinen *et al.*, 1999	4	1.1	0.8–1.7
Michels *et al.*, 2000 (F,C)	5	0.96	0.89–1.03
Michels *et al.*, 2000 (F,R)	5	0.96	0.83–1.11
Michels *et al.*, 2000 (M,C)	5	1.08	1.00–1.16
Michels *et al.*, 2000 (M,R)	5	1.09	0.94–1.26
Voorrips *et al.*, 2000a (M,C)	5	1.33	0.90–1.97
Voorrips *et al.*, 2000a (M,R)	5	0.85	0.55–1.32
Voorrips *et al.*, 2000a (F,C)	5	0.73	0.48–1.11
Voorrips *et al.*, 2000a (F,R)	5	0.67	0.34–1.33
Terry *et al.*, 2001a (CR)	4	0.68	0.52–0.89
Flood *et al.*, 2002	5	1.15	0.86–1.53
Sauvaget *et al.*, 2003	3	0.97	0.73–1.29
McCullough *et al.*, 2003 (M, C)	5	1.11	0.76–1.62
McCullough *et al.*, 2003 (F, C)	5	0.74	0.47–1.16
SUMMARY VALUE		1.00	0.96–1.05

Heterogeneity test: χ^2 (18df) =37; p=0.0046

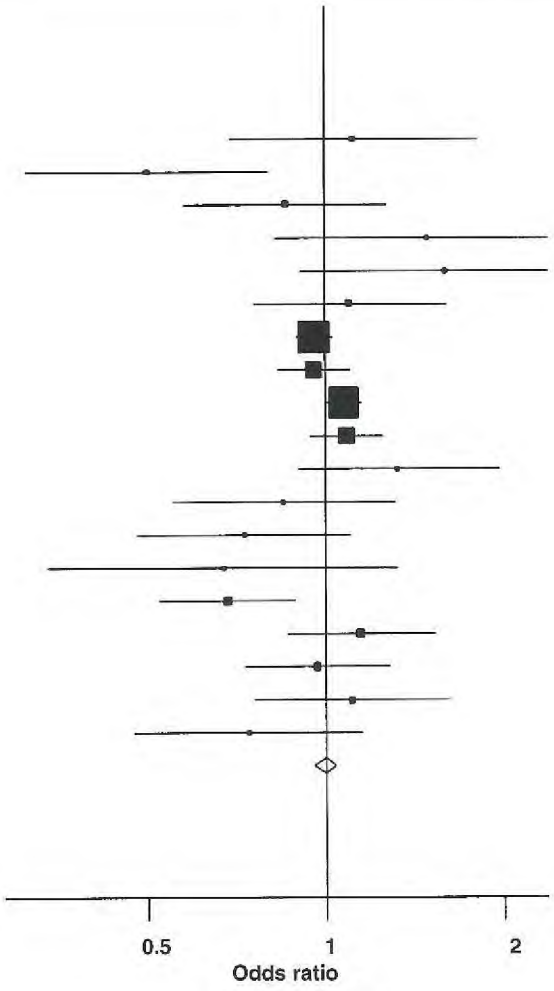

Figure 24 Cohort studies of colorectal cancer and fruit consumption (see Table 28)
M = males; F = females; CR = colorectal; C = colon; R = rectal

matous polyps (see above). However, this trial, in which most of the endpoints were small recurrent adenomas, could not rule out the possibility that fruit and vegetable intake operates to prevent the growth of small into large adenomas, or large adenomas into carcinomas. Thus, the null results of this trial do not definitively exclude a protective role for fruit and vegetables against malignant disease of the large bowel.

However, no clear pattern of protection by fruit or vegetables is evident from the case–control studies of colorectal adenomas. Nevertheless, in the one cohort study that has so far reported data, there was a statistically significant inverse association with fruit consumption.

Limitations of the data

The case–control studies of fruit and vegetables in relation to colorectal cancer have been carried out over more than two decades in several countries among both men and women. Although the aggregate risks from these studies suggest that total fruit and total vegetables confer protection against colorectal cancer, the case–control studies taken as a whole reflect considerable heterogeneity in association (Riboli & Norat, 2003).

The most serious problem with the case–control studies, however, is the possibility that recall and selection biases account for the observed asso-

Case-control studies	No. of categ.	OR	95% CI
Slattery *et al.*, 1988 (M)	4	0.3	0.1–0.6
Slattery *et al.*, 1988 (F)	4	0.6	0.3–1.3
Steinmetz & Potter 1993 (M)	4	1.74	0.88–3.46
Steinmetz & Potter 1993 (F)	4	0.90	0.38–2.11
Centonze *et al.*, 1994 (CR)	3	1.02	0.53–1.95
Kampman *et al.*, 1995 (M)	3	1.00	0.49–2.03
Kampman *et al.*, 1995 (F)	3	0.54	0.23–1.23
Kotake *et al.*, 1995 (C)	4	0.8	0.27–2.41
Kotake *et al.*, 1995 (R)	4	0.7	0.21–2.08
Shannon *et al.*, 1996 (M)	4	0.77	0.44–1.36
Shannon *et al.*, 1996 (F)	4	0.44	0.24–0.82
Boutron-Ruault *et al.*, 1999	4	1.0	0.6–1.6
Murata *et al.*, 1999 (C)	4	0.94	0.78–1.13
Murata *et al.*, 1999 (R)	4	0.98	0.79–1.22
Deneo-Pellegrini *et al.*, 2002 (CR)	4	0.7	0.5–0.9
SUMMARY VALUE		0.87	0.78–0.97

Heterogeneity test: χ^2 (14df)=21; p=0.095

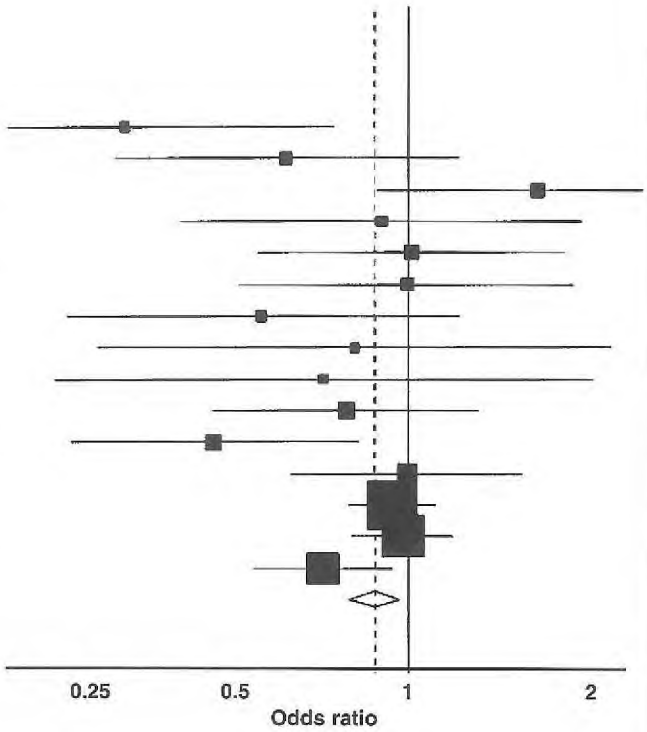

Figure 25 Case–control studies of colorectal cancer and fruit consumption (see Table 29)
M = males; F = females; CR = colorectal; C = colon; R = rectal; * = not applicable

ciations. This possibility is lent credence by the qualitatively different aggregate findings for the cohort studies of fruit and vegetables and colorectal cancer. Cohort studies are generally not susceptible to either recall or selection bias (though the cohort studies of this question also exhibit considerable heterogeneity of association). Case–control studies of adenomas avoid recall bias if dietary assessment is carried out before endoscopy—the adenomas are generally asymptomatic—but sigmoidoscopic screening (a frequent setting for such studies) can result in selection bias and allows study only of left-sided colorectal lesions.

In the report of one cohort study (Terry *et al.*, 2001a), it was suggested that a threshold phenomenon exists, whereby extremely low intake of fruit and vegetables, relative to virtually all higher categories of consumption, is associated with increased risk. The overall data are currently too sparse to further evaluate this possibility.

There may be systematic bias (e.g., overreporting) at the individual level and this bias may be present—and correlated—in both the food frequency questionnaire and the reference instrument (24-hour recalls or dietary records) typically used to 'calibrate' a food frequency questionnaire in cohort studies. The existence of this correlated 'person-specific' bias may lead to considerably greater relative risk attenuation than has been previously appreciated (Kipnis *et al.*, 2003).

Cohort studies	No. of categ.	OR	95% CI
Shibata *et al.*, 1992 (M)	3	1.39	0.84–2.30
Shibata *et al.*, 1992 (F)	3	0.72	0.45–1.16
Steinmetz *et al.*, 1994	4	0.73	0.47–1.13
Kato *et al.*, 1997	4	1.63	0.92–2.89
Hsing *et al.*, 1998a (CR)	4	1.3	0.8–2.4
Pietinen *et al.*, 1999	4	1.2	0.8–1.9
Michels *et al.*, 2000 (C)	5	1.00	0.72–1.38
Michels *et al.*, 2000 (R)	5	1.17	0.63–2.18
Voorrips *et al.*, 2000a (M,C)	5	0.85	0.57–1.27
Voorrips *et al.*, 2000a (M,R)	5	0.88	0.55–1.41
Voorrips *et al.*, 2000a (F,C)	5	0.83	0.54–1.26
Voorrips *et al.*, 2000a (F,R)	5	1.78	0.94–3.38
Terry *et al.*, 2001a (CR)	4	0.84	0.65–1.09
Flood *et al.*, 2002	5	0.95	0.71–1.26
McCullough *et al.*, 2003 (M, C)	5	0.69	0.47–1.02
McCullough *et al.*, 2003 (F, C)	5	0.91	0.56–1.48
SUMMARY VALUE		0.97	0.87–1.08

Heterogeneity test: χ^2 (15df)=19; p=0.21

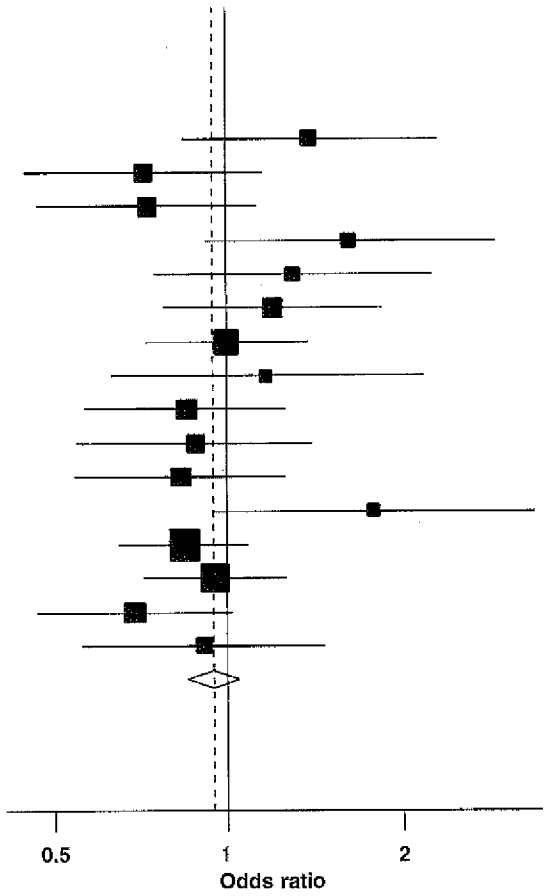

Figure 26 Cohort studies of colorectal cancer and vegetable consumption (see Table 30)
M = males; F = females; CR = colorectal; C = colon; R = rectal

Because the risk reductions for fruit and vegetables are so modest, it is virtually impossible to rule out confounding by unknown or unmeasured lifestyle and other factors associated with fruit and vegetable consumption as an explanation for the observed associations.

Liver

Fruit

Cohort study

One study of liver cancer showed no effect of fruit intake (Table 39).

Case–control studies

Many of the case–control studies of liver cancer were conducted with principal objectives other than consideration of fruit and vegetables. Frequently, therefore, the dietary instrument used was not very detailed. None of three studies of hepatocellular carcinoma found a significant inverse association with fruit consumption (Table 40). Hadziyannis *et al.* (1995) reported that "for fruits ... the association was essentially null". In the study of Parkin *et al.* (1991) related to cholangiocarcinoma, the significant association for fresh fruit was from a

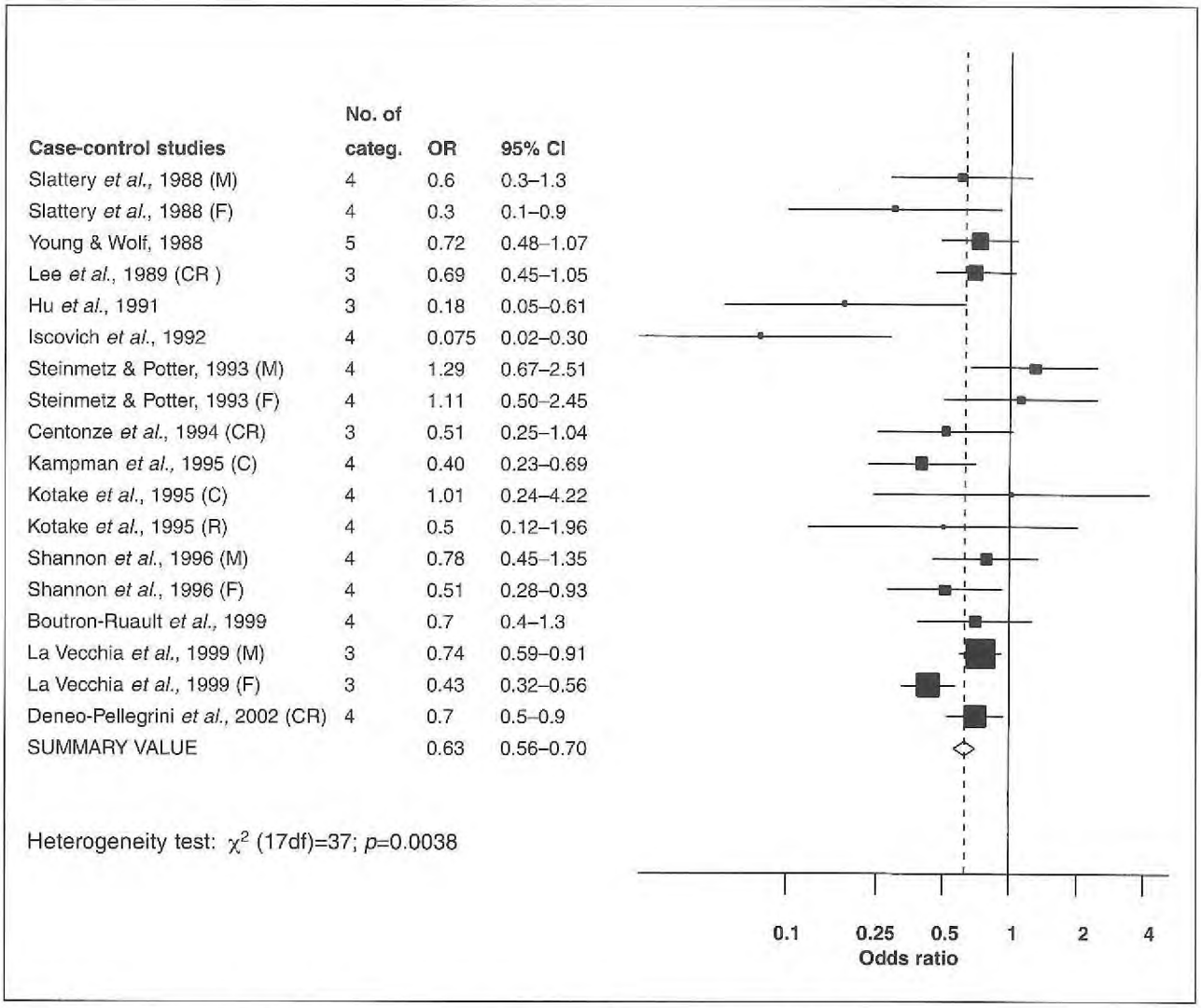

Figure 27 Case–control studies of colorectal cancer and vegetable consumption (see Table 31)
M = males; F = females; CR = colorectal cancer; C = colon; R = rectal

univariate analysis; when included in a multivariate model with all other food items, the association was no longer significant.

Vegetables

Cohort studies

The largest of the three cohort studies (Table 41), that of Hirayama (1990), included only limited information on diet, and for the class of vegetables, only frequency of consumption of green-yellow vegetables. Death from liver cancer was the end-point. [The Working Group noted that it is not clear whether all of these were from hepatocellular carcinoma].

The study of Yu *et al.* (1995) was a full cohort analysis of vegetable consumption, previously reported as a nested case–control study by Yu *et al.* (1993). Yu *et al.* (1995) noted that the inverse association for vegetable consumption appeared to be restricted to carriers of hepatitis B surface antigen (HBsAg) [RR 0.21, 0.09–0.50] and cigarette smokers [0.26, 0.12–0.59].

In the study of Sauvaget *et al.* (2003), green-yellow vegetable consumption was associated with a

significant reduction in liver cancer mortality.

Case–control studies

Six case–control studies have reported data, two with significant inverse associations for vegetable consumption (Table 42). No numerical data were reported in the study of Fukuda *et al.* (1993), which was primarily designed to evaluate viral risk factors for hepatocellular carcinoma. However, the authors appear to have considered only mean consumption levels of fresh and green-yellow vegetables, and these were said to be similar for cases and controls. Similarly, Hadziyannis *et al.* (1995) reported that "for ... vegetables, the association was essentially null."

Combined fruit and vegetables

Cohort studies

No studies were identified by the Working Group.

Case–control studies

Only one study assessed the combination of fruit and vegetables, with an inverse association reported in both males and females (Table 43).

Discussion

Consumption of total fruit was not significantly associated with liver cancer, in either cohort or case–control studies. Consumption of total vegetables was significantly inversely associated with liver cancer only in one cohort study.

Biliary tract

Fruit

Cohort study

One cohort study has reported that there was no significant association between fruit consumption and gallbladder cancer (Table 44).

Case–control studies

No studies were identified by the Working Group.

Vegetables

Cohort studies

Hirayama (1990) tabulated gallbladder cancer as one of the end-points, but in the table in the section devoted to dietary factors, it is linked to bile-duct cancer. It is unclear whether the numbers of cases cited in Table 45 include bile-duct cancer. Comparison of daily with less frequent consumption of vegetables revealed no association. The study of Sauvaget *et al.* (2003) did not show any significant association.

Case–control studies

No studies were identified by the Working Group.

Combined fruit and vegetables

Case–control study

One case–control study has been reported of fruit and vegetable consumption and biliary tract cancer. The results were presented separately for gallbladder and bile duct cancer, and data for gallbladder cancer are summarized in Table 48. For bile-duct cancer, there were inverse associations for fruits, lettuce/cabbage, green-yellow vegetables and other vegetables in the univariate analysis, but these did not persist in the multivariate analysis.

Discussion

The available studies of biliary tract cancer in relation to fruit and vegetable consumption are too few to allow any conclusion to be drawn.

Pancreas

Fruit

Cohort studies

Of six cohort studies on diet and pancreas cancer, four used death from pancreas cancer as end-point and none found a significant inverse association with fruit consumption (Table 47). That of Mills *et al.* (1988) did not evaluate fruit consumption *per se*, but did report a protective effect of high consumption of vegetarian protein products, including raisins, dates and dry fruit. Zheng *et al.* (1993) provided no numerical data on risks for fruit consumption but reported that fruit consumption showed no clear association with pancreatic cancer risk.

Case–control studies

Many of the studies reported used proxy interviews for dead cases. For the few that used only direct interviews (with consequent exclusion of many cases who died within a short period), this is indicated in the comments section of Table 48. Eight of the 13 studies reported inverse associations for estimated fruit intake, one also for citrus fruit.

Farrow & Davis (1990), however, while reporting no numerical data, indicated that cases and controls did not differ with respect to total intake of all fruit or citrus fruit. Howe *et al.* (1990) also reported negative findings for associations with fruit consumption, on the basis of a model that included fibre, but they reported a significant protective effect of estimated intake of fibre (RR = 0.38 for 28 g/d of fibre from fruit). This study had been designed to obtain estimates of effects of nutrients, rather than of food groups.

The studies of Howe *et al.* (1990), Baghurst *et al.* (1991) and Bueno de Mesquita *et al.* (1991) were part of the IARC multi-country SEARCH programme, designed to evaluate associations using similar protocols in several different countries, also including studies in Montreal, Canada and Poland, that did not report specifically on fruit and vegetable intake. Howe *et al.* (1992) reported a combined analysis of these studies, with a total of 802 cases and 1669 controls. Like the

study of Howe *et al.* (1990), the analysis was primarily related to nutrients. However, the authors comment that the results provide "strong evidence" of an inverse association of pancreas cancer with markers of fruit intake, particularly dietary fibre and vitamin C. The RR for the highest versus lowest quintile of vitamin C intake was 0.55 (95% CI 0.39–0.78) in a model that included all nutrient variables and lifetime cigarette consumption.

Vegetables

Cohort studies

Of the six cohort studies with data on vegetable consumption and pancreas cancer, none found a significant inverse association (Table 49). Mills *et al.* (1988) did not evaluate vegetable consumption *per se*, but did report a protective effect of high consumption of vegetarian protein products (beans, lentils or peas). Zheng *et al.* (1993) provided no numerical data on risks for vegetable consumption but reported that consumption of vegetables showed "no clear association" with pancreatic cancer risk.

Case–control studies

Many of the studies have used proxy interviews for dead cases. For the few that used only direct interviews (with consequent exclusion of many cases who died within a short period), this is indicated in the comments section of Table 50.

Seven of the 13 studies found protective effects for estimated intake of vegetables. Some found significant associations only for cruciferous vegetables or carrots. Farrow & Davis (1990), however, while reporting no numerical data, indicated that apart from a non-significant higher consumption of green and yellow vegetables by cases, cases and controls did not differ with respect to their total intake of all vegetables and raw vegetables. Howe *et al.* (1990) also reported negative findings for associations with vegetable consumption, on the basis of a model that included fibre, and they reported a significant protective effect of estimated intake of fibre (RR = 0.56 for 28 g/d of fibre from vegetables). This study had been designed to obtain estimates of effects of nutrients, rather than of food groups.

Baghurst *et al.* (1991) reported no numerical estimates of associations for vegetables, but indicated that cases consumed significantly less of a number of vegetables than controls.

The studies of Howe *et al.* (1990), Baghurst *et al.* (1991) and Bueno de Mesquita *et al.* (1991) were part of the IARC multi-country SEARCH programme, designed to evaluate associations using similar protocols in several different countries, also including studies in Montreal, Canada and Poland, that did not report specifically on fruit and vegetable intake. Howe *et al.* (1992) reported a combined analysis of these studies, with a total of 802 cases and 1669 controls. Like the study of Howe *et al.* (1990), the analysis was primarily related to nutrients. However, the authors comment that the results provide "strong evidence" of an inverse association of pancreas cancer with several markers of vegetable intake, particularly dietary fibre. The RR for the highest versus lowest quintile of dietary fibre intake was 0.50 (0.34–0.72) in a model that included all nutrient variables and lifetime cigarette consumption.

Combined fruit and vegetables

Case–control studies

Two case–control studies have been reported with estimates of risk for combined fruit and vegetable consumption (Table 51). Both showed inverse associations.

Discussion

Six case–control studies on fruit consumption and pancreas cancer were evaluable. The mean OR was 0.72 (95% CI 0.63–0.83), range 0.07–0.92 (Figure 28). The mean OR for the five evaluable case–control studies of vegetable consumption was 0.80 (95% CI 0.69–0.93), range 0.32–1.03 (Figure 29).

Although inverse associations for fruit or vegetable consumption were seen in many case–control studies, these have largely not been replicated in the cohort studies. There has to be some concern over the mainly inverse associations with fruit and or vegetables found in many of the case–control studies when the response rates for controls were low. It is possible that responders are more likely to be health-conscious than non-responders and thus tend to eat more fruit and vegetables. Selection bias is also possible if the case series was restricted to those subjects still alive at the time of interview. In the two largest individual case–control studies, only living cases were interviewed. This involved many more exclusions in the study of Silverman *et al.* (1998) conducted in the USA than in that of Ji *et al.* (1995) conducted in China. Whether this accounts for the difference between the largely negative findings of Silverman *et al.* (1998) and the significant association in men for fruit in the study of Ji *et al.* (1995) is uncertain.

Larynx

Fruit

Cohort studies

No studies were identified by the Working Group.

Case–control studies

The ten case–control studies on total fruit intake in relation to larynx cancer risk (Table 52) all included men and some also included women. The majority of the studies were hospital-based.

Case-control studies	No. of categ.	OR	95% CI
Falk *et al.*, 1988	2	0.63	0.49–0.82
Olsen *et al.*, 1989	3	0.88	0.48–1.62
Howe *et al.*, 1990	4	0.92	0.74–1.14
Lyon *et al.*, 1993 (M)	3	0.81	0.40–1.62
Lyon *et al.*, 1993 (F)	3	0.37	0.18–0.81
Ji *et al.*, 1995 (M)	4	0.66	0.43–1.01
Ji *et al.*, 1995 (F)	4	0.58	0.34–1.00
Mori *et al.*, 1999	3	0.07	0.02–0.21
SUMMARY VALUE		0.72	0.63–0.83

Heterogeneity test: χ^2 (7df)=25; p=0.00065

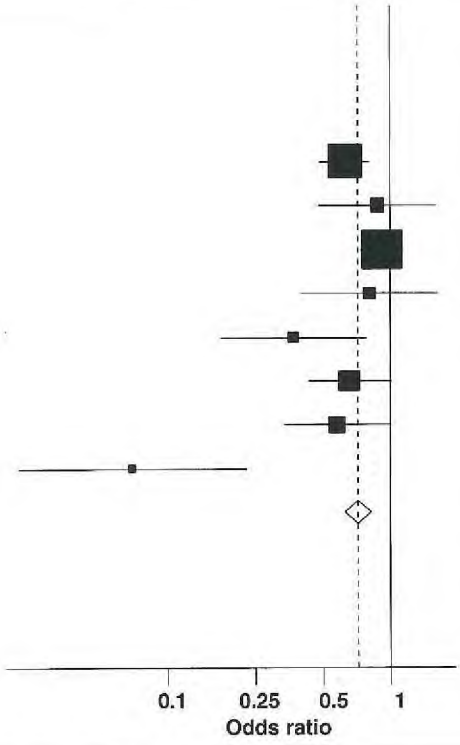

Figure 28 Case–control studies of pancreas cancer and fruit consumption (see Table 48)
M = males; F = females

Case-control studies	No. of categ.	OR	95% CI
Falk *et al.*, 1988	2	0.88	0.68–1.14
Howe *et al.*, 1990	4	1.03	0.79–1.34
Lyon *et al.*, 1993 (M)	3	0.99	0.50–2.01
Lyon *et al.*, 1993 (F)	3	0.32	0.13–0.74
Ji *et al.*, 1995 (M)	4	0.63	0.45–1.03
Ji *et al.*, 1995 (F)	4	0.67	0.39–1.14
Mori *et al.*, 1999	3	0.42	0.24–0.74
SUMMARY VALUE		0.80	0.69–0.93

Heterogeneity test: χ^2 (6df)=15; p=0.017

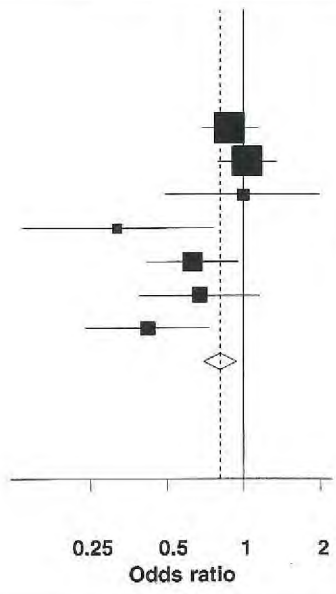

Figure 29 Case–control studies of pancreas cancer and vegetable consumption (see Table 50)
M = males; F = females

Most studies used a food frequency questionnaire to measure dietary intake, while one study used a diet history interview. The total number of measured food items varied widely between studies, as did the number of fruit items. This implies that very different numbers of fruits may be included in the category labelled 'total fruit'. Several reports do not state what is included under '(total) fruit'.

Almost all studies controlled for confounding by smoking (in different ways and detail) and alcohol, except three (De Stefani *et al.*, 1987; Zheng *et al.*, 1992b; Guo *et al.*, 1995).

The (extreme) contrasts in intake of fruits considered were most often high versus low intake, based on tertiles or quartiles of intake.

All case–control studies showed inverse associations between intake of total fruit and risk of larynx cancer, with ORs for high versus low intake varying between 0.3 and 0.8. Although some studies did not show significant associations, the overall pattern of the case–control studies is of a consistent inverse association between total intake of fruit and risk of larynx cancer.

Only one study investigated these associations within subgroups of smoking, age and alcohol, or of supraglottis versus epiglottis and other subsites (Bosetti *et al.*, 2002a). The observed ORs were weaker in the subgroups.

Vegetables

Cohort studies

No studies were identified by the Working Group.

Case–control studies

Nine case–control studies have reported on intake of (total) vegetables in relation to larynx cancer risk (Table 53). These studies all included men, and some also included women. The majority of the studies were hospital-based.

Most studies used a food frequency questionnaire to measure dietary intake, while one study used a diet history interview. The total number of measured food items varied widely between studies, as did the number of vegetable items. Not all studies reported the number of items but for the ones that did, the number of vegetable items varied up to 26. This implies that very different numbers of vegetables may be included in the category labelled 'total vegetables'.

Almost all studies controlled for confounding by smoking (in different ways and detail) and alcohol, except three (De Stefani *et al.*, 1987; Zheng *et al.*, 1992b; Guo *et al.*, 1995).

All except one of the studies found inverse associations between intake of total vegetables and risk of larynx cancer, with ORs for high versus low intake varying between 0.17 and 0.9. Although most of the studies did not show significant associations, the overall pattern of the case–control studies is of a consistent inverse association between total intake of vegetables and risk of larynx cancer.

Only one study investigated these associations within subgroups of smoking, age and alcohol, or supraglottis versus epiglottis and other subsites (Bosetti *et al.*, 2002a). No different ORs were found, however.

Combined fruit and vegetables

Cohort study

In one cohort study in the USA on upper aerodigestive tract cancer (Kasum *et al.*, 2002), a non-significant inverse association of larynx cancer with intake of vegetables and fruits was mentioned, but no data were shown.

Case–control studies

In two case–control studies, there were significant inverse associations between combined fruit and vegetable intake and larynx cancer risk (Table 54).

Discussion

Only case–control studies on larynx cancer were available for evaluation. These studies were conducted in Europe, Asia and South America. For four evaluable case–control studies with total fruit, the mean OR was 0.63 (95% CI 0.52–0.77), range 0.38–0.80 (Figure 30). For four evaluable studies with vegetable consumption, the mean OR was 0.49 (95% CI 0.40–0.61), range 0.17–1.1 (Figure 31).

Control for smoking was rather crude and incomplete in the early studies; more recent studies have used more elaborate models and still observed inverse associations with fruit and vegetable intake. Only one study addressed associations between fruit and vegetables and larynx cancer in subgroups of smoking and alcohol intake. ORs for fruit became weaker in these subgroups, which might indicate residual confounding by smoking and alcohol. The possibility of recall and selection bias in the case–control studies cannot be excluded.

Lung

Fruit

Cohort studies

A total of 16 cohort studies have been reported on fruit intake and risk of lung cancer and in addition, results are available from a pooled analysis of primary data from eight cohort studies (Table 55).

Six studies used mortality from lung cancer as the end-point. Follow-up times ranged from 4 to 25 years. All but two studies used a self-administered food frequency questionnaire to measure dietary intake. The number of fruit items varied up to 23. The considered contrasts in fruit intake also varied considerably between studies. All but one study (Wang & Hammond, 1985) corrected for possible confounding by smoking (often in more detail than in the case–control studies), as well as

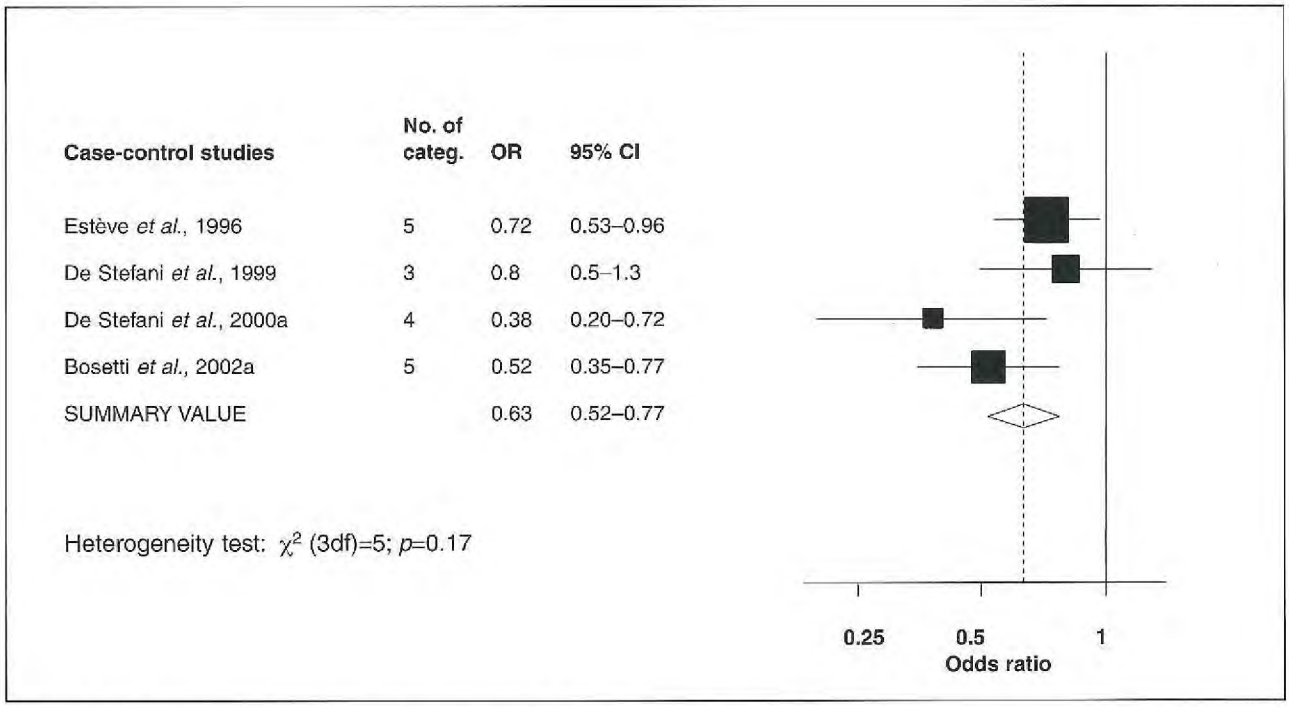

Figure 30 Case–control studies of larynx cancer and fruit consumption (see Table 52).

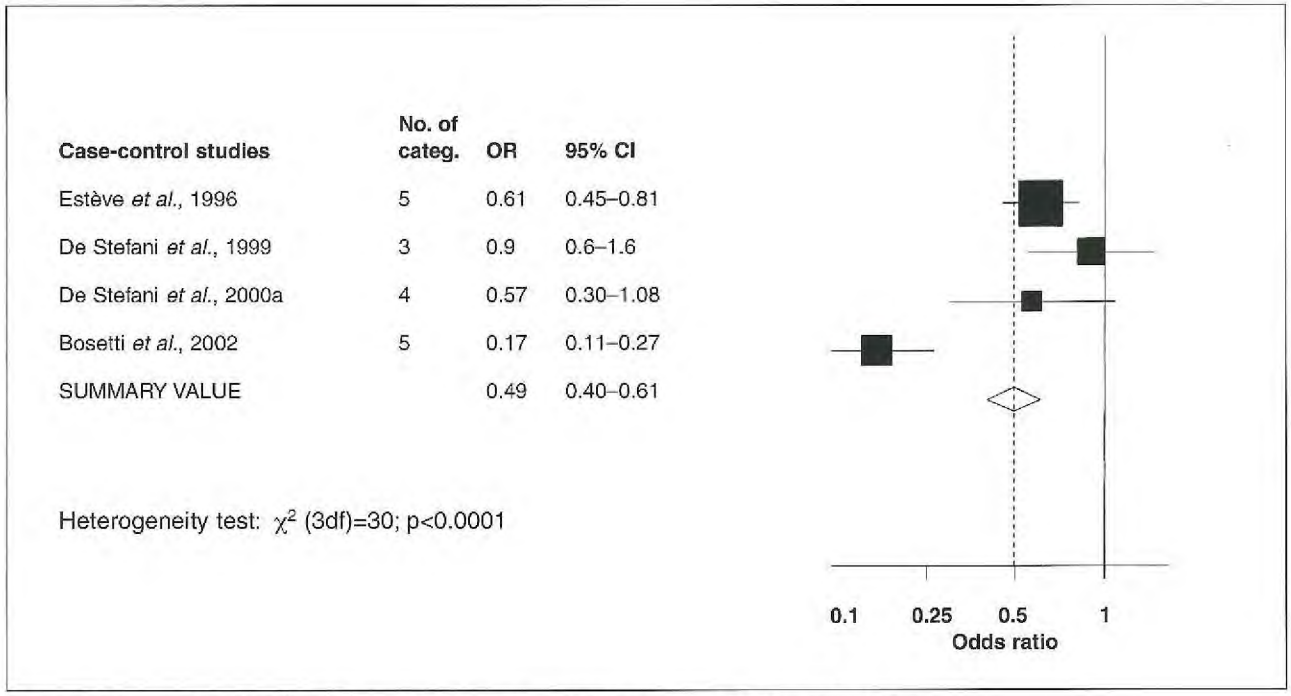

Figure 31 Case–control studies of larynx cancer and vegetable consumption (see Table 53)

age and several other confounders (e.g., education, occupation).

In most studies, there were inverse associations between fruit intake and lung cancer, although these were not always significant. The pooled analysis of cohort studies also showed a significant inverse association. The more recent cohort studies attempted more complete control for confounding by smoking (for example, incorporating duration and amount smoked as well as smoking status rather than pack-years in their final models) and similar associations were seen to those in the earlier studies.

Non-significant positive associations were observed in men in one study (Feskanich *et al.*, 2000). Subgroup analyses in the studies did not clearly indicate that the inverse association was limited to particular morphological types of lung cancer. There is also no clear indication that a protective effect is seen only in (ex-)smokers. Several studies show inverse associations in never-smokers, including the pooled analysis of cohort studies; however, statistical significance was often not reached.

Case–control studies

30 case–control studies have reported on intake of (total) fruit and the association with lung cancer risk (Table 56). Ten were hospital-based, while the remainder used population controls. Almost all studies that included smokers controlled for confounding by age and smoking (smoking in different ways and detail), except two (Lei *et al.*, 1996; Alavanja *et al.*, 2001). Most studies also controlled for some measure of education or socioeconomic status. Other confounders considered have varied between studies. Eight studies were conducted among never- or non-current smokers, mostly in women.

The total number of measured food items varied widely between studies, as did the number of fruit items. Not all studies reported the number of items; for the ones that did, the number of fruit items varied up to 16. Several reports do not state what was included under '(total) fruit'.

In 22 of the studies, there were inverse associations between intake of fruit and risk of lung cancer; in 15 of these there were significant inverse associations, some only in sub-groups. Six studies, however, reported (non-significantly) increased odds ratios. Dorgan *et al.* (1993) reported inverse associations for white men or women and positive associations for black men or women.

Three studies showed separate results for men and women and in two of these, the inverse associations were somewhat stronger in women than men (Dorgan *et al.*, 1993; Takezaki *et al.*, 2001). Of the studies that evaluated effects in morphological subgroups, most reported somewhat stronger effects for squamous- and small-cell carcinoma than for other types. Effects were often stronger in ex- or current smokers. Among nine studies conducted among never- or non-smokers, four found significant inverse associations.

Vegetables

Cohort studies

Among a total of 15 cohort studies on intake of (total or specific) vegetables in relation to lung cancer risk (Table 57), 12 reported on total vegetable consumption. In addition, results from a pooled analysis of primary data from eight cohort studies, some also included in Table 57, are available (Smith-Warner *et al.*, 2003).

Five studies used lung cancer mortality as the end-point. Follow-up times varied from 4 to 25 years. All but two studies used a self-administered food frequency questionnaire to measure dietary intake. The number of vegetable items mentioned varied considerably.

Many of the studies found inverse associations between vegetable intake and lung cancer risk, of which five were significant, at least in one gender. In the pooled analysis of eight cohort studies, inverse associations were seen in men and women, but were of only borderline significance in men (Smith-Warner *et al.*, 2003). All studies corrected for possible confounding by smoking (often in more detail than in the case–control studies), as well as age and several other confounders (e.g., education, occupation).

Subgroup analyses in several studies indicated stronger inverse associations for squamous-cell, small- or large-cell carcinoma (sometimes aggregated as Kreyberg I) than for adenocarcinoma (Kreyberg II). Several studies showed stronger effects in ex-smokers.

Case–control studies

Of 25 case–control studies that have reported on intake of (total) vegetables in relation to lung cancer risk (Table 58), nine were hospital-based, while the remainder used population controls. Almost all studies that included smokers controlled for confounding effects of age and smoking (smoking in different ways and detail). Most studies also controlled for some measure of education or socioeconomic status. Seven studies were conducted among never- or non-current smokers, mostly in women.

Most studies used a food frequency questionnaire (or diet history) by interview to measure dietary intake. The total number of food items measured has varied widely between studies, as has the number of vegetable items. Not all studies reported the number of items, but in those that did, the number of vegetable items varied up to 28.

Regarding the associations between intake and lung cancer risk, the considered (extreme) contrasts in intake of

vegetables were most often high versus low intake, based on tertiles, quartiles or quintiles of intake. Intake levels varied considerably between studies, as did the considered contrasts.

In most studies there were inverse associations between vegetable intake and risk of lung cancer and in 14 there were one or more significant inverse associations (sometimes for only one subgroup, e.g. females).

In the three studies that reported separate results for men and women, the inverse associations were somewhat stronger in women than men. Of the studies that evaluated effects by morphological subgroup, most reported somewhat stronger effects for squamous- and small-cell carcinoma than for other morphological types. Effects were often stronger in ex- or current smokers. Three of the seven studies conducted among never- or non-smokers reported significant inverse associations, one of them in females but not in males.

Combined fruit and vegetables

Cohort studies

Reports of six cohort studies included data on combined intake of fruit and vegetables in relation to lung cancer risk (Table 59). In all there were inverse associations, with RRs between 0.49 and 0.79 (mostly significant), two only in women. In the pooled analysis of eight cohort studies, there was a significant inverse association in both sexes combined (Smith-Warner *et al.*, 2003).

Case–control studies

Reports of four case–control studies included data on intake of vegetables and fruits together in relation to risk of lung cancer (Table 60). All four showed inverse associations (mostly significant) when high versus low intake was compared, with odds ratios ranging from 0.40 to 0.77.

Discussion

The cohort studies considered for evaluation were conducted in North America, Europe or Japan, the case–control studies also in Australasia, other parts of Asia and South America. These studies mostly show an inverse association between intake of total fruit and/or vegetables and risk of lung cancer, although non-significant positive associations have also been observed. For fruit consumption, 13 cohort studies and 21 case–control stuides were evaluable. For cohort studies the mean RR was 0.77 (95% CI 0.71–0.84), range 0.26–1.22 (Figure 32), and for case–control studies the mean OR was 0.70 (95% CI 0.45–1.07), range 0.33–2.04 (Figure 33). For vegetable consumption, 11 cohort studies were evaluable. The mean RR was 0.80 (95% CI 0.73–0.88), range 0.47–1.37 (Figure 34). For the 18 evaluable case–control studies the mean OR was 0.69 (95% CI 0.63–0.76), range 0.30–1.49 (Figure 35).

The latest results from the cohort studies and a meta-analysis (Riboli & Norat, 2003) suggest a stronger inverse association for fruit than for vegetables. Studies vary considerably in terms of the number of items included in the fruit or vegetable group. There was no clear difference in results between men and women, between hospital- and population-based case–control studies or between morphological categories of lung cancer. The strength of the association was generally less for cohort studies than for case–control studies, leaving open the possibility of recall and/or selection bias in the case–control studies.

Because smoking is a strong risk factor for lung cancer, while smoking and fruit (and to a lesser extent, vegetable) consumption are inversely associated, appropriate control for confounding by smoking is crucial. Although the newer cohort studies have attempted to control for confounding by smoking much better than earlier ones, residual confounding by smoking cannot be excluded (Marshall & Hastrup, 1996; Stram *et al.*, 2002), and cohort studies often fail to capture changes in smoking and diet after the baseline measurement. Subgroup analyses among categories of smoking also showed inverse associations in never-smokers (often non-significant) in the cohort studies. Case–control studies among never- or non-smokers were not entirely consistent in showing an inverse association with fruit or vegetables.

Breast

Studies of fruit and vegetable consumption in relation to breast cancer risk have been conducted over the past 40 years in North and South America, Australia, Asia and Europe. Most have focused on breast cancer in women; studies of breast cancer risk in men are discussed separately. The usual end-point has been breast cancer incidence, but some studies have examined associations with mortality. Cohort studies generally have measured recent diet at baseline, although diets during follow-up and during childhood also have been measured. Most case–control studies measured dietary intake during the 1–5 years preceding diagnosis, although some assessed dietary intake during childhood, adolescence and young adulthood.

Fruit

Cohort studies

Among the seven cohort studies, no statistically significant inverse association with fruit consumption was observed, although the relative risk of breast cancer was often well below 1.0 (Table 61). Reported menopausal status did not modify the association between fruit consumption and risk of breast cancer.

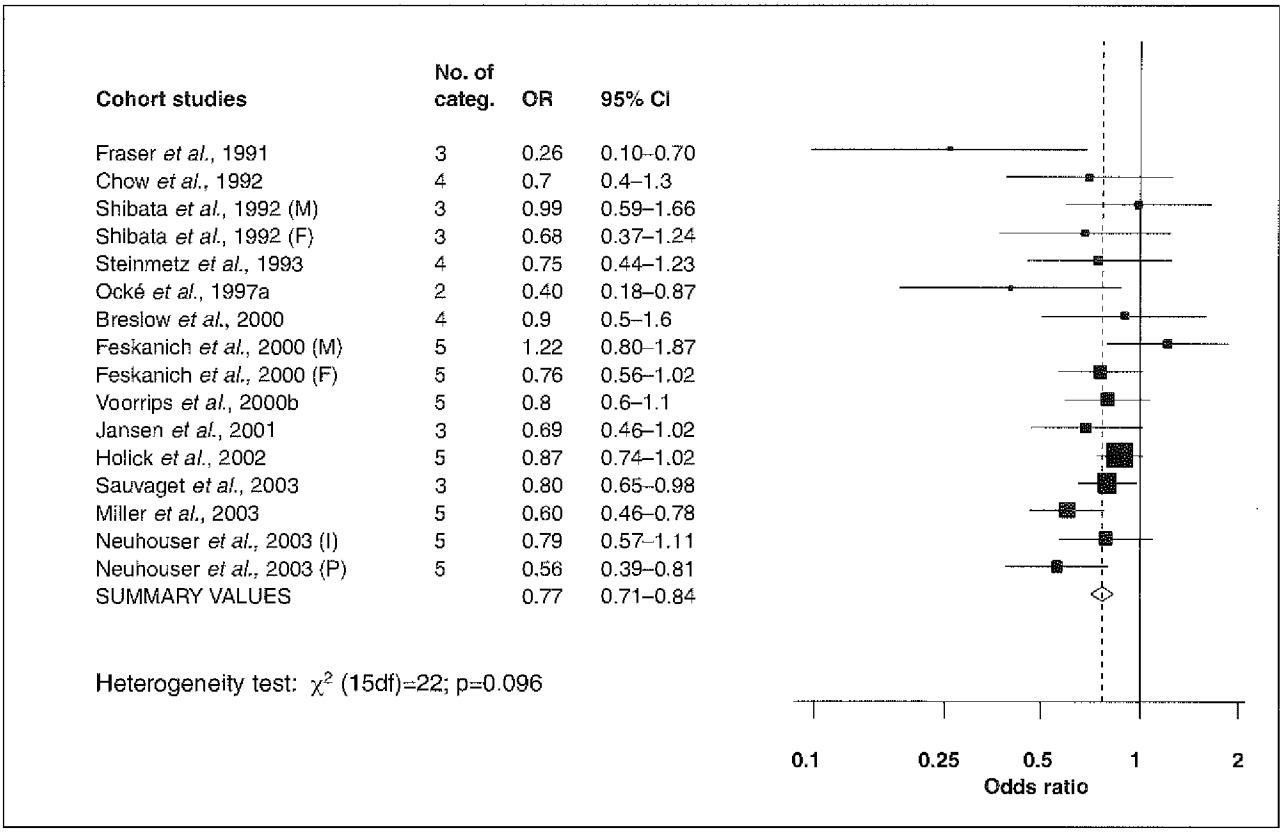

Figure 32 Cohort studies of lung cancer and fruit consumption (see Table 55)
M = males; F = females; I = intervention arm; P = placebo arm

In a meta-analysis of 10 case–control and two cohort studies including 9429 cases (Gandini *et al.*, 2000), there was no association of breast cancer risk with fruit consumption when comparing high and low fruit intake (Table 61). However, when the analysis was restricted to the 11 studies for which dose–response information could be obtained, there was a 17% reduction in the risk of breast cancer for comparisons of six portions of fruit versus one per week (RR = 0.83, 95% CI 0.79–0.87). In this meta-analysis, for both comparisons, there was statistically significant between-study heterogeneity in the summary estimate ($p < 0.001$). This heterogeneity could have arisen because study-specific estimates were combined for total fruit, citrus fruit, other fruit and fruit rich in β-carotene for different comparison categories from studies using different study designs. In contrast, a more recent meta-analysis of eight case–control and ten cohort studies found no statistically significant association with fruit intake among cohort studies or case–control studies when considered separately or when combined (Riboli & Norat, 2003). However, there was significant heterogeneity across studies when the case–control studies were considered separately. Studies included in this meta-analysis were limited to those that considered total fruit, all fruit, fruit or fresh fruit and the study-specific relative risks were re-expressed based on an increase of 100 g per day of fruit consumption.

In a pooled analysis of the primary data from eight cohort studies (some of which were discussed above) using standardized criteria (Table 61), fruit consumption was not associated with breast cancer risk overall (n = 7377 cases) or when stratified by menopausal status (Smith-Warner *et al.*, 2001).

Case–control studies

An inverse association with fruit consumption seen in about half of the 20 case–control studies was statistically significant in five (Table 62). The strongest association was observed in a small case–control study in Spain (Landa *et al.*, 1994). In other case–

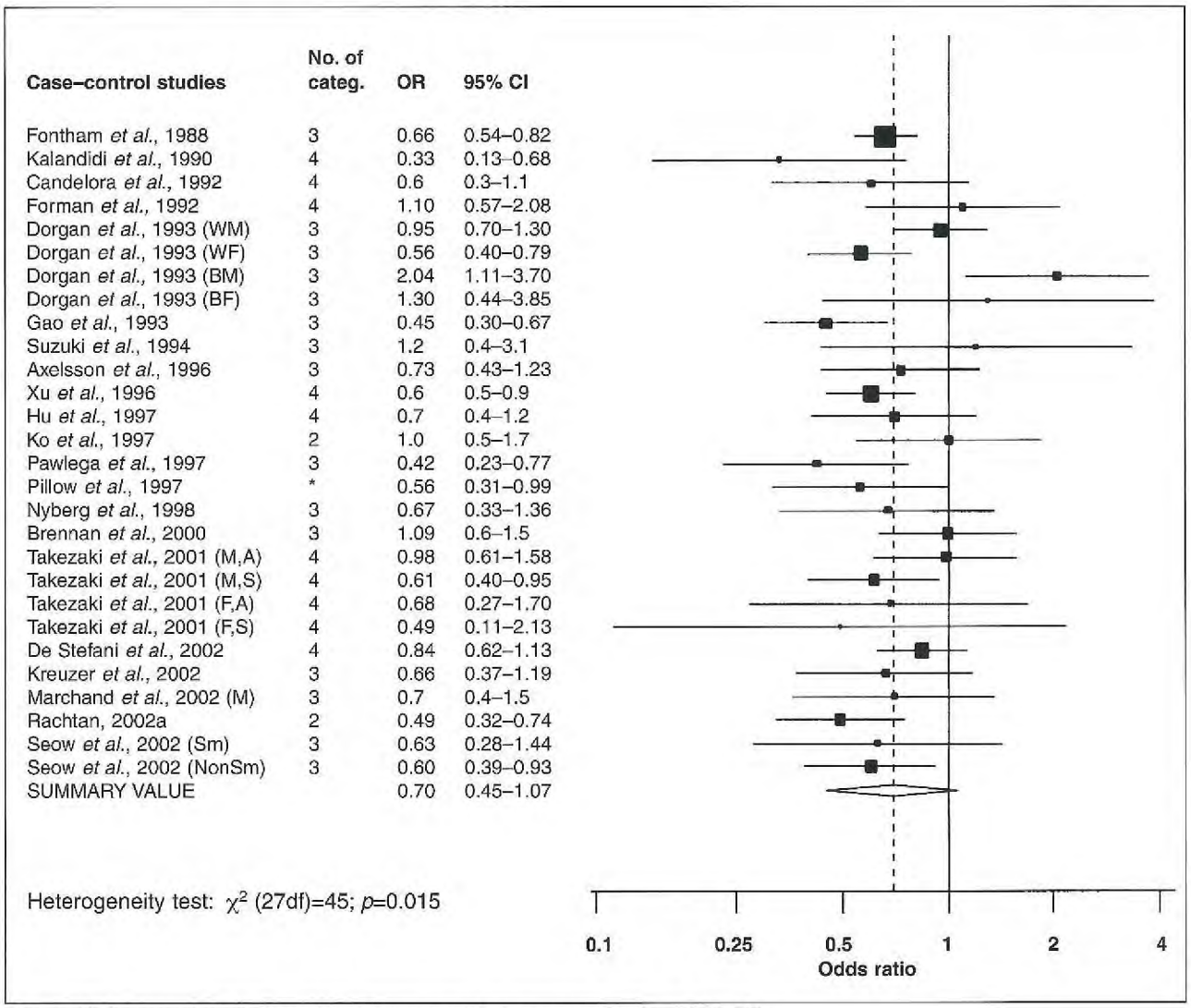

Figure 33 Case–control studies of lung cancer and fruit consumption (see Table 56)
W = white; B = black; M = males, F = females; A = adenocarcinoma; S = squamous and small cell carcinoma; Sm = smokers; NonSm = non smokers; * = not applicable

control studies, the relative risks have shown no more than a 10% increase or decrease in the risk of breast cancer for comparisons of high versus low consumption. A few studies have reported in the text that fruit consumption was not associated with the risk of breast cancer. In a Swedish case–control study, the OR was elevated in women over 50 years of age but not associated with breast cancer risk in women 50 years and younger (Holmberg *et al.*, 1994). The test for effect modification by age group was not statistically significant. A similar pattern was observed in a Russian case–control study (Zaridze *et al.*, 1991).

Vegetables

Cohort studies

Among the seven cohort studies (Table 63), a statistically significant inverse association with vegetable consumption was observed only in the Nurses' Health Study when the analysis was limited to premenopausal breast cancer (Zhang *et al.*, 1999). When only postmenopausal women who were

Cohort studies	No. of categ.	OR	95% CI
Chow *et al.*, 1992	4	1.2	0.6–2.3
Shibata *et al.*, 1992 (M)	3	1.37	0.74–2.25
Shibata *et al.*, 1992 (F)	3	0.58	0.32–1.05
Steinmetz *et al.*, 1993	4	0.50	0.29–0.87
Ocké *et al.*, 1997	2	0.47	0.21–1.03
Breslow *et al.*, 2000	4	0.9	0.5–1.5
Feskanich *et al.*, 2000 (M)	5	1.04	0.69–1.57
Feskanich *et al.*, 2000 (F)	5	0.68	0.51–0.90
Voorips *et al.*, 2000b	5	0.7	0.5–1.0
Jansen *et al.*, 2001	3	0.90	0.61–1.33
Holick *et al.*, 2002	5	0.75	0.63–0.88
Miller *et al.*, 2003	5	1.00	0.76–1.30
Neuhouser *et al.*, 2003 (I)	5	0.81	0.65–1.21
Neuhouser *et al.*, 2003 (P)	5	0.82	0.59–1.14
SUMMARY VALUE		0.80	0.73–0.88

Heterogeneity test: χ^2 (13df)=18; p=0.16

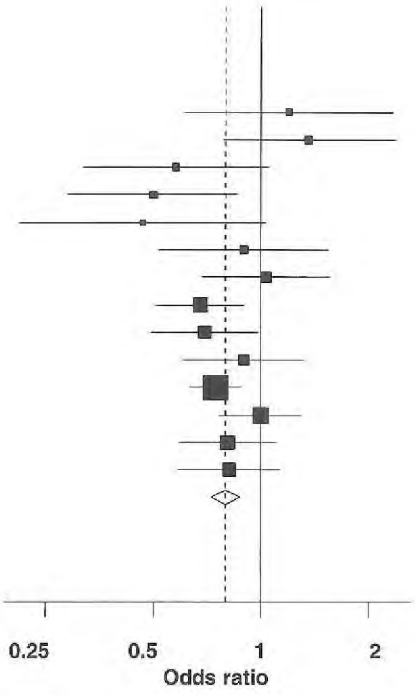

Figure 34 Cohort studies of lung cancer and vegetable consumption (see Table 57)
M = males; F = females; I = intervention arm; P = placebo arm

current users of hormone replacement therapy were examined, there was a suggestion of an inverse association. In three other cohort studies, a reduction of less than 15% in the risk of breast cancer was observed for higher versus lower vegetable consumption.

In a meta-analysis of 10 case–control and 10 cohort studies, breast cancer risk was decreased by 4% for an increment of 100 grams of vegetables per day (Riboli & Norat, 2003). When the two study designs were examined separately, an inverse association was suggested only in the case–control studies, but there was statistically significant heterogeneity in the results across the studies. Studies included in this meta-analysis were limited to those that considered total fruit, all fruit, fruits or fresh fruits and the study-specific relative risks were re-expressed based on an increase of 100 g per day of fruit consumption.

In a pooled analysis of eight cohort studies including 7377 breast cancer cases, total vegetable consumption was not associated with the risk of breast cancer (Table 63) (Smith-Warner *et al.*, 2001). There was also no evidence of effect modification by family history, history of benign breast disease, hormone replacement therapy use, body mass index, fat consumption, alcohol consumption and several reproductive factors.

Case–control studies

In most of the 24 case–control studies, inverse associations with vegetable consumption have been found (Table 66). The strongest association observed was in a small case–control study in Greece (Katsouyanni *et al.*, 1986). In the 13 case–control studies that found a statistically significant inverse association, the risk of breast cancer was generally 40–60% lower for comparison of the highest versus lowest intakes of total vegetables. In one study in Russia, the risk of breast cancer was reported to be lower among women who had increased their vegetable consumption during the past 10 years compared with those who had decreased consumption (Zaridze *et al.*, 1991). In none of the case–control studies showing an odds ratio of at least 1.2 with higher vegetable consumption was the association statistically significant.

Some case–control studies of premenopausal women have suggested that higher vegetable consumption is

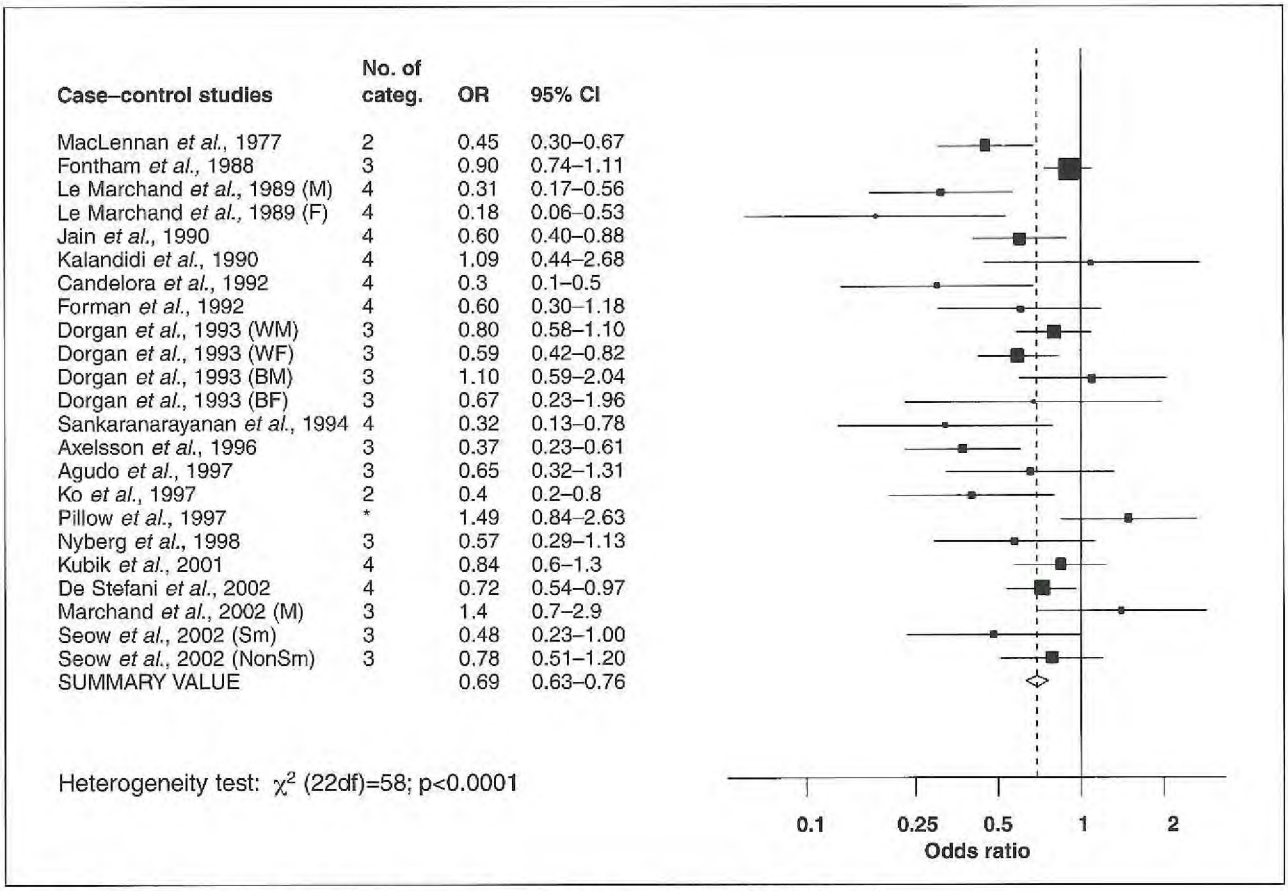

Figure 35. Case–control studies of lung cancer and vegetable consumption (see Table 58)
M = males; F = females; W = white; B = black; Sm = smokers; NonSm = non-smokers.

associated with reduced risk of breast cancer. However, relatively few studies have examined whether the association between vegetable consumption and breast cancer risk is modified by menopausal status. In those studies that have examined both premenopausal and postmenopausal breast cancer, no effect modification by menopausal status or by age group was generally observed. However, in a large Italian case–control study, raw vegetable consumption was inversely associated with the risk of premenopausal, but not postmenopausal, breast cancer (p-value for interaction = 0.01) (Franceschi *et al.*, 1995; Braga *et al.*, 1997b). Educational level also has not been found to modify the association between vegetable consumption and the risk of breast cancer.

In a meta-analysis of 14 case–control studies and three cohort studies of 16 052 cases (Gandini *et al.*, 2000), a summary estimate for vegetables was generated by combining study-specific risk estimates for vegetables, cooked vegetables, raw vegetables, green vegetables and other vegetables (Table 63). Overall, there was a 25% reduction in the relative risk of breast cancer for comparison of the highest versus lowest categories of vegetable intake; however, there was statistically significant between-study heterogeneity ($p < 0.001$). When the analysis was restricted to the 16 studies with dose–response information, reductions in the risk of breast cancer were observed for intakes as low as three portions compared to one per week (RR = 0.91, 95% CI 0.89–0.93). A 20% reduction in risk was observed for eating six portions versus one per week (RR = 0.79, 95% CI 0.77–0.80). Again, there was statistically significant between-study heterogeneity for these summary estimates ($p < 0.001$). The results for vegetable consumption were suggestive of weaker associations among studies using a validated

questionnaire (RR = 0.85, 95% CI 0.71–1.01 for high versus low consumption) than with a non-validated one (RR = 0.66, 95% CI 0.55–0.81; *p* for interaction = 0.13), among studies reporting univariate (RR = 0.86, 95% CI 0.77–0.97) versus multivariate relative risks (RR = 0.68, 95% CI 0.56–0.83; *p* for interaction = 0.22), and among non-Mediterranean (RR = 0.77, 95% CI 0.66–0.92) compared with Mediterranean countries (RR = 0.67, 95% CI 0.54–0.87; *p* for interaction = 0.48). Other sources of heterogeneity are that relative risks for different categories of intake for different vegetable groups were combined into a summary estimate.

Combined fruit and vegetables

Cohort studies

Total fruit and vegetable consumption was not significantly associated with breast cancer risk in two out of three cohort studies (Table 65). In the Nurses' Health Study, there was an inverse association with total fruit and vegetable consumption among premenopausal women (Zhang *et al.*, 1999). The association was stronger among premenopausal women with a family history of breast cancer or who drank at least 15 grams of alcohol per day. In this study, fruit and vegetable consumption was not associated with breast cancer risk among postmenopausal women, but an inverse association was suggested among postmenopausal women who were current users of hormone replacement therapy.

In a pooled analysis of eight prospective studies (including the Nurses' Health Study mentioned above), total fruit and vegetable consumption was not associated with breast cancer risk overall or for premenopausal or postmenopausal breast cancer (*p* for interaction by menopausal status = 0.57) (Smith-Warner *et al.*, 2001).

Case–control studies

Among the four case–control studies that considered combined fruit and vegetable consumption, a significant inverse association was found in only one (Ronco *et al.*, 1999) (Table 66).

Breast cancer in men

In three case–control studies of the association between fruit and vegetable consumption and risk of breast cancer in men (Table 67), the results are inconsistent and the evidence is too limited to allow any conclusion to be drawn.

Discussion

About 30 studies have evaluated the categories of total fruit or total vegetables in relation to risk of breast cancer. Total fruit consumption generally has not been significantly associated with risk in either a protective or harmful direction, the relative risks being mostly between 0.8 and 1.2 for comparisons of high versus low fruit intake. For the six evaluable cohort studies, the mean RR was 0.82 (95% CI 0.71–0.95), range 0.74–1.08 (Figure 36) and for the 12 case–control studies the mean OR was 0.99 (95% CI 0.92–1.07), range 0.57–1.82 (Figure 37). For total vegetable consumption, case–control studies have been more suggestive of an inverse association than the cohort studies, but they are more susceptible to recall and selection bias than cohort studies. For the five evaluable cohort studies, the mean RR was 0.94 (95% CI 0.83–1.07), range 0.64–1.43 (Figure 38) and for the 12 case–control studies the mean OR was 0.66 (95% CI 0.57–0.75), range 0.09–1.40 (Figure 39). There was little suggestion that associations between fruit and vegetable consumption and breast cancer risk differ by menopausal status. The Working Group could not exclude the possibility that fruit and vegetable consumption is associated with a slight decrease in the risk of breast cancer. Errors in the measurement of fruit and vegetable consumption may have attenuated the results, so it is possible that stronger inverse associations could be observed if more accurate dietary assessment methods were used to estimate fruit and vegetable intake. There are inadequate data on effects of diet during early life on subsequent risk of developing breast cancer. Few studies have examined effect modification.

Cervix

Fruit

Cohort studies

No studies were identified by the Working Group.

Case–control studies

In five studies that addressed the association of intake of fruit with invasive cervix cancer, most point estimates were below 1.0, although confidence intervals generally included the null (Table 68). The exception with a significant inverse association reported was a hospital-based study in Japan (Hirose *et al.*, 1996).

Vegetables

Cohort studies

No studies were identified by the Working Group.

Case–control studies

There is evidence of an inverse association, but confidence intervals often included the null (Table 69).

Combined fruit and vegetables

Two studies have examined total fruit and vegetable intake with regard to risk of cancer of the cervix (Table 70), one showing evidence of an inverse association and the other no significant effect.

Cohort studies	No. of categ.	OR	95% CI
Shibata *et al.*, 1992	3	0.82	0.60–1.12
Rohan *et al.*, 1993	5	0.81	0.57–1.14
Verhoeven *et al.*, 1997a (post)	5	0.76	0.54–1.08
Zhang *et al.*, 1999 (pre)	5	0.74	0.45–1.24
Zhang *et al.*, 1999 (post)	5	0.84	0.64–1.09
Maynard *et al.*, 2002 (I)	4	1.08	0.52–2.25
Sauvaget *et al.*, 2003	3	0.91	0.48–1.72
SUMMARY VALUE		0.82	0.71–0.95

Heterogeneity test: χ^2 (6df)=1.0; p=0.98

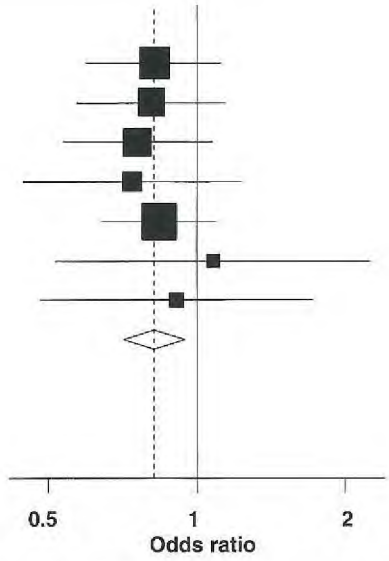

Figure 36 Cohort studies of breast cancer in women and fruit consumption (see Table 61)
Pre = premenopausal; post = postmenopausal; I = incidence

Case–control studies	No. of categ.	OR	95% CI
Ingram *et al.*, 1991	2	0.9	0.5–1.6
Negri *et al.*, 1991	3	1.1	1.0–1.3
Zaridze *et al.*, 1991 (post)	2	1.82	0.46–7.14
Zaridze *et al.*, 1991 (pre)	2	0.82	0.13–5.26
Holmberg *et al.*, 1994	4	1.4	0.9–2.3
Hirose *et al.*,1995 (post)	2	1.05	0.82–1.35
Hirose *et al.*,1995 (pre)	2	0.95	0.78–1.17
Trichopoulou *et al.*, 1995a	5	0.65	0.47–0.90
Freudenheim *et al.*, 1996 (pre)	4	0.67	0.42–1.09
Thorand *et al.*, 1998 (post)	*	0.82	0.51–1.32
Potischman *et al.*, 1999	4	1.2	0.8–1.4
Ronco *et al.*, 1999	4	0.57	0.36–0.89
Terry *et al.*, 2001c (post)	4	0.96	0.79–1.17
Dos Santos Silva *et al.*, 2002	4	0.89	0.50–1.57
SUMMARY VALUE		0.99	0.92–1.07

Heterogeneity test: χ^2 (13df)=23; p=0.039

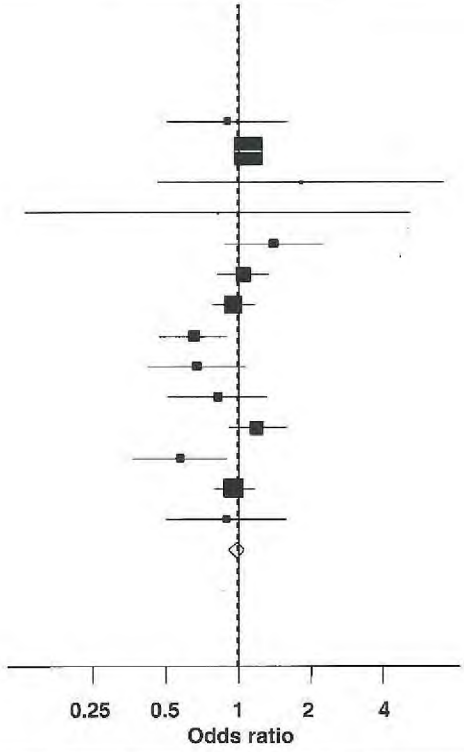

Figure 37 Case–control studies of breast cancer in women and fruit consumption (see Table 62)
Pre = premenopausal; post = postmenopausal; * = not applicable

Cohort studies	No. of categ.	OR	95% CI
Shibata *et al.*, 1992	3	0.96	0.69–1.34
Rohan *et al.*, 1993	5	0.86	0.61–1.23
Verhoeven *et al.*, 1997a (post)	5	0.94	0.67–1.31
Zhang *et al.*,1999 (pre)	5	0.64	0.43–0.95
Zhang *et al.*, 1999 (post)	5	1.02	0.85–1.24
Maynard *et al.*, 2002 (I)	4	1.43	0.70–2.92
SUMMMARY VALUE		0.94	0.83–1.07

Heterogeneity test: χ^2 (5df)=5.9; p=0.31

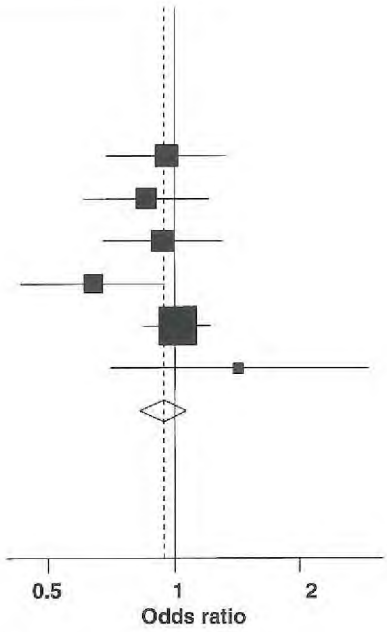

Figure 38 Cohort studies of breast cancer in women and vegetable consumption (see Table 63)
Pre = premenopausal; post = postmenopausal; I = incidence

Case–control studies	No. of categ.	OR	95% CI
Katsouyanni *et al.*, 1986	5	0.09	0.03–0.30
Ewertz & Gill, 1990	7	1.05	0.76–1.47
Ingram, 1991	2	1.4	0.8–2.4
Zaridze *et al.*, 1991 (pre)	2	0.31	0.03–3.70
Zaridze *et al.*, 1991 (post)	2	0.69	0.10–4.54
Pawlega *et al.*, 1992	3	0.4	0.2–0.8
Holmberg *et al.*, 1994	4	0.7	0.4–1.1
Qi *et al.*, 1994	4	0.26	0.14–0.47
Trichopoulou *et al.*, 1995a	5	0.54	0.40–0.74
Freudenheim *et al.*, 1996 (pre)	4	0.46	0.28–0.74
Thorand *et al.*, 1998 (post)	*	0.86	0.51–1.46
Potischman *et al.*, 1999	4	0.86	0.6–1.1
Ronco *et al.*, 1999	4	0.41	0.26–0.65
SUMMARY VALUE		0.66	0.57–0.75

Heterogeneity test: χ^2 (12df)=50; p<0.0001

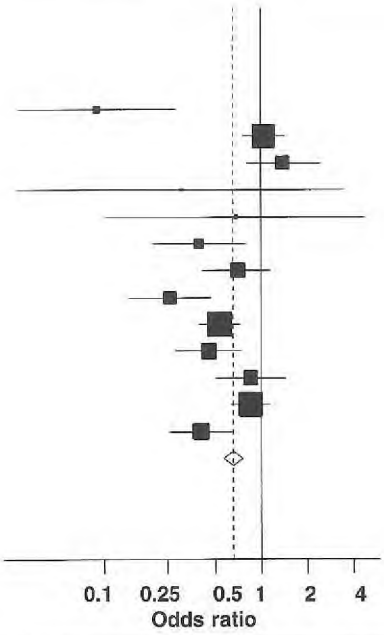

Figure 39 Case–control studies of breast cancer in women and vegetable consumption (see Table 64)
pre = premenopausal; post = postmenopausal; * = not applicable

In situ cervical cancer

The association of fruit and vegetable intake with risk of *in situ* cervical cancer has been examined in only one case–control study (Table 71); there was an inverse association with fruit intake but not with vegetables.

Cervical dysplasia

One case–control study examining risk for cervical dysplasia in relation to intake of fruit and vegetables has been reported (Table 72). Cervical dysplasia is difficult to study because of problems with case ascertainment. In this study, there is some concern about the comparability of the study base for the cases and controls. Fruit intake appeared to be associated with reduced risk. There was no analysis of total vegetable intake.

Discussion

In all, nine case–control studies have addressed associations between fruit and vegetable intake and either invasive cancer or precancerous lesions of the cervix. The findings are not completely consistent and there is little evidence for a strong effect of intake of these foods on risk.

In considering these findings, several limitations need to be kept in mind. The lack of evidence from cohort studies makes it hard to evaluate the effect of recall and selection bias on the results. Further, there are concerns with measurement error. As in all observational studies, confounding is possible. Of particular concern for cervical cancer is the role of diet in a pathway that includes human papillomavirus (HPV). If fruit and vegetable intake is important in a causal pathway that includes HPV, it would be important to determine the HPV status of controls. Alternatively, HPV may operate as a confounder if both diet and HPV status are related to social status. However, in a study conducted in India where HPV was measured in both cases and controls, there was little difference between the OR measured for the full control group and that for the group of controls who were HPV-positive (Rajkumar *et al.*, 2003a).

Endometrium

Fruit

Cohort studies

No studies were identified by the Working Group.

Case–control studies

Eleven studies have examined the association between intake of fruit and risk of endometrial cancer (Table 73). In many of these, ORs were close to one and confidence intervals included the null. For the four studies where there was a significant inverse association, ORs were in the range 0.45–0.7.

Vegetables

Cohort studies

No studies were identified by the Working Group.

Case–control studies

Of 11 case–control studies that evaluated intake of vegetables, inverse associations were reported in eight, six being statistically significant (Table 74). In one study in Japan, a significant increase in risk was associated with consumption of raw but not green vegetables (Hirose *et al.*, 1996).

Combined fruit and vegetables

Cohort studies

In one cohort study, an inverse association between risk of endometrium cancer and combined fruit and vegetable intake was reported, but the confidence interval was wide and included the null (Table 75).

Case–control studies

In all three studies, total intake of fruit and vegetables was inversely associated with risk of endometrium cancer; in one the trend was significant (Table 76).

Discussion

Fruit consumption was evaluable in seven case–control studies, resulting in a mean OR of 1.03 (95% CI 0.90–1.17), range 0.67–1.97 (Figure 40). For the five evaluable studies on vegetable consumption, the mean OR was 0.75 (95% CI 0.64–0.89), range 0.65–1.00 (Figure 41). It is difficult to make comparisons among these studies because of differences in the composition of the diet in different regions and because of considerable differences in dietary assessment. There appears to be inconsistent evidence of an inverse association with these foods.

An important confounder to consider in the study of endometrial cancer is body mass index; most but not all of the studies included control for this.

Overall these results provide weak evidence at best for an effect of fruit and vegetable intake on risk of endometrial cancer.

Ovary

Fruit

Cohort studies

Neither of two cohort studies of fruit intake and ovary cancer risk found an association (Table 77).

Case–control studies

Among four case–control studies of total fruit intake in relation to risk of ovary cancer (Table 78), one found a significant inverse association, but in another fruit intake was positively associated with risk.

Vegetables

Cohort studies

In the two available studies, the association of vegetable intake with risk was inverse, but for both, the confi-

Case–control studies	No. of categ.	OR	95% CI
Potischman *et al.*, 1993	4	1.1	0.6–1.9
Hirose *et al.*, 1996	2	1.97	1.37–2.82
Tzonou *et al.*, 1996b	4	0.96	0.76–1.21
Jain *et al.*, 2000	4	1.29	0.88–1.89
McCann *et al.*, 2000	4	0.9	0.5–1.7
Littmann *et al.*, 2001	5	0.67	0.47–0.95
Terry *et al.*, 2002	4	0.9	0.7–1.2
SUMMARY VALUE		1.03	0.90–1.17

Heterogeneity test: χ^2 (6df)=21; p=0.0018

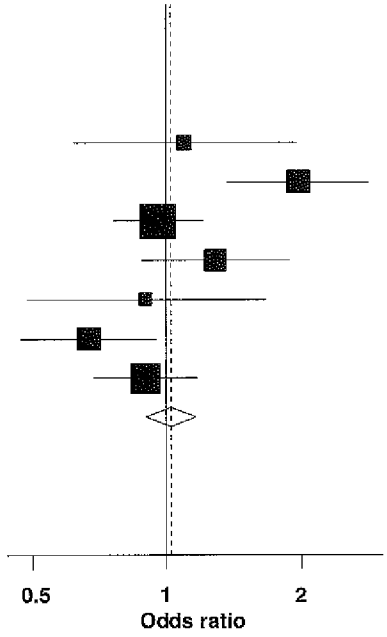

Figure 40 Case–control studies of endometrium cancer and fruit consumption (see Table 73)

Case–control studies	No. of categ.	OR	95% CI
Potischman *et al.*, 1993	4	1.0	0.6–1.6
Tzonou *et al.*, 1996b	4	0.85	0.66–1.11
Jain *et al.*, 2000	4	0.65	0.44–0.96
McCann *et al.*, 2000	4	0.5	0.3–0.9
Littmann *et al.*, 2001	5	0.69	0.48–1.0
SUMMARY VALUE		0.75	0.64–0.89

Heterogeneity test: χ^2 (4df)=5; p=0.29

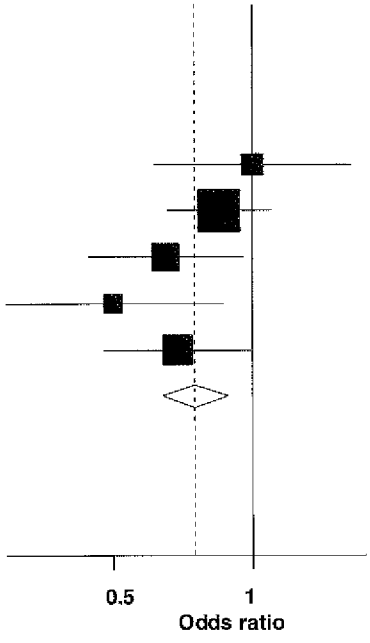

Figure 41 Case-control studies of endometrium cancer and vegetable consumption (see Table 74)

dence intervals included the null (Table 79).

Case–control studies

Among six case–control studies of vegetable intake, a significant inverse association was seen in three (Table 80).

Combined fruit and vegetables

Cohort study

In one study, although adult intake was not associated with risk (Table 81), the reported intake of six fruits and vegetables during adolescence was associated with decreased risk (OR 0.54, 95% CI 0.29–1.03, *p* for trend 0.04) (Fairfield *et al.*, 2001).

Case–control study

In one hospital-based study, there was an inverse association with intake of combined fruit and vegetable intake (Table 82).

Discussion

In general, the limited number of cohort and case–control studies that considered fruit intake found little indication of an inverse association. Findings from two cohort studies indicated an approximately 25% reduction in risk with increased intake of vegetables; of the six case–control studies that addressed vegetable intake, five yielded point estimates below 1.0, although many of the confidence intervals included the null.

Wide confidence intervals may be the result of relatively small numbers of cases, especially in the cohort studies. The inverse association in one study with fruit and vegetable intake in adolescence is suggestive that early dietary exposures may be of importance.

Overall, these studies suggest that there may be a protective effect for ovary cancer associated with vegetable intake. The association with fruit intake is less consistent.

Prostate

The etiology of prostate cancer is very poorly understood and there are no established risk factors other than male sex, age, family history and ethnic group. The international variation in prostate cancer rates, together with ecological analyses, has suggested that dietary factors including fruit and vegetables may be associated with risk.

The surgical procedure trans-urethral resection of the prostate (TURP), employed for the treatment of urinary obstruction due to non-malignant enlargement of the peri-urethral zone of the prostate, became common in many countries in the late 1980s and led to increased diagnosis of small prostate cancers when the material removed was examined histologically. In the 1990s, the use of measurements of serum concentrations of prostate-specific antigen (PSA) became common both as part of the investigation of urinary symptoms and for testing asymptomatic men for prostate cancer. As a result, an increasing proportion of the prostate cancers diagnosed in the last 15 years have been small tumours which may behave non-aggressively, whereas in studies conducted in the 1970s and early 1980s most were diagnosed clinically. Thus the end-point in epidemiological studies has changed somewhat and this could potentially affect any associations of prostate cancer risk with dietary factors.

Some recent studies have suggested that tomatoes have a specific protective effect against prostate cancer. No attempt was made by the Working Group to evaluate this hypothesis. Lycopene (a constituent of tomatoes) was evaluated previously (IARC, 1998).

Fruit

Cohort studies

Results from ten cohort studies on the association of total fruit intake with prostate cancer risk have been published (Table 83). In three, non-significant inverse associations were found, but in six the relative risks for high fruit consumption were greater than 1.0.

Case–control studies

Eleven case–control studies with results on the association of total fruit intake with prostate cancer risk have been published (Table 84). In only one was a significant inverse association found, while in eight the relative risks for high fruit consumption were greater than 1.0.

Vegetables

Cohort studies

Eight cohort studies with results on the association of total vegetable intake with prostate cancer risk have been published (Table 85). In four, relative risks for high vegetable consumption were less than 1.0, but none significantly so.

Case–control studies

Thirteen case–control studies with results on the association of total vegetable intake with prostate cancer risk have been published (Table 86). In nine, relative risks for high fruit consumption were less than 1.0, and significant reductions in risk were observed in four studies.

Combined fruit and vegetables

Cohort studies

In the two studies that considered combined fruit and vegetable consumption, there was no evidence of an inverse association (Table 87).

Case–control study

In one case–control study, there was evidence of an association between combined fruit and vegetable consumption and prostate cancer risk (Table 88).

Discussion

There is little evidence to support a protective effect of fruit intake on prostate cancer risk. For fruit consumption, eight evaluable cohort studies gave a mean RR of 1.11 (95% CI 0.98–1.26), range 0.84–1.57 (Figure 42) and nine evaluble case–control studies gave a mean OR of 1.08 (95% CI 0.98–1.18), range 0.40–1.70 (Figure 43). Vegetable consumption was evaluable in six cohort studies; mean RR 0.95 (95% CI 0.84–1.08), range 0.7–1.04 (Figure 44) and nine case–control studies, mean OR 0.90 (95% CI 0.82–1.00), range 0.6–1.39 (Figure 45).

Testis

Testicular cancer accounts for less than 2% of malignant neoplasms in men, but is the most common malignancy in young adult men aged 15–44 years in most developed countries, and its incidence has been increasing in developed countries throughout the world. An ecological association with consumption of fat, energy intake and dairy products was identified (Armstrong & Doll, 1975), but only two case–control studies (Table 89) have investigated the influence of total fruit and vegetable consumption on testicular cancer risk. In neither were there significant inverse associations with fruit or vegetable consumption.

An additional case–control study conducted in East Anglia, UK, aiming to test the hypothesis that milk and dairy products are risk factors for testicular cancer collected data on fresh fruit and vegetable consumption in adolescence (Davies *et al.*, 1996). Although cases tended to have eaten fewer oranges, apples and fruit salads than the population controls, the difference was not statistically significant, while the reverse was the case for vegetable salads.

Discussion

The information available is too sparse to allow any conclusion on the association of fruit and vegetables with testis cancer to be drawn.

Bladder

The Working Group adopted the usual convention of including studies of all urothelial cancers among the general group of bladder cancers.

Fruit

Cohort studies

Of five cohort studies (Table 90), two show a statistically significant inverse association with fruit consumption. However, in the study by Zeegers *et al.* (2001), the trend is inconsistent and varies between different categories of smokers. In this study, stratified ORs by smoking habits indicated a non-significant inverse association among current smokers and in ex-smokers who smoked more than 15 cigarettes per day.

Case–control studies

Among the four case–control studies identified (Table 91), inverse associations were seen in three for total fruit intake, two of which were statistically significant.

Meta-analyses

Results of two formal meta-analyses considering fruit consumption and bladder cancer risk have been reported. Steinmaus *et al.* (2000) included nine studies with data on fruit (four cohort and five case–control). The OR for high versus low consumption was [0.71 (95% CI adjusted for heterogeneity statistic 0.55–0.92)]. There was little variation by study type. Riboli & Norat (2003) included eight studies in their meta-analysis (three cohort and five case–control); the OR for an increase in consumption of 100 g of fruit per day was 0.81 (0.73–0.91). Again there was little variation by study type.

Vegetables

Cohort studies

None of the four cohort studies reporting information on vegetables (Table 92) reported a statistically significant inverse association with the consumption of vegetables. Two reported non-significant inverse associations, but one was with green-yellow vegetables.

Case–control studies

Out of four case–control studies identified, only three reported information on total vegetables and one on green-yellow and other vegetables separately (Table 93). Two studies found inverse associations with vegetable consumption, but neither was statistically significant. In the study by Zeegers *et al.* (2001), stratified ORs by smoking habits indicated a non-significant inverse association only among current heavy smokers.

Meta-analyses

Results of two formal meta-analyses considering vegetable consumption and bladder cancer risk have been reported. Steinmaus *et al.* (2000) included 10 studies with data on vegetables (three cohort and seven case–control). The OR for high versus low consumption was [0.86 (95% CI adjusted for heterogeneity statistic 0.75–0.99)]. There was little variation by study type. Riboli & Norat (2003) included six studies in their meta-analysis (two cohort and four case–control); the OR for an increase in consumption of 100 g of vegetables per day was 0.91 (95% CI 0.82–1.00). Again there was little variation by study type.

Combined fruit and vegetables

Cohort studies

In two cohort studies, no association of combined fruit and vegetable intake with bladder cancer risk was seen (Table 94).

Cohort studies	No. of categ.	OR	95% CI
Mills *et al.*, 1989	3	1.07	0.72–1.58
Severson *et al.*, 1989	3	1.57	0.95–2.61
Hsing *et al.*, 1990	4	0.9	0.6–1.4
Shibata *et al.*, 1992	3	1.04	0.74–1.46
Giovannucci *et al.*, 1995	*	0.84	0.59–1.84
Schuurman *et al.*, 1998	5	1.31	0.96–1.79
Chan *et al.*, 2000	5	1.3	0.8–2.2
Key *et al.*, 2003	5	1.06	0.84–1.34
SUMMARY VALUE		1.11	0.98–1.26

Heterogeneity test: χ^2 (7df)=5.5; p=0.6

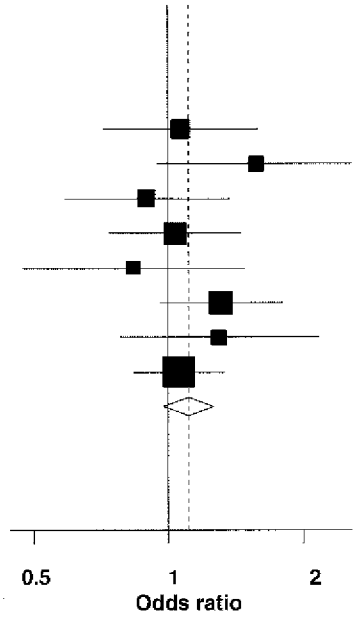

Figure 42 Cohort studies of prostate cancer and fruit consumption (see Table 83)
*Not applicable

Case–control studies	No. of categ.	OR	95% CI
Negri *et al.*, 1991	3	0.4	0.3–0.8
De Stefani *et al.*, 1995	3	1.7	1.1–2.8
Deneo-Pellegrini *et al.*, 1999	4	0.8	0.4–1.4
Jain *et al.*, 1999	4	1.51	1.14–2.01
Sung *et al.*, 1999	2	1.16	0.57–2.35
Tzonou *et al.*, 1999	5	0.98	0.86–1.13
Villeneuve *et al.*, 1999	4	1.5	1.1–1.9
Cohen *et al.*, 2000	4	1.07	0.72–1.60
Kolonel *et al.*, 2000	5	1.01	0.79–1.28
SUMMARY VALUE		1.08	0.98–1.18

Heterogeneity test: χ^2 (8df)=33; p<0.0001

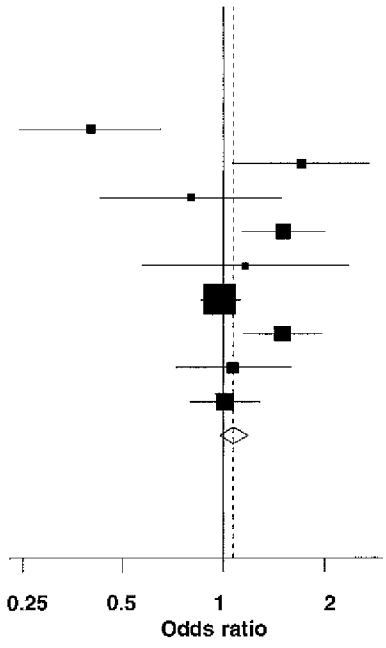

Figure 43 Case–control studies of prostate cancer and fruit consumption (see Table 84)

Cohort studies	No. of categ.	OR	95% CI
Hsing *et al.*, 1990	4	0.7	0.4–1.2
Shibata *et al.*, 1992	3	1.04	0.74–1.46
Giovannucci *et al.*, 1995	*	1.04	0.81–1.34
Schuurman *et al.*, 1998	5	0.80	0.57–1.12
Chan *et al.*, 2000	5	0.8	0.5–1.3
Key *et al.*, 2003	5	1.00	0.81–1.23
SUMMARY VALUE		0.95	0.84–1.08

Heterogeneity test: χ^2 (5df)=3.7; p=0.6

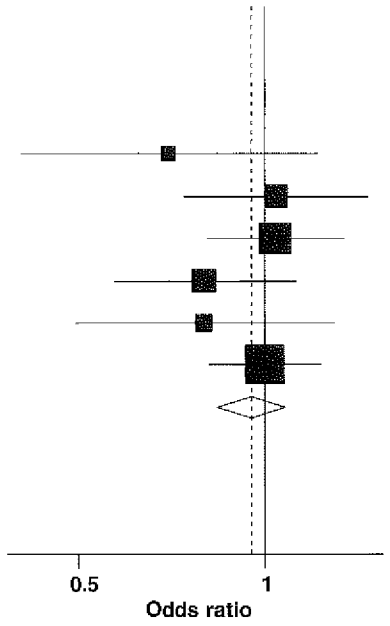

Figure 44 Cohort studies of prostate cancer and vegetable consumption (see Table 85)
*Not applicable

Case–control studies	No. of categ.	OR	95% CI
Oishi *et al.*, 1988	3	0.87	0.43–1.76
Talamini *et al.*, 1992	3	1.39	0.88–2.17
De Stefani *et al.*, 1995	3	1.1	0.6–1.9
Deneo-Pellegrini *et al.*, 1999	4	0.6	0.3–1.1
Jain *et al.*, 1999	4	0.95	0.68–1.33
Tzonou *et al.*, 1999	5	0.94	0.81–1.10
Villeneuve *et al.*, 1999	4	1.0	0.8–1.3
Cohen *et al.*, 2000	4	0.65	0.45–0.94
Kolonel *et al.*, 2000	5	0.74	0.58–0.96
SUMMARY VALUE		0.90	0.82–1.00

Heterogeneity test: χ^2 (8df)=12; p=0.15

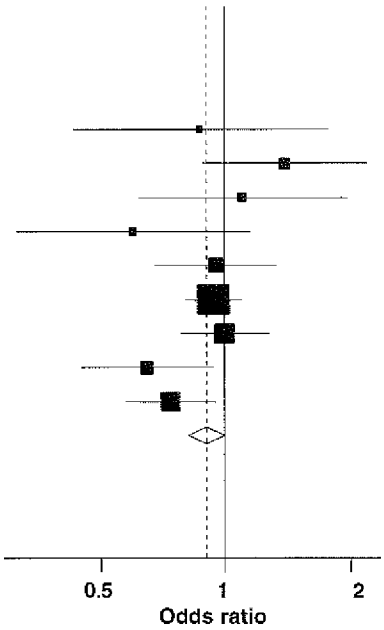

Figure 45 Case–control studies of prostate cancer and vegetable consumption (see Table 86)

Case–control studies

Inverse associations were noted in two out of three case–control studies in which combined fruit and vegetable intake was considered, but the association was significant only for males in one (Table 95).

Discussion

Cohort studies of the relationship between fruit and vegetable consumption and bladder cancer risk were generally set up to investigate diet, with the exception of that of Nagano *et al.* (2000), whose main goal was to study survivors of the atomic bombings. Most case–control studies had a hospital-based design; this design has limitations related to the recruitment of subjects with diet-associated diseases in the control group. Virtually all studies used food frequency questionnaires and adjusted for relevant confounders (gender, age, smoking and energy intake). The case–control studies more often found inverse associations than the cohort studies, but the findings were not consistent. For the five evaluable cohort studies on fruit consumption, the mean RR was 0.87 (95% CI 0.72–1.04), range 0.63–1.12 (Figure 46); for the four evaluable case–control studies, the mean OR was 0.74 (95% CI 0.59–0.92), range 0.53–0.95 (Figure 47). For vegetable consumption, the mean OR for the three evaluable cohort studies was 0.94 (95% CI 0.76–1.16), range 0.72–1.16 (Figure 48), and the mean OR for the three evaluable case–control studies was 0.89 (95%CI 0.69–1.14), range 0.66–1.04 (Figure 49).

Although both formal meta-analyses suggest protective effects of fruit and vegetables, the criteria for inclusion of studies varied, and in particular, that of Steinmaus *et al.* (2000) included studies that used surrogate estimates of fruit or vegetable consumption that were not considered by the Working Group.

Therefore, although the evidence of protective effects for fruit and vegetables and bladder cancer is suggestive, especially from the case–control studies, the Working Group felt it was not possible to exclude bias as accounting for the findings.

Kidney

In adults, cancer of the kidney encompasses two major histopathological entities, namely renal-cell (parenchymal) cancer and renal pelvis cancer. The epidemiology of renal pelvis cancer resembles that of bladder cancer more than that of renal-cell cancer and in some studies is included in the grouping urothelial cancer; it would thus have been covered in the previous section. The present review is therefore restricted to renal-cell cancer, which accounts for 80–90% of kidney cancers.

Fruit

Cohort studies

Of two cohort studies of renal-cell cancer reporting data on total fruit consumption (Table 96), only the one with the smaller numbers of cases found an inverse, but non-significant, association.

Case–control studies

The association between total fruit consumption and renal-cell cancer has been considered in seven case–control studies covering populations in North America, northern, central and southern Europe, Asia and Australia (Table 97). Significant inverse associations with fruit consumption were noted in four, but in one study only in males and in another only in non-smokers.

Data from three of these case–control studies (Chow *et al.*, 1994; Mellemgaard *et al.*, 1996; Lindblad *et al.*, 1997) as well as from an Australian study (McCredie & Stewart, 1992) were included in a multicentre analysis of 1185 renal-cell cancer cases and 1526 control subjects (Wolk *et al.*, 1996). In this analysis, there was a suggestion of an inverse association with total fruit consumption, but the association was not significant. In an analysis stratified by smoking status, the inverse association was confined to non-smokers. In the multicentre analysis, only a subset of 260 cases from the US study (Chow *et al.*, 1994) with direct interviews was included.

In a recent large case–control study among non-Asians of Los Angeles, California, which did not present results for total fruit, a strong significant inverse association was observed for citrus fruit (p for trend = 0.003) (Yuan *et al.*, 1998).

Vegetables

Cohort studies

In the one cohort study, there was no significant association with vegetable consumption (Table 98).

Case–control studies

Among five case–control studies with information on vegetable consumption, four found inverse associations, but they were significant only in men in one, and in another that considered dark green and yellow-orange vegetables separately (Table 99). In the multicentre study (Wolk *et al.*, 1996), there was a weak non-significant inverse association.

Combined fruit and vegetables

Cohort study

No significant association was observed in the one cohort study that considered combined intake of fruit and vegetables (Table 100).

Case–control studies

In one case–control study, a non-significant inverse association with combined intake of fruit and vegetables was noted in women, but not in men (Table 101).

Cohort studies	No. of categ.	OR	95% CI
Chyou *et al.*, 1993	3	0.63	0.37–1.08
Michaud *et al.*, 1999	5	1.12	0.70–1.78
Nagano *et al.*, 2000	3	0.75	0.46–1.22
Zeegers *et al.*, 2001	5	0.74	0.53–1.04
Michaud *et al.*, 2002	5	1.10	0.77–1.57
SUMMARY VALUE		0.87	0.72–1.04

Heterogeneity test: χ^2 (4df)=5.4; p=0.25

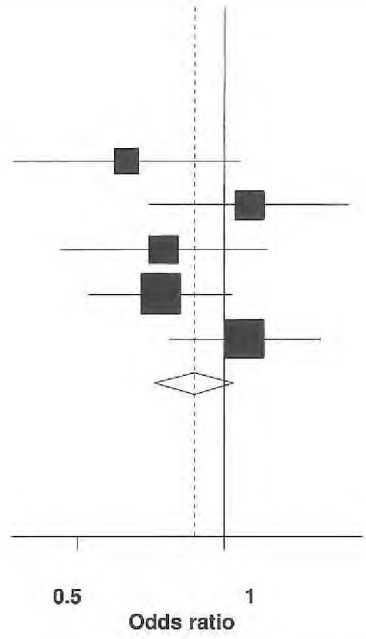

Figure 46 Cohort studies of bladder cancer and fruit consumption (see Table 90)

Case–control studies	No. of categ.	OR	95% CI
Riboli *et al.*, 1991	4	0.95	0.67–1.35
Bruemmer *et al.*, 1996	4	0.53	0.30–0.93
Wakai *et al.*, 2000	4	0.65	0.40–1.06
Balbi *et al.*, 2001	3	0.65	0.40–1.04
SUMMARY VALUE		0.74	0.59–0.92

Heterogeneity test: χ^2 (3df)=3.8; p=0.28

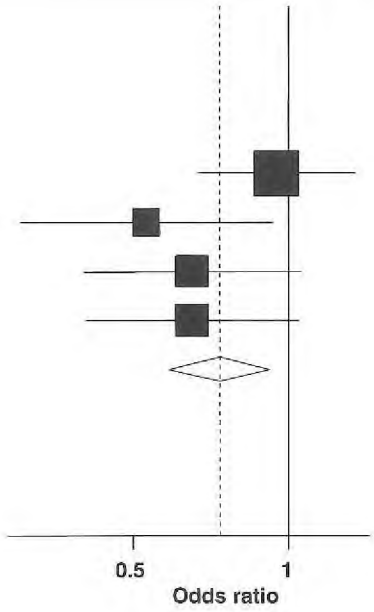

Figure 47 Case–control studies of bladder cancer and fruit consumption (see Table 91)

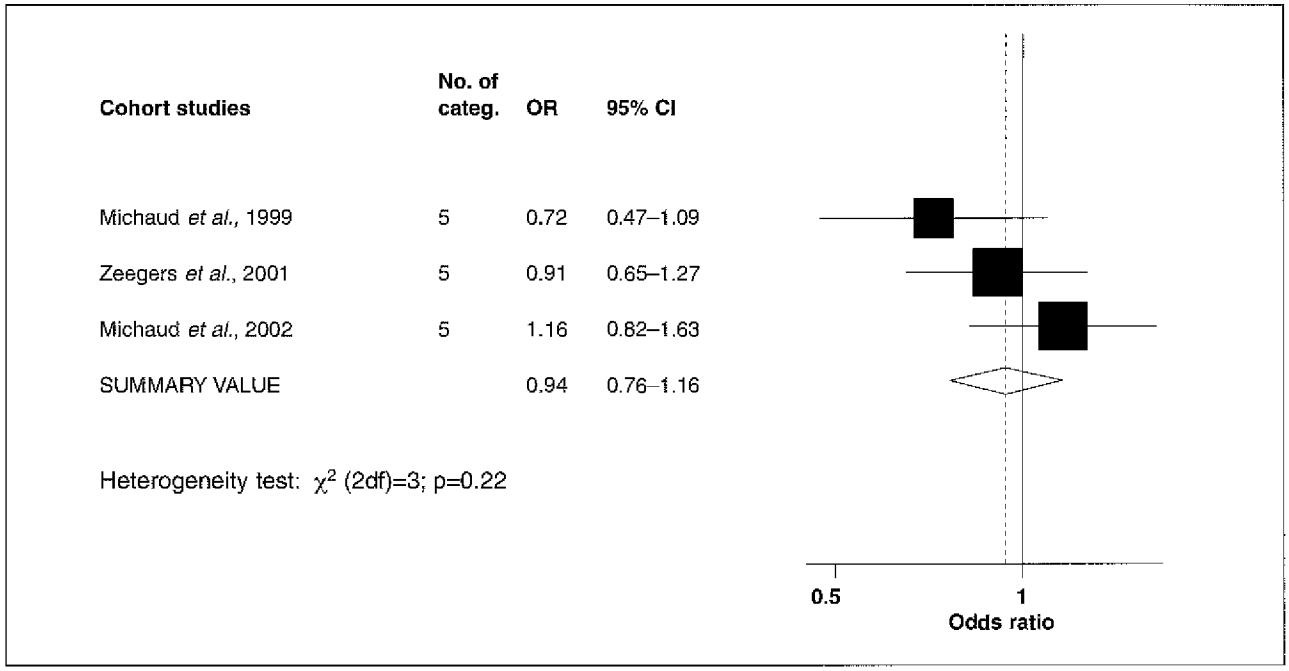

Figure 48 Cohort studies of bladder cancer and vegetable consumption (see Table 92)

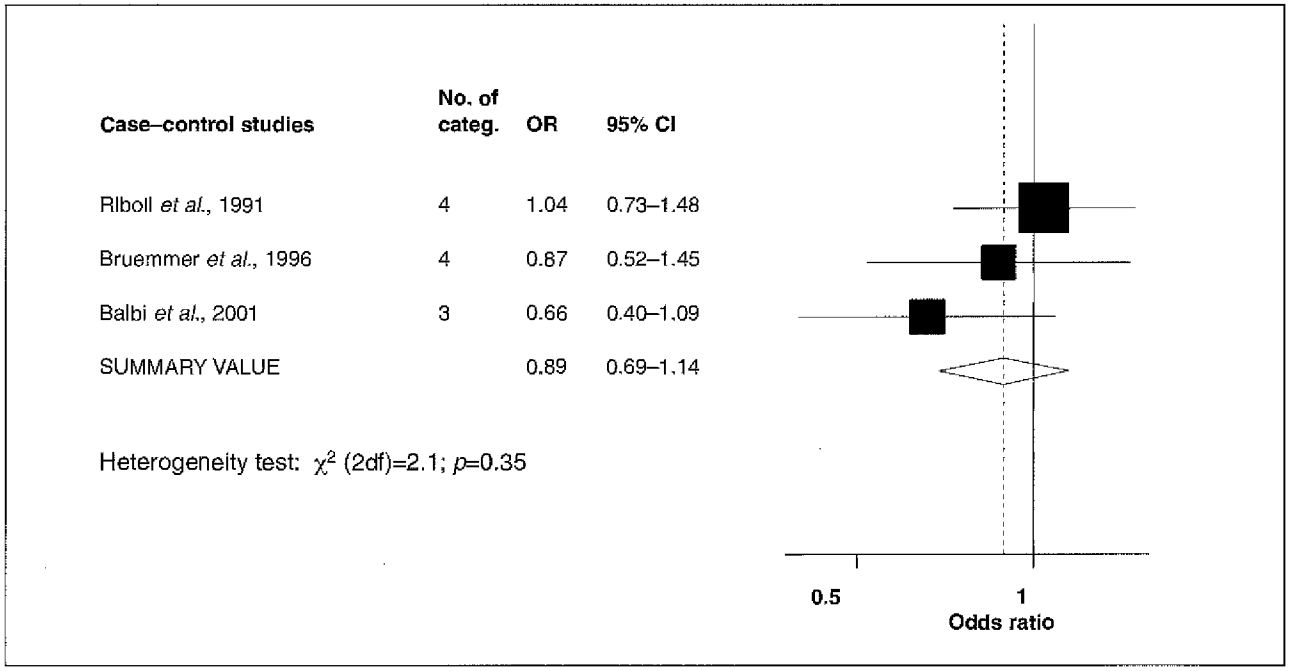

Figure 49 Case–control studies of bladder cancer and vegetable consumption (see Table 93)

Discussion

A number of studies have examined fruit and vegetable consumption in relation to kidney cancer risk. There were only two cohort studies with small numbers of cases and nine case–control studies of which three were also analysed together with another as a multicentre study (Wolk *et al.*, 1996). The studies were performed in Australia, China, Europe and the USA and all renal-cell cancer cases were histologically confirmed. Most studies used population-based controls. Response rates were relatively high in most studies and adjustment was made for potential confounding by body mass index and smoking. However, recall bias cannot be excluded in the case–control studies.

The results are not consistent. For the seven evaluable case–control studies on fruit consumption, the mean OR was 0.76 (95% CI 0.63–0.91), range 0.20–1.20 (Figure 50) and for the four evaluable case–control studies on vegetable consumption, the mean OR was 0.86 (95% CI 0.67–1.09), range 0.30–1.60 (Figure 51).

Because smoking increases oxidative stress, it is of interest to examine the association with fruit and vegetables in subgroups of smokers and non-smokers. However, only two case–control studies took smoking status into account when analysing associations of fruit and vegetables with risk of renal-cell cancer. The results from these two studies and from the multicentre analysis are not consistent; one showing a significant inverse association for cruciferous/dark green vegetables both in ever-smokers and non-smokers (Yuan *et al.*, 1998), whereas the other study (Lindblad *et al.*, 1997) and the multicentre analysis found this relationship only among non-smokers.

Brain

Adult brain cancer

Fruit

Cohort studies. No cohort studies on adult brain cancer were identified by the Working Group.

Case–control studies: In two reports on a case–control study in north-east China, a significant inverse association with fruit consumption and risk of adult brain cancer was found (Table 102). No association with citrus fruit consumption was found in a study in the USA (Chen *et al.*, 2002b).

Vegetables

Cohort studies. No cohort studies on adult brain cancer were identified by the Working Group.

Case–control studies. In one case–control study in the USA and in two reports (possibly not independent) on a case–control study in north-east China, inverse associations between vegetable consumption and risk of adult brain cancer were found (Table 103).

Childhood brain cancer

Fruit

Cohort studies. No cohort studies on childhood brain cancer were identified by the Working Group.

Case–control studies. Although there have been several studies of dietary variables and childhood cancer (especially brain tumours), few have considered fruit and vegetables *per se.*

Four case–control studies have considered fruit consumption, with contrasting results (Table 104). Two of the three studies that considered maternal diet during pregnancy found inverse associations. In the study in Australia that did not find an overall association, however, there was an inverse association for fruit consumption in the first year of life of the child.

Vegetables

Cohort studies. No cohort studies on childhood brain cancer were identified by the Working Group.

Case–control studies. Three case–control studies have considered vegetable consumption, with contrasting results (Table 105). The two that found inverse associations both considered the diet of the mother during pregnancy, while the third found no association either during gestation or in the first year of life.

Discussion

Information on adult and childhood brain cancer in relation to consumption of fruit and vegetables is sparse and comes entirely from case–control studies. Although inverse associations have been found, the number of studies was considered by the Working Group to be too few to permit evaluation.

Thyroid

Thyroid cancer is a rare disease, which occurs more frequently among females than males. The majority of thyroid malignancies are well differentiated, and survival is high. Papillary carcinoma comprises between 50 and 80% of thyroid cancers and follicular carcinoma between 10 and 40%. Anaplastic carcinoma is less common (5–10%), occurs in the sixth to seventh decade of life and is highly malignant. Medullary carcinoma arises from parafollicular or C-cells, and is even rarer. The majority of the information that follows refers to differentiated thyroid carcinoma.

Fruit

Cohort studies

No cohort studies were identified by the Working Group.

Case–control studies	No. of categ.	OR	95% CI
Talamini *et al.*, 1990	3	0.92	0.63–1.35
Negri *et al.*, 1991	3	0.6	0.4–1.0
McLaughlin *et al.*, 1992 (M)	4	0.2	0.0–0.5
McLaughlin *et al.*, 1992 (F)	4	0.7	0.2–2.0
Chow *et al.*, 1994	4	1.2	0.8–1.7
Mellemgaard *et al.*, 1996 (M)	4	0.6	0.3–1.4
Mellemgaard *et al.*, 1996 (F)	4	0.9	0.4–2.3
Boeing *et al.*, 1997	3	0.40	0.23–0.69
Lindblad *et al.*, 1997	4	0.65	0.42–1.02
SUMMARY VALUE		0.76	0.63–0.91

Heterogeneity test: χ^2 (8df)=16; p=0.47

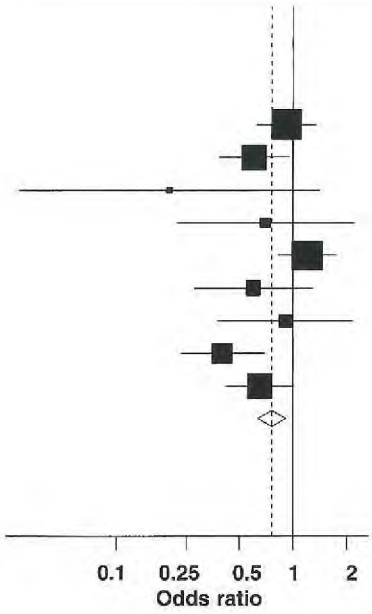

Figure 50 Case–control studies of renal-cell cancer and fruit consumption (see Table 97)
M = males; F = females

Case–control studies	No. of categ.	OR	95% CI
McLaughlin *et al.*, 1992 (M)	4	0.3	0.1–0.7
McLaughlin *et al.*, 1992 (F)	4	1.6	0.6–4.6
Chow *et al.*, 1994	4	1.0	0.7–1.5
Boeing *et al.*, 1997	3	0.75	0.44–1.27
Lindblad *et al.*, 1997 (NonSm)	4	0.84	0.53–1.31
SUMMARY VALUE		0.86	0.67–1.09

Heterogeneity test: χ^2 (4df)=6.8; p=0.15

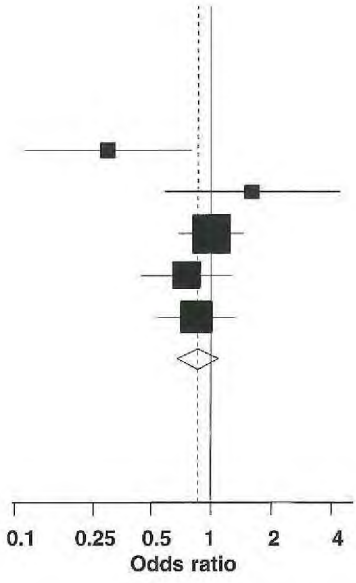

Figure 51 Case–control studies of renal-cell cancer and vegetable consumption (see Table 99)
M = males; F = females; NonSm = non-smokers

Case–control studies

Only two case–control studies have reported on the relationship between fruit consumption and thyroid cancer risk (Table 106). Neither reported a significant inverse association with total fruit consumption.

Vegetables

Cohort studies

No cohort studies were identified by the Working Group.

Case–control studies

Three case–control studies have reported on intake of either total or green/root vegetables and their association with thyroid cancer risk (Table 107). None reported a significant inverse association for vegetable consumption.

The association between cruciferous vegetables and other vegetable intake and thyroid cancer risk has been systematically re-analysed in a collaborative pooled analysis of 11 case–control studies (Bosetti *et al.*, 2002b). A significant inverse association for intake of vegetables other than cruciferous was found (OR 0.82, 95% CI, 0.69–0.98).

Discussion

Information on thyroid cancer in relation to consumption of fruit and vegetables is sparse and comes entirely from case–control studies. Although an inverse association with consumption of vegetables other than cruciferous has been found in a collaborative re-analysis, the overall number of studies of total fruits or total vegetables was considered by the Working Group to be too low to permit evaluation.

Non-Hodgkin lymphoma

Fruit

Cohort studies

In two cohort studies, non-significant inverse associations between total fruit consumption and risk for non-Hodgkin lymphoma were found (Table 108).

Case–control studies

In the only case–control study of total fruit consumption and non-Hodgkin lymphoma identified (Table 109), there was no evidence of an inverse association.

Vegetables

Cohort studies

Three cohort studies of non-Hodgkin lymphoma include data on vegetable consumption. Hirayama (1990) mentioned malignant lymphoma as one of the end-points in relation to green-yellow vegetable consumption (Table 110), but gave no further details. In one study there was a significant inverse association for vegetable consumption, but there was no association in the other.

Case–control study

In the one case–control study of total vegetable consumption and non-Hodgkin lymphoma (Table 111), there was no evidence of an inverse association.

Discussion

Information on non-Hodgkin lymphoma in relation to consumption of fruit and vegetables is sparse and comes from two cohort and two case–control studies. Although inverse associations were found, the overall number of studies of total fruits or total vegetables was considered by the Working Group to be too low to permit evaluation.

Leukaemia

Fruit

No studies were identified by the Working Group.

Vegetables

Cohort study

Hirayama (1990) included leukaemia as one of the end-points in relation to green-yellow vegetable consumption (Table 112), but gave no further details.

Case–control studies

No studies were identified by the Working Group.

Table 10. Cohort study of combined fruit and vegetable consumption and risk of cancer at all sites of the upper gastrointestinal tract

Author, year, country	Cases/ cohort size, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.	Adjustment for confounding	Comments
Boeing, 2002, Europe	124/ 387 144, M,F	FFQ	> 456 g/d vs ≤ 287 g/d (3)	0.55 (0.32–0.95)		Follow-up time, sex, education, BMI, smoking, alcohol, energy	Incidence Preliminary results of EPIC

Table 11. Case–control studies of fruit consumption and risk of oral/pharyngeal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
North America/Australia							
Winn *et al.*, 1984, USA	227 (156 incident/prevalent and 99 dead cases/405 (both hospital-based and dead), F	FFQ about usual adulthood diet (21), interviewed	Fresh fruit: ≥ 7.0 vs ≤ 1.0 times/wk (3)	0.6 (0.4–0.8)	$p = 0.001$	Respondent status, race, education, residence, cigarette smoking–snuff dipping, alcohol, relative weight, presence or absence of dentures, teeth missing, gum–tooth quality, regular or irregular use of mouthwash, number of meals/day, other food groups	Hospital-based
McLaughlin *et al.*, 1988, USA	871 (oral and pharyngeal cancer)/979, M, F	FFQ about usual adulthood diet (61), interviewed	Highest vs lowest (4)	M 0.4 F 0.5	$p < 0.001$ $p = 0.01$	Smoking, alcohol	Population-based study on whites only In 22% of cases, closest next of kin was interviewed
Gridley *et al.*, 1990, USA	190 (cancer of pharynx, tongue and other parts of oral cavity)/201, M, F	FFQ about usual adulthood diet (61), interviewed	Highest vs lowest (4)	M 0.2 F 0.6	$p = 0.006$ $p = 0.66$	Smoking, alcohol, energy	Population-based study among blacks
Day *et al.*, 1993, USA	1065 (871 white, 194 black) (cancer of tongue, gums, other parts of the mouth, pharynx)/1182 (979 whites, 203 blacks), M, F	FFQ about usual adulthood diet(61), interviewed	Highest vs lowest (4)	Whites 0.3 Blacks 0.6 (95% CI includes 1)	$p < 0.001$ $p = 0.22$	Sex, age, study location, respondent status, smoking, drinking, energy	Population-based Response rate: 75–78%
Kune *et al.*, 1993, Australia	41 (SCC of mouth and pharynx)/389, M	Dietary questionnaire, interviewed	Highest vs lowest (3)	0.1 (0.0–0.3)	$p < 0.001$	Age	Population-based
South America Franco *et al.*, 1989, Brazil	232 (cancer of tongue, gum floor of the mouth, other parts of the oral cavity)/464, M, F	FFQ about average past consumption (20), interviewed	Citrus fruit: ≥ 4/wk vs < 1/mo (3)	0.5 (0.3–0.9)	$p = 0.03$	Matched by age, sex, study site, admission period. Adjusted for tobacco and alcohol consumption	Hospital-based Three hospitals covering 20, 100 and 100% of cases of the respective areas

Table 11 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Oreggia *et al.*, 1991, Uruguay	57 (SCC of the tongue)/353, M	Short FFQ	≥ 5 vs < 1 times/wk (4)	[0.42 (0.14–1.25)]	$p = 0.03$	Age, county, type of tobacco, smoking intensity, total alcohol and other foods	Hospital-based
De Stefani *et al.*, 1999, Uruguay	33 (oral and pharyngeal cancer)/-393, M, F	FFQ (64), interviewed	Highest vs lowest (3)	0.7 (0.4–1.3)		Age, sex, residence, urban/rural status, education, BMI, tobacco smoking (pack-years), alcohol, energy	Hospital-based; Controls for analysis of oral/pharyngeal, laryngeal and oesophageal cancer
Garrote *et al.*, 2001, Cuba	200 (cancer of oral cavity, pharynx)/200, M, F	FFQ about lifetime dietary habits	> 13 vs < 7 servings/wk (3)	0.43 (0.21–0.89)	$p < 0.05$	Gender, age, area of residence, education, smoking and drinking habits and all four major foods (starchy foods, animal foods, vegetables)	Hospital-based
Europe							
Franceschi *et al.*, 1991a, Italy	302 (cancer of oral cavity, and pharynx/699, M, F	FFQ about recent diet (40)	Fresh fruit: Highest vs lowest (3)	1.1	$p = 0.75$	Age, sex, occupation, smoking, drinking	Hospital-based No cancer registry – unknown number of cases in the area; no individual matching performed, but catchment areas of cases and controls were strictly comparable
Negri *et al.*, 1991, Italy	119 (cancer of oral cavity and pharynx)/6147, M, F	FFQ (14–37, depending on cancer site)	Highest vs lowest (3)	0.2 (0.1–0.3)	$p < 0.01$	Age, area of residence, education, smoking, sex, vegetables	Hospital-based Data from a network of case–control studies
Levi *et al.*, 1998, Switzerland	156 (oral and pharyngeal cancer)/284, M, F	FFQ about diet of recent 2 years (79), interviewed	Citrus fruit: > 3.5 vs ≤ 1.5 servings/wk (3)	0.38 (0.20–0.73)	$p < 0.01$	Age, sex, education, smoking, alcohol and non-alcohol energy intake	Hospital-based
			Other fruit: > 11 vs ≤ 5.2 servings/wk (3)	0.22 (0.11–0.44)	$p < 0.01$		

Table 11 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Franceschi *et al.*, 1999, Italy	598 (oral and pharyngeal cancer)/ 1491, M, F	FFQ about diet of recent two years (78), interviewed	Diversity of consumption: ≥ 6 vs < 4 servings/wk (3)	0.7 (0.4–1.2)	$p < 0.05$	Age, centre, sex, education, smoking habit, energy, alcohol, number of servings of all fruits and veg. consumed weekly	Hospital-based in specific areas
Tavani *et al.*, 2001, Italy	132 (cancer of oral cavity, pharynx, tongue, mouth, oro-pharynx)/148, M, F	FFQ about recent year (25), interviewed	Total fruit: > 13 vs < 7 portions/wk (3)	0.34 (0.13–0.87)	$p < 0.05$	Age, sex, education, total number of portions, smoking, alcohol	Hospital-based
Lissowska *et al.*, 2003, Poland	122 (cancers of oral cavity and pharynx)/124, M, F	FFQ (25), interviewed	≥ 7/wk vs < 3 wk (3)	0.40 (0.17–0.95)	$p < 0.01$	Gender, age, residence, smoking, alcohol	Hospital-based
Sanchez *et al.*, 1984, USA	375 (cancer of oral and oropharynx)/ 375, M, F	FFQ (25)	≥ 11 vs ≤ 6 servings/wk (3)	0.52 (0.34–0.79)	$p < 0.001$	Gender, age, centre, years of schooling, smoking, alcohol	Hospital-based, three areas of Spain
Southern Asia							
Jafarey *et al.*, 1977, Pakistan	1192 (carcinoma of oral cavity and oropharynx)/ 10 749 from an earlier study, M, F	FFQ	5–7 times/ wk vs < 1/wk (4)	Males: [0.08 (0.06–0.12)] Females: [0.10 (0.07–0.15)]			Population-based Only frequencies of fruit and veg. consumption of males and females in five categories reported
Notani & Jayant, 1987, India	278 (cancer of oral cavity) plus 225 (pharyngeal cancer)/215 (hospital-based, H) and 177 (from population, P)	FFQ about usual diet before onset of the disease	At least once a week vs less than once a week (2)	Oral cavity: H: [1.15 (0.77–1.67)] P: [1.12 (0.71–2.0)] Pharynx: H: [1.16 (0.77–1.67)] P: [1.01 (0.63–1.67)]		Age, tobacco habits	Partly hospital-based, partly population-based
Rajkumar *et al.*, 2003b, India	591 (cancers of oral cavity)/582, M, F	FFQ (21), interviewed	≥ 4 vs ≤ 2 servings/wk (3)	0.55 (0.38–0.81)	$p < 0.001$	Age, sex, centre, education, chewing, smoking, alcohol	Hospital-based

Table 11 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Northern Asia							
Zheng *et al.*, 1992a, China	204 (oral and pharyngeal cancer) (115 M, 89 F)/414 (269 M, 145 F)	FFQ about usual diet of previous ten years (4, 30 fruits and veg.)	Oranges + tangerines: Highest vs lowest (3)	M 0.40 F 0.42	$p \leq 0.05$	Smoking, education	Population-based
			Other fruit: Highest vs lowest (3)	M 0.66 F 0.83	$p \leq 0.05$		
Takezaki *et al.*, 1996, Japan	266 (oral cancers)/ 36 527, M, F	FFQ about diet before onset of symptoms	Highest vs lowest (3)	0.5 (0.4–0.7)	$p < 0.01$	Age, sex, smoking, drinking, year of visit	Hospital-based

*p for trend when applicable

Table 12. Case-control studies of vegetable consumption and risk of oral/pharyngeal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
North America/Australia							
Winn *et al.*, 1984, USA	227 (156 incident/prevalent cases and 99 dead cases)/405 (both hospital-based and dead), F	FFQ about usual adulthood diet (21), interviewed	Green leafy veg: ≥ 7.0 vs ≤ 2.0 times/wk (3)	0.7 (0.5–1.1)	$p = 0.06$	Respondent status, race, education, residence, cigarette smoking–snuff dipping, alcohol, relative weight, presence or absence of dentures, teeth missing, gum-tooth quality, regular or not regular use of mouth-wash, number meals/day, other food groups	Hospital-based
			Other veg.: ≥ 7.1 vs ≤ 6.9 times/wk (3)	0.7 (0.4–1.3)	$p = 0.08$		
McLaughlin *et al.*, 1988, USA	871 (oral and pharyngeal cancer)/979, M, F	FFQ about usual adulthood diet (61), interviewed	Highest vs lowest (4)	M 1.0 F 0.8	$p = 0.69$ $p = 0.20$	Smoking, alcohol	Population based study of Whites only In 22% of cases closest next of kin was interviewed
Gridley *et al.*, 1990, USA	190 (cancer of pharynx, tongue, and other parts of oral cavity)/201, M, F	FFQ about usual adulthood diet (61), interviewed	Highest vs lowest (4)	M 0.3 F 0.8	$p = 0.004$ $p = 0.92$	Smoking, alcohol, energy	Population-based study among Blacks
Day *et al.*, 1993, USA	1065 (871 whites, 194 blacks) (cancer of tongue, gums, other parts of the mouth, pharynx)/1182 (979 whites, 203 blacks), M, F	FFQ about usual adulthood diet(61), interviewed	Highest vs lowest (4)	Whites 0.8 Blacks 0.5 (95% CI includes 1)	$p = 0.15$ $p = 0.07$	Sex, age, study location, respondent status, smoking, drinking, energy	Population-based
Kune *et al.*, 1993, Australia	44 (SCC of mouth and pharynx)/398, M	Dietary questionnaire, interviewed	Highest vs lowest (3)	0.3 (0.1–0.8)	$p = 0.001$	Age	Population-based
South/Central America							
Franco *et al.*, 1989, Brazil	232 (cancer of tongue, gum, floor of mouth, other parts of oral cavity)/464, M, F	FFQ about average past consumption (20), interviewed	Green veg.: ≥ 4/wk vs < 1/mo (3)	0.7 (0.4–1.4)		Matched by age, sex, study site, admission period Adjusted for tobacco and alcohol consumption	Hospital-based Three hospitals covering 20, 100 and 100% of cases of the respective areas

Table 12 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Oreggia *et al.*, 1991, Uruguay	57 (SCC of tongue)/353, M	Short FFQ	≥ 5 vs < 1 times/wk (4)	[0.19 (0.05–0.67)]	$p = 0.002$	Age, county, type of tobacco, smoking intensity, alcohol, other foods	Hospital-based
De Stefani *et al.*, 1999, Uruguay	33 (oral and pharyngeal cancer)/393, M, F	FFQ (64), interviewed	Highest vs lowest (3)	0.8 (0.4–1.4)		Age, sex, residence, urban/rural status, education, BMI, tobacco smoking (pack-years), alcohol, energy	Hospital-based Controls for analysis of oral/pharyngeal, laryngeal and oesophageal cancer
Garrote *et al.*, 2001, Cuba	200 (cancer of oral cavity, pharynx)/200, M, F	FFQ about lifetime dietary habits	> 19 vs < 12 servings/wk (3)	0.78 (0.40–1.51)	$p = 0.49$	Gender, age, area of residence, education, smoking, alcohol, all major foods (starchy foods, animal foods, fruits)	Hospital-based
Europe							
Franceschi *et al.*, 1991a, Italy	302 (cancer of oral cavity and pharynx)/699, M, F	FFQ about recent diet (40)	Highest vs lowest (3)	0.8	$p = 0.34$	Age, sex, occupation, smoking, alcohol	Hospital-based No cancer registry—unknown number of cases in the area No individual matching performed, but catchment areas of cases and controls were strictly comparable
Negri *et al.*, 1991, Italy	119 (cancer of oral cavity and pharynx)/6147, M, F	FFQ (14–37, depending on cancer site)	Green veg.: Highest vs lowest (3)	0.3 (0.1–0.5)	$p < 0.01$	Age, area of residence, education, smoking, sex, veg.	Hospital-based Data from a network of case–control studies
Levi *et al.*, 1998, Switzerland	156 (oral and pharyngeal cancer)/284, M, F	FFQ about diet of recent 2 y (79), interviewed	Raw veg.: > 8.5 vs ≤ 5 servings/wk (3)	0.30 (0.16–0.58)	$p < 0.01$	Age, sex, education, smoking, alcohol and non-alcohol total energy intake	Hospital-based
			Cooked veg.: > 8.6 vs ≤ 5.2 servings/wk (3)	0.14 (0.07–0.19)	$p < 0.01$		

Table 12 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Franceschi *et al.*, 1999, Italy	598 (oral and pharyngeal cancer)/1491, M, F	FFQ about diet of recent two years (78), interviewed	Diversity of consumption: ≥ 7 vs < 4 servings/wk (3)	0.6 (0.3–1.0)	NS	Age, centre, sex, education, smoking, energy, alcohol, number of servings of all fruits and veg. consumed weekly	Hospital-based in specific areas
Tavani *et al.*, 2001, Italy	132 (cancer of oral cavity, pharynx, tongue, mouth/ 148, M, F	FFQ about recent year (25), interviewed	Total green veg.: > 13 vs < 7 portions/ wk (3)	0.37 (0.16–0.88)	$p < 0.01$	Age, sex, education, total number of portions, smoking, alcohol	Hospital-based
Lissowska *et al.*, 2003, Poland	122 (oral cavity, and pharynx)/124, M, F	FFQ (25), interviewed	≥ 9/wk vs ≤ 6/wk (3)	0.17 (0.07–0.45)	$p < 0.01$	Gender, age, residence, smoking, alcohol	Hospital-based
Sanchez *et al.*, 2003, Spain	375 (cancer of oral cavity and oropharynx)/375, M, F	FFQ (25)	≥ 8 vs < 3 servings/wk (3)	0.54 (0.34–0.79)	$p = 0.001$	Gender, age, centre, years of schooling, smoking, alcohol	Hospital-based, three areas in Spain
Southern Asia							
Jafarey *et al.*, 1977, Pakistan	1192 (carcinoma of oral cavity and oropharynx)/ 10 749 from an earlier study, M, F	FFQ	5–7 times a week vs once a week or less (3)	M: [0.40 (0.29–0.56)] F: [0.47 (0.31-0.76)]			Population based Only frequencies of fruit and veg. consumption in 5 categories reported
Notani & Jayant, 1987, India	278 (cancer of oral cavity) plus 225 (pharyngeal cancer)/215 (hospital, H) and 177 (population, P), M	FFQ about usual diet before onset of the disease	Daily vs not daily (2)	Oral cavity H: [1.05 (0.71–1.67)] P: [0.42 (0.25–0.71)] Pharynx H: [1.03 (0.67–1.67)] P: [0.38 (0.22–0.63)]		Age, tobacco habits	Partly hospital-based, partly population-based
Rajkumar *et al.*, 2003b, India	591 (cancers of oral cavity)/582, M, F	FFQ (21), interviewed	≥ 14 vs ≤ 7 servings/wk (3)	0.44 (0.28–0.69)	$p = 0.002$	Age, sex, centre, education, chewing, smoking, alcohol	Hospital-based

Table 12 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Northern Asia							
Zheng *et al.*, 1992a, China	204 (oral and pharyngeal cancer), 115 M, 89 F)/414 (269 M, 145 F)	FFQ about usual diet of the previous ten years (41, 30 fruits and veg.)	Dark green veg.: Highest vs lowest (3)	M 1.37 F 1.22	NS NS	Smoking and education	Population-based
			Dark yellow veg.: Highest vs lowest (3)	M 0.32 F 0.78	$p < 0.05$ NS		
			Raw veg.: Highest vs lowest (3)	M 0.45 F 1.18	$p < 0.05$ NS		
Takezaki *et al.*, 1996, Japan	266 (oral cancers)/36 527, M, F	FFQ about diet before onset of the symptoms	Green-yellow veg.: Highest vs lowest (3)	1.0 (0.7–1.3)	$p > 0.05$	Age, sex, smoking, drinking, year of visit	Hospital-based
			Raw veg: Highest vs lowest (3)	0.5 (0.4–0.7)	$p < 0.01$		

*p for trend when applicable

Table 13. Case–control studies on combined fruit and vegetable consumption and risk of oral and pharyngeal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Winn *et al.*, 1984, USA	227 (156 incident/-prevalent cases and 99 dead cases/405 (both hospital-based and dead)	FFQ about usual adulthood diet (21), interviewed	> 21 vs 11 times/wk (3)	0.5 (0.3–0.8)	$p = 0.0002$	Respondent status, race, education, residence, cigarette smoking–snuff dipping, alcohol, relative weight, presence or absence of dentures, teeth missing, gum-tooth quality, regular or irregular use of mouthwash, number of meals/day, other food groups	Hospital-based
Gridley *et al.*, 1992, USA	1103 (oral and pharyngeal cancers)/1262, M, F	FFQ, interviewed	Highest vs lowest (4)	No vitamin E supplement: 0.6 Vitamin E supplement: 0.2		Race, sex, tobacco and alcohol use	Population-based

*p for trend when applicable

Table 14. Case–control studies on fruit and vegetable consumption and oral/pharyngeal precancerous lesions

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Gupta *et al.*, 1998, India	318 (168 oral leukoplakia, 149 oral submucous fibrosis)/318, M	FFQ (92), interviewed	Fruit: Continuous variable Veg.: (pulses, roots and tubers excluded) Continuous variable	Submucous fibrosis 0.85 (0.70–1.04) Leukoplakia 0.78 (0.61–1.00)	$p = 0.1$ $p = 0.05$	Socioeconomic status, tobacco exposure, energy	Population-based study in state of Gujarat
Gupta *et al.*, 1999, India	226 (oral leukoplakia, oral submucous fibrosis) 226, M	FFQ (81), interviewed	Fruit: Highest vs lowest (4) Veg.: Highest vs lowest (4)	1.01 (0.54–1.87) 0.83 (0.42–1.67)	NS	Tobacco, energy, economic status	Population-based study in state of Kerala Cases and controls all tobacco users
Morse *et al.*, 2000, USA	105 (epithelial dysplasia)/103, M, F	FFQ (61)	Fruit: ≥ 2.9 vs < 1.8 servings/d Veg.: ≥ 3.6 vs < 2.25 servings/d Fruit and veg: ≥ 6.5 vs <4.6 servings/d	0.91 (0.33–2.5) 0.76 (0.28–2.1) 0.63 (0.21–1.9)	$p = 0.86$ $p = 0.70$ $p = 0.44$	Matched by age, gender, surgeon appointment date Adjusted for current smoking, number of drinks/week, education, season, energy	Hospital-based Only 87 case–control pairs utilized for this analysis

*p for trend when applicable

Table 15. Case–control study on fruit and vegetable consumption and risk of salivary gland cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Zheng *et al.*, 1996	41/414, M, F	FFQ about usual frequency in the previous 10 years (41, 30 fruits and veg.)	Fruit: Daily vs never or occasionally (3) Veg: Daily vs never or occasionally (3)	1.3 (0.6–2.9) 0.9 (0.4–1.9)	$p > 0.10$ $p > 0.10$	Gender, age, income	Population-based

*p for trend when applicable

Table 16. Case–control studies on fruit and vegetable consumption and risk of cancer of naso-pharynx

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Armstrong *et al.*, 1998, Malaysia	282/282, M, F	FFQ about diet five years before diag-nosis and at age 10 y (55), interviewed	Oranges/tan-gerines: ≥ weekly vs < monthly (3) Chinese flowering cabbage: ≥ weekly vs < weekly (2) Other veg.: ≥ weekly vs < monthly (3)	0.52 (0.31–0.85)[1] 0.98 (0.51–1.86)[2] 0.64 (0.40–1.04)[1] 0.47 (0.29–0.77)[2] 0.50 (0.23–1.07)[1] 0.59 (0.33–1.06)[2] [1] diet of recent 5 y [2] diet at age 10	$p < 0.01$ $p < 0.1$		Population-based
Yu *et al.*, 1989, China	306/306, M, F	FFQ as reported by mother: 110 mothers of cases/139 mothers of controls Diet of children aged 10 y (41) and aged 1–2 y (19)	Oranges/tan-gerines: Diet at age 10 y: daily vs rarely (4) Diet at age 1–2 y: weekly vs rarely (3) Other fresh fruit: Diet at age 10 y: daily vs rarely (4) Diet at age 1–2 y: weekly vs rarely (3) Fresh green veg.: children diet at age 10 y: daily vs less than daily (2) children diet at age 1–2 y: weekly vs rarely (3)	0.3 (0.1–0.9)[1] 0.0 (0.0–0.8)[2] 0.6 (0.3–1.2)[1] 0.3 (0.1–1.1)[2] [0.59 (0.20–1.67)][1] [0.77 (0.20–3.33)][2] [1] during ages 1–2 y [2] at age 10 y	$p < 0.05$ NS NS NS NS NS		Neighbour-hood controls Analysis of subjects' diet as reported by mothers; Only 82 matched case–mother control–mother pairs

*p for trend when applicable

Table 17. Cohort studies of fruit consumption and risk of oesophageal cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Yu *et al.*, 1993, China	1162/12 693, M, F 15 y	Interview	Fresh fruit: regular or occasional vs never (2)	0.99 (0.85–1.15)	$p > 0.1$	Age, sex	Incidence Interviews performed in 1989 in subjects recruited in 1974 for screening
Guo *et al.*, 1994, China	639/3200, M, F, 5 y	FFQ for diet during the past 12 months, interviewed	Fresh fruit: ≥ once vs none/mo (2)	0.9 (0.8–1.1)	NS	Years of smoking, cancer history in first-degree relatives	Incidence Nested case–control study in randomized control trial
Sauvaget *et al.*, 2003, Japan	80/38 540, M, F 17 y	FFQ (22), self-administered	Daily vs once/wk or less (3)	0.57 (0.31–1.04)	$p = 0.07$	Sex, age, radiation dose, city, BMI, smoking status, alcohol, education level	Mortality Atomic bombing survivors

*p for trend when applicable

Table 18. Case–control studies of fruit consumption and risk of oesophageal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
North America							
Ziegler *et al.*, 1981, USA	120/250, M, black	FFQ about subjects' usual adult diet before 1974 (31, 3 fruits), interviewed	Highest vs lowest (3)	[0.50]	$p < 0.05$	Alcohol	Population-based Deaths from oesophageal cancer (cases) or other causes (controls) Interviews with next of kin completed for 67% of cases and 71% of controls
Brown *et al.*, 1988, USA	Incidence: 74/157, M Mortality: 143/285, M	FFQ about usual adult diet, interviewed	Highest vs lowest (3)	0.5 (0.3–0.9)	$p < 0.01$	Use of cigarettes and alcohol	Hospital- and population-based Incidence series

Table 18 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Brown *et al.*, 1995, USA	174 ADC/750, M (white)	FFQ about usual adult diet (60), interviewed	Highest vs lowest (4)	0.7	$p = 0.24$	Age, area, smoking, liquor use, income, energy, BMI	Population-based
Brown *et al.*, 1998, USA	333 SCC (114 white, 219 black)/ 1238 (681 whites, 557 black), M	FFQ about usual adult diet (60)	Highest vs lowest (4)	White: 0.5 Black: 0.4	$p = 0.04$ $p = 0.001$	Age, area, smoking, alcohol, energy	Population-based
Chen *et al.*, 2002a, USA	124 (ADC)/449, M, F	Short FFQ about diet before 1985 (54), interviewed by telephone	Citrus fruit and juices: Highest vs lowest (4)	0.48 (0.21–1.1)	$p = 0.03$	Age, sex, energy, respondent type, BMI, alcohol, tobacco, education, family history, vitamin supplement use, age squared	Population-based For 76% of cases and for 61% of controls, interviews conducted with next of kin
South America							
Victora *et al.*, 1987, Brazil	164 SCC/327, M, F	FFQ (9), interviewed	log days/mo +1	0.66 (90% CI 0.52–0.83)	$p = 0.002$	Cachaça drinking, residence, smoking status, fruit and meat consumption	Hospital-based
De Stefani *et al.*, 1990b, Uruguay	261 SCC/ 522, M, F	FFQ of recent diet, interviewed	Daily vs < once/wk (4)	0.33 (0.2–0.5)		Age, residence, smoking duration, type of tobacco, alcohol	Hospital-based
Castelletto *et al.*, 1994, Argentina	131 (SCC)/ 262, M, F	FFQ about recent diet and diet 10 y before admission (10), interviewed	Citrus fruit: > 3/wk vs < 1/wk (3) Non-citrus fruit: > 3/wk vs < 1/wk (3)	1.6 (0.8–3.1) 0.7 (0.3–1.5)		Age, sex, hospital, education, average number of cigarettes/day, alcohol, barbecued meat, potatoes, raw and cooked veg.	Hospital-based
Rolón *et al.*, 1995, Paraguay	131/381, M, F	FFQ about current diet (50), interviewed	Citrus fruit: Highest vs lowest (4) Non-citrus fruit: Highest vs lowest (4)	0.8 (0.4–1.7) 0.9 (0.4–2.1)	$p = 0.43$ $p = 0.98$	Lifetime consumption of alcohol, cigarette smoking, age group, sex, hospital group, meats, fats, fish, milk	Hospital-based

Table 18 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Castellsagué *et al.*, 2000, Argentina, Brazil, Paraguay, Uruguay	830 SCC/1779, M, F	FFQ about recent diet (50), interviewed	Almost daily/daily vs never/-rarely (3)	0.37 (0.27–0.51)	$p < 0.00001$	Sex, age group, hospital, residence, years of education, average number of cigarettes/day, alcohol	Hospital-based Pooled analysis from four main studies (Victora *et al.*,1987; De Stefani *et al.*, 1990b; Castelletto *et al.*, 1994; Rolón *et al.*, 1995); together with additional subjects from Uruguay.
De Stefani *et al.*, 1999, Uruguay	66/393, M, F	FFQ (64), interviewed	Highest vs lowest (3)	0.4 (0.3–0.6)		Age, sex, residence, urban/rural status, education, BMI, tobacco smoking (pack-years), alcohol, energy	Hospital-based Controls for analysis of oral/pharyngeal, laryngeal and oesophageal cancer
De Stefani *et al.*, 2000b, Uruguay	111 SCC/444, M, F	FFQ (64), interviewed	≥ 216.8 vs ≤ 74.7 g/d (4)	0.18 (0.09–0.39)	$p < 0.001$	Age, gender, residence, urban/rural status, education, BMI, tobacco smoking, alcohol drinking, energy	Hospital-based
Europe							
Tuyns *et al.*, 1987, France	331/1975, M, F	FFQ about usual diet (40), interviewed	Citrus fruit: Highest vs lowest (4) Other fresh fruit: Highest vs lowest (4)	0.33 0.72	$p = 0.004$ $p = 0.034$	Age, alcohol, smoking, urban or rural residence	Population-based

Table 18 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Franceschi *et al.*, 1990, Italy	68/505, M	FFQ about diet of last year (40), interviewed	Fresh fruit: ≥ 13 vs ≤ 4 servings/wk (3)	[0.49]			Hospital-based No cancer registry, unknown number of cases in the area OR computed from distribution of intake
Negri *et al.*, 1991, Italy	294/6147, M, F	FFQ (14–37, depending on cancer site)	Highest vs lowest (3)	0.3 (0.2–0.4)	$p < 0.01$	Age, area of residence, education, smoking, sex, veg.	Hospital-based Data from a network of case–control studies
Tzonou *et al.*, 1996a, Greece	43 SCC plus 56 ADC/200, M, F	FFQ about diet 1 y before onset of the disease (115), interviewed	Highest vs lowest (5)	SCC: 0.90 (0.67–1.21) ADC: 0.84 (0.65–1.08)	$p = 0.49$ $p = 0.17$	Gender, age, birthplace, schooling, height, analgesics, coffee drinking, alcohol, smoking, energy	Hospital-based
Launoy *et al.*, 1998, France	208 SCC/399, M	FFQ about diet of previous year (39), interviewed	Fresh fruit: > 180 vs < 60 g/d (4) Citrus fruit: > 60 vs < 20 g/d (4)	0.59 (0.35–1.00) 0.54 (0.33–0.89)	$p < 0.05$ $p < 0.05$	Age, interviewer, smoking, beer, aniseed aperitifs, hot Calvados, whisky, total alcohol, energy	Hospital-based
Bosetti *et al.*, 2000a, Italy	304 (SCC)/743, M, F	FFQ about diet 2 y before diagnosis (78), interviewed	Citrus fruit (5) Other fruit (5)	0.42 (0.25–0.71) 0.52 (0.31–0.87)	$p < 0.01$ $p < 0.05$	Age, sex, area of residence, education, smoking, alcohol, non-alcohol energy	Hospital-based in specific areas
Levi *et al.*, 2000, Switzerland	101 (SCC and ADC)/ 327, M, F	FFQ about diet of recent 2 y (79), interviewed	Citrus fruit: > 3.5 vs ≤ 1.5 servings/wk (3) Other fruit: > 3.5 vs ≤ 1.5 servings/wk (3)	0.22 (0.1–0.6) 0.20 (0.1–0.4)	$p < 0.01$ $p < 0.01$	Age, sex, education, smoking, alcohol and non-alcohol energy	Hospital-based

Table 18 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Cheng *et al.*, 2000a, UK	74 ADC/74, F	FFQ about diet of previous 3 y, interviewed	≥ 25.73 vs ≤ 12 items/wk (4)	0.18 (0.05–0.57)	$p = 0.003$	None	Population-based
Sharp *et al.*, 2001, UK	158 SCC/158, F	FQQ about diet of previous 3 y, interviewed	> 25.73 vs <12 times/wk (4)	0.64 (0.25–1.67)	$p = 0.394$	Slimming diet, breakfast, salad, years smoking, regular use of aspirin, centre, temperature of tea/coffee	Population-based
Terry *et al.*, 2001b, Sweden	189 ADC plus 167 SCC/815, M, F	FFQ about diet 20 y before interview (63) Information on fruits contributing to 13.1% of total fruit consumed in Sweden was not obtained	2.0 vs 0.2 median servings/d (4)	ADC: 0.7 (0.4–1.1) SCC: 0.6 (0.4–1.1)	$p = 0.08$ $p = 0.04$	Age, gender, energy, BMI, gastro-oesophageal reflux symptoms, smoking	Population-based
Wolfgarten *et al.*, 2001, Germany	85 (45 SCC, 40 ADC)/100, M, F	Interview about nutritional habits (1100)	≥ 101–180 g vs < 100 g/d (2)	SCC: [0.33 (0.12–0.91)] ADC: [0.16 (0.04–0.53)]	$p < 0.001$ $p < 0.001$		Population-based
Southern Asia and Turkey							
Notani & Jayant, 1987, India	236/215 (hospital-based) plus 177 (population-based), M	FFQ about usual diet before onset of the disease, interviewed	≥ once/wk vs < once/wk (2)	Hospital controls [1.01 (0.67–1.67)] Population controls [0.81 (0.5–1.25)]		Age, tobacco habits	Partly hospital-based, partly population-based
Memik *et al.*, 1992a, Turkey	78/610, M, F	Interview	Fresh fruit: 5 times/wk vs 0–1/wk (3)	[0.30 (0.14–0.64)]	$p < 0.001$		Hospital based [OR computed based on reported distribution of intake]

Table 18 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Phukan *et al.*, 2001, India	502/1004	Interview	Occasionally vs never (2)	0.3 (0.08–4.2)	$p < 0.01$		Hospital-based
Onuk *et al.*, 2002, Turkey	44/100, M, F	Information on dietary habits	Highest vs lowest (2)	[0.14 (0.06–0.31)]	$p < 0.001$		Hospital-based
Northern Asia							
Chang-Claude *et al.*, 1990, China	52 Subjects diagnosed with oesophagitis (42 M, 10 F)/486 (312 M, 174 F)	FFQ about diet in the past 5 y	Fresh fruit in summer: ≥ 1/wk vs < 1/wk (2)	0.31 (0.15–0.60)		Household status, age, gender, oesophagitis among siblings	Population-based All subjects underwent oesophagoscopy with biopsy. One third of subjects selected from a household with a case of oesophageal cancer
Li *et al.*, 1989, China	1242 (SCC, ADC and unknown types of oesophageal cancer)/1311, M, F	FFQ of diet in the late 1970s (recent) (72), interviewed	Fresh fruit: > 35 vs 0 times/y (4)	1.0 (0.8–1.2)		Age, sex, smoking	Population-based
Cheng *et al.*, 1992a, Hong Kong	400 (SCC, ADC and other)/1598, M, F	FFQ about recent diet (22), interviewed	Citrus fruit: Daily or more vs < once/y (6) Other fruit: Daily or more vs < once/y (6)	0.096 (0.036–0.26) 0.15 (0.05–0.45)	$p < 0.001$ $p < 0.001$	Age, educational attainment, birthplace	Hospital-based Chinese population
Gao *et al.*, 1994, China	902 (624 M, 278 F)/1552 (85 M, 701 F)	FFQ of diet 5 y before interview (81), interviewed	Highest vs lowest (4)	M 0.6 F 0.6	$p < 0.001$ $p = 0.11$	Age, education, birthplace, tea drinking, smoking and alcohol (only for men)	Population-based
Hu *et al.*, 1994, China	196/392, M, F	FFQ about recent diet and diet in 1966 (32), (interviewed, no mention which data were used)	Highest vs lowest (4)	1.5 (0.8–2.9)	$p = 0.29$	Alcohol, smoking, income, occupation	Hospital-based

Table 18 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hanaoka *et al.*, 1994, Japan	139/136, M	FFQ of diet before onset of the disease	5–7 vs < 1/wk (4)	0.50 (0.18–1.39)	$p = 0.19$	Alcohol	Hospital-based
Cheng *et al.*, 1995, Hong Kong	67 never-smokers and 53 never-drinkers/ 539 never-smokers, 407 never-drinkers, M, F	FFQ about recent diet (22), interviewed	Citrus fruit: Daily vs ≤ 3 times/wk (3)	Never smokers: 0.39 (0.16–0.98) Never drinkers: 0.59 (0.23–1.52)	$p = 0.007$ $p = 0.183$	Gender, age, educational attainment, place of birth, preference for hot drinks or soups, green leafy veg., pickled veg., alcohol, tobacco	Hospital-based Chinese population
Gao *et al.*, 1999, China	81/234, M, F	FFQ, interviewed	≥ once/wk vs < once/mo (3)	0.75 (0.36–1.55)		Age, sex	Population-based
Yokoyama *et al.*, 2002, Japan	234/634, M	FFQ (na)	Almost every day vs seldom (5)	[0.78 (0.28–2.17)]		Age	Hospital-based. Controls were attending for health check-ups

*p for trend when applicable. ADC, adenocarcinoma; SCC, squamous-cell carcinoma

Table 19. Cohort studies of vegetable consumption and risk of oesophageal cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hirayama, 1990, Japan	585/265 118, M, F 17 y	FFQ (7)	Green-yellow veg.: Daily vs non-daily (2)	1.06 (90% CI, 0.91–1.24)		Age-adjusted rates	Mortality Census-based cohort in seven prefectures
Yu *et al.*, 1993, China	1162/12 693. M, F 15 y	Interview about diet	Fresh veg.: Regular, occasionally vs never (2)	0.66 (0.44–0.99)	$p = 0.044$	Age, sex	Incidence Interviews performed in 1989 in subjects recruited in 1974 for screening
Guo *et al.*,1994, China	639/3200, M, F	FFQ for diet during the past 12 months	Fresh veg.: ≥ 60 vs ≤ 30 times/mo (3)	0.8 (0.6–1.0)	$p = 0.08$	Years of smoking, cancer history in first-degree relatives	Incidence Nested case–control study in randomized control trial
Sauvaget *et al.*, 2003, Japan	80/38 540, M, F	FFQ (22) self-administered	Green-yellow veg.: Daily vs once/wk or less (3)	0.89 (0.48–1.63)	$p = 0.63$	Sex, age, radiation dose, city, BMI, smoking status, alcohol habits, education level	Mortality Atomic bombing survivors

*p for trend when applicable

Table 20. Case–control studies of vegetable consumption and risk of oesophageal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
North America							
Ziegler *et al.*, 1981, USA	120/250, M, black	FFQ about subjects' usual adult diet before 1974 (31, 4 veg.), interviewed	Highest vs lowest (3)	[0.63]	$p < 0.10$	Alcohol	Study based on death from oesophageal cancer (cases) or other causes (controls) Interviews with next of kin completed for 67% of cases and 71% of controls
Brown *et al.*, 1988, USA	Incidence 74/156, M Mortality 143/285, M	FFQ about usual adult diet, interviewed	Highest vs lowest (3)	0.7 (0.4–1.3)	NS	Smoking, alcohol	Hospital- and population-based Incidence and mortality series
Brown *et al.*, 1995, USA	174 ADC/750, M white	FFQ about usual adult diet (60), interviewed	Highest vs lowest (4)	0.6	$p = 0.20$	Age, area, smoking, liquor use, income, energy, BMI	Population-based
Brown *et al.*, 1998,USA	333 (114 white, 219 black) SCC/1238 (681 white, 557 black) M	FFQ about usual adult diet (60)	Highest vs lowest (4)	White: 0.4 Black: 1.0	$p = 0.06$ $p = 0.89$	Age, area, smoking, alcohol, energy	Population-based
Chen *et al.*, 2002a, USA	124 ADC/449, M, F	Short FFQ about diet before 1985 (54), interviewed by telephone	Highest vs lowest (4)	0.45 (0.2–1.0)	$p = 0.04$	Age, sex, energy, respondent type, BMI, alcohol, education, family history, vitamin supplement use, age squared	Population-based
South America							
De Stefani *et al.*, 1990b, Uruguay	261 SCC/522, M, F	FFQ of recent diet, interviewed	Daily vs < once/wk (4)	0.56 (0.3–1.0)		Age, residence, smoking duration, type of tobacco, alcohol	Hospital-based
Castelletto *et al.*, 1994, Argentina	131 SCC/262, M, F	FFQ about recent diet and diet 10 y before admission (10), interviewed	> 3/wk vs < 1/wk (3)	Raw veg.: 0.9 (0.3–2.6) Cooked veg.: 0.7 (0.2–2.2)		Age, sex, hospital, education, average number of cigarettes/d, alcoho, barbecued meat, potatoes, raw or cooked veg.	

Table 20 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Rolón *et al.*, 1995, Paraguay	131/381, M, F	FFQ about current diet (50), interviewed	Highest vs lowest (4)	0.8 (0.3–1.8)	$p = 0.71$	Lifetime consumption of alcohol, smoking, age group, sex, hospital group, meats, fats, fish, milk	Hospital-based
De Stefani *et al.*, 1999, Uruguay	66/393, M, F	FFQ (64), interviewed	Highest vs lowest (3)	0.7 (0.5–0.9)		Age, sex, residence, urban/rural status, education, BMI, smoking (pack-years), alcohol, energy	Hospital-based Controls for analysis of oral/pharyngeal, laryngeal and oesophageal cancer
Castellsagué *et al.*, 2000, Argentina, Brazil, Paraguay, Uruguay	830 SCC/1779, M, F	FFQ about recent diet (50) interviewed	Almost daily/daily vs never/rarely (3)	0.62 (0.44–0.88)	$p = 0.08$	Sex, age group, hospital residence, years of education, smoking, alcohol	Hospital-based Pooled analysis from four main studies (Victora *et al.*,1987; De Stefani *et al.*, 1990b; Castelletto *et al.*, 1994; Rolón *et al.*, 1995); together with additional subjects from Uruguay
De Stefani *et al.*, 2000b, Uruguay	111 SCC/444, M, F	FFQ (64), interviewed	≥ 127.7 vs ≤ 53.8 g/d (4)	0.64 (0.34–1.20)	$p = 0.04$	Age, gender, residence, urban/rural status, education, BMI, smoking, alcohol, energy	Hospital based
Europe							
Francheschi *et al.*, 1990, Italy	68/505, M	FFQ about diet of last year (40), interviewed	≥ 14 vs < 7 servings/wk (3)	[0.37]			Hospital-based No cancer registry, unknown number of cases in the area OR computed based upon distribution of cases/controls

Table 20 (contd)

Author, year, country	Cases/controls gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Negri *et al.*, 1991, Italy	294/6147, M, F	FFQ (14–37, depending on cancer site)	Green veg.: Highest vs lowest (3)	0.2 (0.1–0.3)	$p < 0.01$	Age, area of residence, education, smoking, sex, fruit consumption	Hospital-based Data from a network of case–control studies
Tuyns *et al.*, 1987, France	331/1975, M, F	FFQ about usual diet (40), interviewed	Fresh veg.: Highest versus lowest (4)	0.58	$p = 0.029$	Age, alcohol, smoking, urban or rural residence	Population-based
Tzonou *et al.*, 1996a, Greece	43 SCC plus 56 ADC/200, M, F	FFQ about diet one year before onset of disease (115), interviewed	(5)	SCC: 0.97 (0.74–1.28) ADC: 0.62 (0.48–0.80)	$p = 0.83$ $p = 0.0003$	Gender, age, birthplace, schooling, height, analgesics, coffee drinking, alcohol, smoking, energy	Hospital-based
Launoy *et al.*,1998, France	208 SCC/399, M	FFQ about diet of previous year (39), interviewed	> 400 vs < 200 g/d (4)	0.24 (0.11–0.55)	$p < 0.001$	Age, interviewer, smoking, beer, aniseed aperitifs, hot Calvados, whisky, total alcohol, energy, other significant food groups (butter, fresh fish, oil, veg.)	Hospital-based
Bosetti *et al.*, 200a, Italy	304 SCC/743, M, F	FFQ about diet of 2 y before diagnosis (78), interviewed	Raw veg.: 12.6 vs < 3.9 servings/wk (5) Cooked veg: > 4.3 vs < 1.4 servings/wk (5)	0.32 (0.19–0.55) 0.79 (0.47–1.31)	$p < 0.001$ NS	Age, sex, area of residence, education, smoking, alcohol, non-alcohol energy	Hospital-based in specific areas
Cheng *et al.*, 2000a, UK	74 ADC/74, F	FFQ about diet of previous 3 y, interviewed	≥ 25.90 vs ≤ 15.37 items/wk (4)	0.58 (0.22–1.55)	$p = 0.371$		Population-based

Table 20 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Levi *et al.*, 2000, Switzerland	101 (SCC and ADC)/327, M, F	FFQ about diet of recent 2 y (79), interviewed	Raw veg.: > 9.5 vs ≤ 5.5 servings/wk (3) Cooked veg.: > 8.0 vs ≤ 5.3 servings/wk (3)	0.14 (0.1–0.4) 0.19 (0.1–0.3)	$p < 0.01$ $p < 0.01$	Age, sex, education, smoking, alcohol and non-alcohol total energy intake	Hospital-based
Terry *et al.*, 2001b, Sweden	189 ADC plus 167 SCC/ 815, M, F	FFQ about diet 20 y before interview (63)	3.3 vs 1.1 median servings/d (4)	ADC: 0.5 (0.3–0.8) SCC: 0.6 (0.4–1.0)	$p = 0.001$ $p = 0.02$	Age, gender, energy, BMI, gastro-oesophageal reflux symptoms, smoking	Population-based Information on vegetables which contribute to 3.5% of total veg. consumed in Sweden were not obtained
Southern Asia and Turkey							
Notani & Jayant, 1987, India	236/215 (hospital-based)/177 (from population), M	FFQ about usual diet before onset of the disease, interviewed	Daily vs not daily (2)	Population controls [0.38 (0.23–0.67)] Hospital controls [1.08 (0.71–1.67)]		Age, tobacco habits	Partly hospital-based, partly population-based
Memik *et al.*, 1992a, Turkey	78/610, M, F	Interview	≥ 5 vs 0–1 times/wk (3)	[0.34]			Hospital-based
Phukan *et al.*, 2001, India	502/1004	Interview	Green leafy veg.: Daily vs never (4)	0.26 (0.01–2.9)	$p < 0.01$	NA	Hospital-based
Onuk *et al.*, 2002, Turkey	44/100, M, F	Information on dietary habits	Highest vs lowest (2)	[0.10 (0.04–0.23)]	$p < 0.001$		Hospital-based
Northern Asia							
Chang-Claude *et al.*, 1990, China	52 subjects with oesophagitis (42 M, 10 F)/486 (312 M, 174 F)	FFQ about diet in the past five years, interviewed	Green veg.: in winter: ≥ 1 vs < 1/wk (2) Raw veg.: ≥ 1 vs < 1/mo (2)	M 0.9 (0.4–2.1) F 0.3 (0.1–1.4) M 1.3 (0.6–2.6) F 0.2 (0.1–0.7)		Household status	All subjects underwent oesophagoscopy with biopsy One third of subjects selected from a household with a case of oesophageal cancer

Table 20 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Li *et al.*, 1989, China	1243 (SCC, ADC and unknown types of cancer)/ 1314, M, F	FFQ of diet in the late 1970s (recent) (72), interviewed	Fresh veg.: > 973 vs < 483 times/y (4)	1.5 (1.2–1.9)		Age, sex, smoking	Population-based
Cheng *et al.*, 1992a, Hong Kong	400 (SCC, ADC, other)/1598, M, F	FFQ about recent diet (22), interviewed	Green leafy veg.: Daily or more vs ≤ 3 times/ wk (3)	0.39 (0.26–0.59)	$p > 0.001$	Age, educational attainment, birth-place	Hospital-based Chinese popu-lation
Gao *et al.*,1994, China	902 (624 M, 278 F)/ 1552 (851 M, 701 F)	FFQ of diet five years before interview (81), interviewed	Highest vs lowest (4)	M 0.8 F 0.9	$p < 0.05$ $p = 0.25$	Age, education, birthplace, tea drinking, smoking and alcohol (only for men)	Population-based
Cheng *et al.*, 1995, Hong Kong	67 never-smokers, and 53 never-drinkers/539 never-smokers and 406 never-drinkers, M, F	FFQ about recent diet (22), inter-viewed	Green leafy veg.: Daily vs ≤ 3 times/wk (3)	Never-smokers: 0.33 (0.14–0.80) Never-drinkers: 0.65 (0.23–1.83)	$p = 0.026$ $p = 0.231$	Gender, age, educational attain-ment, place of birth, preference for hot drinks or soups, citrus fruits, pickled veg., smoking, alcohol	Hospital-based Chinese popula-tion
Hanaoka *et al.*, 1994, Japan	139/136, M, F	FFQ of diet before onset of the disease	5–7 vs < 1/wk (4)	Green veg.: (0.82 (0.20–3.09) Yellow veg.: 2.32 (0.70–7.61)	$p = 0.79$ $p = 0.16$	Alcohol	Hospital-based
Hu *et al.*, 1994, China	196/392, M, F	FFQ about recent diet and diet in 1966 (32), inter-viewed (no men-tion which data were used)	Total fresh veg.: highest vs lowest (4)	0.6 (0.3–1.06)	$p = 0.05$	Alcohol, smoking, income, occupation	Hospital-based
Gao *et al.*, 1999, China	81/228, M, F	FFQ, inter-viewed	Raw veg.: Frequently vs never (3)	0.07 (0.03–0.19)		Age, sex	Population-based
Yokoyama *et al.*, 2002, Japan	234/634, M	FFQ	Green-yellow veg.: Almost every day vs seldom (5)	[0.87 (0.10–7.14)]		Age	Hospital based Controls were attending for health check-ups

*p for trend when applicable; ADC, adenocarcinoma, SCC, squamous-cell carcinoma

Table 21. Case–control studies of fruit and vegetable consumption and risk of oesophageal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Pottern *et al.*, 1981, USA	120/250, M, black	FFQ about subjects' usual adult diet before 1974 (31), interviews with next of kin	Highest vs lowest (3)	[0.5]	$p < 0.05$	Alcohol	Study based on death from oesophageal cancer (cases) or other causes (controls) Interviews with next of kin completed for 67% of cases and 71% of controls
Ziegler *et al.*, 1981 ,USA	120/250, M, black	FFQ about subjects' usual adult diet before 1974 (31, 3 fruits, 4 veg.), interviewed	Highest vs lowest (3)	[0.50]	$p < 0.05$	Alcohol	Population-based; deaths from oesophageal cancer (cases) or other causes (controls) Interviews with next of kin completed for 67% of cases and 71% of controls
Yu *et al.*, 1988, USA	275/275, M, F	FFQ about usual consumption, interviewed	Fresh fruit or raw veg.: ≥ 5 vs ≤ 1 items/wk (3)	Directly interviewed: [0.40 (0.15–1.11)] All pairs: [0.43 (0.23–0.83)]	$p < 0.01$ $p < 0.001$		Neighbourhood controls. Only 129 cases directly interviewed, otherwise with next of kin
Brown *et al.*, 2001, USA	347 (SCC)/1354, M	FFQ about usual adult diet (60)	Raw fruits and veg.: > 18.3 vs < 7.1 servings/wk (4)	White: [0.50 (0.26–0.91)] Black: [0.59 (0.32–1.00)]		Age, study area, years of cigarette smoking, alcohol, race	Population-based
Terry *et al.*, 2001b, Sweden	189 ADC plus 167 SCC/815, M, F	FFQ about diet 20 y before interview (63)	4.8 vs 1.5 median servings/d (4)	ADC: 0.5 (0.3–0.8) SCC: 0.6 (0.4–1.0)	$p = 0.005$ $p = 0.01$	Age, gender, energy, BMI, gastro-oesophageal reflux symptoms, smoking	Population-based Information on fruits and veg. which contribute 3.5 % of total veg. and 13.1% of fruit consumed in Sweden was not obtained
De Stefani *et al.*, 2000b, Uruguay	111/444, M, F	FFQ (64), interviewed	≥ 343 vs ≤ 155.7 g/d	0.22 (0.11–0.45)	$p < 0.001$	Age, gender, residence, urban/rural status, education, BMI, smoking, alcohol, energy	Hospital-based

*p for trend when applicable; ADC, adenocarcinoma, SCC, squamous-cell carcinoma

Table 22. Cohort studies of fruit consumption and risk of stomach cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Chyou *et al.*, 1990, Hawaii (Japanese)	111/361 (subcohort), M 18 y	24-h recall, interviewed (54)	≥ 301 vs 0 g/d (4)	0.8 (0.4–1.3)	$p = 0.20$	Age, smoking	Case–cohort Incidence All cohort: 8006
Nomura *et al.*, 1990, Hawaii (Japanese)	149/7839, M 19 y	FFQ (20)	≥ 5 vs ≤ 1/wk (3)	0.8 (0.5–1.3)		Age	Incidence
Kneller *et al.*, 1991, USA	75/17 633, M 20 y	FFQ (35), self-administered	Highest vs lowest (4)	1.5 (0.75–2.93)	NS	Age, cigarette smoking	Mortality
Kato *et al.*, 1992, Japan	57/9753, M, F 6 y	FFQ (25), self-administered	Daily vs ≤ 1–2/wk (3)	1.92 (1.03–3.59)	$p = 0.035$	Age, sex	Mortality
Guo *et al.*, 1994, China	538/2695, M, F 5 y	FFQ, interviewed	≥ once/mo vs none/mo (2)	0.9 (0.8–1.1)		Matched by age and sex. Adjusted for years of smoking and cancer history in first-degree relatives	Incidence Nested case–control in randomized controlled trial Similar finding for cardia/non-cardia cancer
Inoue *et al.*, 1996, Japan	69/972, M, F 6 y	FFQ, self-administered	Daily vs rare (3)	Without atrophic gastritis: 0.55 (0.22–1.35)		Sex, age	Incidence Similar finding in subtypes with atrophic gastritis
Botterweck *et al.*, 1998, Netherlands	281/3123 (subcohort), M, F 6.3 y	FFQ (150, 8 fruits)	≥ 325 vs ≤ 46 g/d (5)	0.97 (0.64–1.48)	$p = 0.51$	Age, sex, smoking, education, stomach disorders, family history of gastric cancer, veg.	Incidence Case–cohort analysis All cohort: 120 852
Galanis *et al.*, 1998, Hawaii (Japanese)	108/11 907, M, F 14.8 y	FFQ (13), interviewed	≥ 7 vs < 7/wk (2)	0.6 (0.4–0.9)		Age, education, Japanese place of birth, gender (analyses among men: smoking, alcohol)	Incidence
McCullough *et al.*, 2001, USA	910/436 654 M, 439/533 391 F 14 y	FFQ (32), self-administered	Citrus fruit: Highest vs lowest (3)	M: 0.88 (0.75–1.03) F: 0.97 (0.78–1.21)	$p = 0.11$ $p = 0.79$	Age, education, smoking, BMI, multivitamin and vitamin C use, aspirin use, race, family history	Mortality

Table 22 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Kobayashi *et al.*, 2002, Japan	404/39 993, M, F 10 y	FFQ (44), self-administered	Almost daily vs < 1 d/wk (4)	0.70 (0.48–1.01)	$p = 0.25$	Age, sex, area, education, smoking, BMI, alcohol, vitamin A, C, E supplement use, energy, salted food, history of peptic ulcer, family history of gastric cancer	Incidence, similar finding when cases in first 2 y excluded
Sauvaget *et al.*, 2003, Japan	617/38 540, M, F 17 y	FFQ (22), self-administered	Daily vs 0–1 d/wk (3)	0.80 (0.65–0.98)	$p = 0.03$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors

*p for trend when applicable

Table 23. Case–control studies of fruit consumption and risk of stomach cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Correa *et al.*, 1985, USA	Whites: 189/190, M, F Blacks 189/190, M, F	FFQ (59), interviewed	Highest vs lowest (4)	Whites: 0.47 (0.24–0.92) Blacks: 0.33 (0.16–0.66)	$p < 0.005$ $p < 0.001$	Matched by race, sex and age (within 5 y). Adjusted for sex, respondent status, income, duration of smoking	Hospital-based Similar finding by histological type
Jedrychowski *et al.*, 1986, Poland	110/110, M, F	FFQ, interviewed	Daily or almost daily vs less frequently (3)	[0.31 (0.15–0.64)]		Matched by sex and age, adjusted for residence and smoking	Hospital-based
La Vecchia *et al.*, 1987b, Italy	206/474, M, F	FFQ (29) interviewed	Fresh fruit: Highest vs lowest (3). Citrus fruit: Highest vs lowest (3)	0.73 0.63	NS $p = 0.11$	Age, sex, education, areas of residence, other dietary factors	Hospital-based
Kono *et al.*, 1988, Japan	26/793 hospital, 91 population, M, F	FFQ, interviewed	Fruit, other than mandarin oranges: Daily vs less (2)	Hospital controls: 0.7 (0.4–1.0) Population controls: 0.5 (0.3–0.8)	$p = 0.08$ $p = 0.008$	Matched by age, sex and residence. Adjusted for smoking, mandarin orange, green tea	Hospital-based and population-based

Table 23 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
You *et al.*, 1988, China	564/1131, M, F	FFQ (85, 9 fruits), interviewed	Fresh fruit: > 30 vs < 5 kg/y (4)	0.6 (0.4–0.8)		Matched by age and sex. Adjusted for sex, age and family income	Population-based
Coggon *et al.*, 1989, UK	94/185, M, F	FFQ (6), interviewed or self-administered	Fresh or frozen fruit: > 5 vs <1 time/wk (3)	0.6 (0.2–1.5)		Matched by age (2 y), sex. Adjusted for length of refrigerator use, salad veg. in winter, salt, smoked meat or fish (including bacon), socioeconomic status	Population-based
De Stefani *et al.*, 1990a, Uruguay	210/630, M, F	FFQ, interviewed	5–7 vs 2 or less times/wk (3)	[0.36 (0.23–0.56)]	$p < 0.001$	Matched by age and sex. Adjusted for age, sex, residence, smoking duration, wine ingestion, meat, salted meat, veg. and 'mate'	Hospital-based
Kato *et al.*, 1990, Japan	289/1247, M 198/1767, F	FFQ (10), self-administered	Almost daily vs ≤ once or twice per month (3)	M: 0.83 (0.51–1.33) F: 0.77 (0.33–1.78)		Age, residence	Hospital-based Significant reduction for intestinal type in females
Lee *et al.*, 1990, Taiwan, China	210/810, M, F	FFQ, interviewed	≥ 6 vs ≤ 1/w Estimated at age ≤ 20 y Estimated at age 20–39 y	0.91 1.0		Matched by age, sex, hospital	Hospital-based
Wu-Williams *et al.*, 1990, USA	130/135, M	FFQ, interviewed or self-administered	5 or more times/wk vs once or less/wk (3)	[0.67 (0.29–1.67)]		Matched by sex, age, race	Population-based
Boeing *et al.*, 1991a, Germany	143/579, M, F	FFQ (74), interviewed	Highest vs lowest (3)	0.56 (0.35–0.91)	$p > 0.05$	Age, sex, hospital	Hospital-based
Gonzalez *et al.*, 1991, Spain	354/354, M, F	Dietary history questionnaire (77), interviewed	Other [than citrus] fruit: Highest vs lowest (4)	0.7 (0.4–1.2)	$p = 0.08$	Matched by age, sex, and area of residence. Adjusted for energy intake	Hospital-based

Table 23 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Yu & Hsieh, 1991, China	52 M, 32 F	Questionnaire, interviewed or self-administered	Users vs non-users (2)	0.5 (0.3–0.8)		Age, sex, family income, family history of gastric cancer, family history of other cancer, history of tuberculosis, blood type, cigarette smoking, alcohol, strong tea, milk	Population-based
Hoshiyama & Sasaba, 1992, Japan	216/483, M	FFQ (24), interviewed	≥ 5 vs ≤ 1/wk (3)	0.8 (0.5–1.3)	$p = 0.34$	Age, smoking, other dietary variables	Population-based
Jedrychowski *et al.*, 1992, Poland	741/741, M, F	FFQ, interviewed	Highest vs lowest (3)	0.72 (0.56–0.94)	$p = 0.015$	Matched by sex and age. Adjusted for age, sex, education, occupation of the index person and for residence, source of veg. and fruits, and status of the respondent (index person, other)	Hospital-based
Memik *et al.*, 1992,Turkey	106/609, M, F	FFQ	≥ 5 vs ≤ 1/w (3)	[0.54]		Matched for age and sex	Population-based
Palli *et al.*, 1992, Italy	923/1159, M, F	FFQ (146), interviewed	Citrus fruit: Highest vs lowest (3) Other fresh fruit: Highest vs lowest (3)	0.3 (0.2– 0.6)[1] 0.6 (0.4–0.7) [2] 0.2 (0.1–0.5) [1] 0.4 (0.3–0.6)[2] [1]Gastric cardia [2]Other sites		Age, sex, area, place of residence, migration from the south, socioeconomic status, familial gastric cancer history, Quetelet index	Population-based
Sanchez-Diez *et al.*, 1992, Spain	87/107, M, F	FFQ, interviewed	Daily vs no (2)	[0.31 (0.11–0.87)]	$p < 0.05$	Matched by age, sex, municipality of residence	Population-based
Tuyns *et al.*, 1992, Belgium	449/3524, M, F	Dietary history questionnaire	Fresh fruit ≥ 1538 vs ≤ 300 g/w (4)	0.56	$p < 0.001$	Sex, age, province	Population-based
Ramon *et al.*, 1993, Spain	117/234, M, F	FFQ (89), interviewed	≥ 461.4 vs ≤ 355.7 g/d (4)	0.85 (0.21–1.11)		Matched by sex, age, telephone ownership. Adjusted for sex, age, education, cigarettes, rice, cereals, pickled veg., salt intake	Population-based

Table 23 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Inoue *et al.*, 1994, Japan	668/668, M, F	FFQ, self-administered	≥ 3 vs < 3/w (2)	0.86 (0.70–1.10)	$p > 0.05$	Matched by age, sex, time of hospital visit. Adjusted for sex	Hospital-based
Cornée *et al.*, 1995, France	92/128, M, F	FFQ (30, 9 for fruits and veg.), interviewed	Highest vs lowest (3)	0.50 (0.25–1.03)	$p = 0.02$	Matched by age, sex (group matching). Adjusted for age, sex, occupation, energy	Hospital-based
Muñoz *et al.*, 1997, Italy	88/103, M, F	FFQ (36), interviewed	≥ 11 vs < 5/w (3)	0.47 (0.21–1.05)	$p < 0.05$	Sex, age, area of residence, education	Hospital-based, subject with family history
Xu *et al.*, 1996, China	293/959, M, F	FFQ, interviewed	≥ 55 vs 0 g/d (4)	0.5 (0.4–0.8)		Matched by sex, age. Adjusted for age, smoking, education, veg. consumption, stomach disease, family stomach cancer, veg. consumption	Iron and steel workers
Harrison *et al.*, 1997, USA	91 (60 intestinal, 31 diffuse)/132, M, F	FFQ, self-administered	Increase in one standard deviation	Intestinal: 0.5 (0.3–0.9) Diffuse: 0.5 (0.2–1.0)	$p < 0.05$ $p < 0.05$	Energy, age, sex, race, education, smoking, alcohol, BMI	Hospital-based
La Vecchia *et al.*, 1997, Italy	746/2053, M, F	FFQ, (29, 3 fruits), interviewed	≥ 3 different types of fruit/wk vs < 2/wk (3)	0.6 (0.5–0.8)	$p < 0.001$	Age, sex, area of residence, education, family history of gastric cancer, total number of serving, BMI, energy	Hospital-based
Ji *et al.*, 1998, China	M: 770/819 F: 354/632	FFQ (74), interviewed	Fresh fruit: ≥ 18.1 vs ≤ 1.6 servings/mo (4)	M 0.4 (0.3–0.6) F: 0.5 (0.3–0.8)	$p < 0.0001$ $p < 0.0006$	Matched by age and sex. Adjusted for age, income, education, smoking, alcohol	Population-based
Gao *et al.*, 1999, China	153/234, M, F	FFQ, interviewed	≥ 1 times/wk vs < 1 time/mo (3)	0.88 (0.47–1.67)		Matched by age, sex and neighbourhood. Adjusted for age and sex	Population-based

Table 23 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Ward & Lopez-Carrillo, 1999, Mexico	220/752, M, F	FFQ (70, 17 fruits), interviewed	≥ 5 times/d vs < 2 times/d (4)	1.0 (0.5–2.2)	$p = 0.67$	Matched by age. Adjusted for age, sex, energy, chili pepper consumption, added salt, history of peptic ulcer, cigarettes, socioeconomic status	Population-based Similar finding by histolory
Ekström *et al.*, 2000, Sweden	Cardia 73, non-cardia 404/1059, M, F	FFQ (45), dietary habits 20 years before interview	< 1/d vs ≤ 2/w (4)	Cardia: 0.5 (0.2–1.0) Non-cardia: 0.6 (0.4–0.8)	$p = 0.03$ $p < 0.01$	Matched by age, sex. Adjusted for age, sex, energy, smoking, BMI area, number of siblings, socioeconomic status, number of meals/day, multivitamin supplements, table salt use, urban environment	Population-based Similar finding by histology
Huang *et al.*, 2000, Japan	1111/26 996, M, F	FFQ, self-administered	≥ 3 times/wk vs ≤ 3 times/mo	Gastric cancer family history (+): 1.39 (0.69–2.82) Gastric cancer family history (–): 1.11 (0.74–1.67)		Age, sex, smoking, drinking, pickled veg., fruit, raw veg., carrots, lettuce, pumpkin	Hospital-based
Mathew *et al.*, 2000, India	194/305, M, F	FFQ, interviewed	> 9 vs ≤ 3/wk (4)	0.7 (0.2–3.6)	$p = 0.99$	Matched by age, sex, religion, residential area. Adjusted for age, sex, religion, income, smoking, alcohol	Hospital-based
De Stefani *et al.*, 2001, Uruguay	160/320, M, F	FFQ (64, 9 fruits), interviewed	≥ 195.9 vs ≤ 99.3 g/d (3)	0.35 (0.21–0.59)	$p < 0.001$	Matched with sex, age, residence and urban/rural status. Adjusted for age, sex, residence, urban/rural status, education, BMI, energy, veg.	Hospital-based Tubers and legumes excluded
Hamada *et al.*, 2002, Brazil	96/192, M, F	FFQ (30), interviewed	Daily vs ≤ 3–4 d/wk (2)	0.4 (0.2–0.9)		Matched by gender, age. Adjusted for country of birth, beef intake	Hospital-based and population-based, Japanese

Table 23 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Kim *et al.*, 2002, Korea	136/136, M, F	FFQ (109) interviewed	Highest vs lowest (3)	0.67 (0.33–1.39)	$p = 0.56$	Matched by sex and age. Adjusted for sex, age, socioeconomic status, family history, refrigerator use	Hospital-based
Nishimoto *et al.*, 2002, Brazil	236/236, M, F	FFQ (30), interviewed	Daily vs ≤ 1 d/wk (4)	0.6 (0.3–1.2)	$p = 0.08$	Matched by gender, age. Adjusted for race, education, smoking, other veg. intake	Hospital-based, non-Japanese
Ito *et al.*, 2003, Japan	508 (156 differentiated, 352 non-differentiated)/ 36 490, F	FFQ, self-administered	Every day vs almost never (4) Differentiated Non-differentiated	0.68 (0.40–1.16) 0.31 (0.15–0.65) 1.16 (0.54–2.52)	$p < 0.001$ $p < 0.05$ $p < 0.05$	Age, year, season of visit, smoking, family history of gastric cancer	Hospital-based Cases restricted to those with histology subtype available (69%) Control response 90%

*p for trend when applicable

Table 24. Cohort studies of vegetable consumption and risk of stomach cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Chyou *et al.*, 1990, Hawaii (Japanese)	111/361 (subcohort), M, 18 y	24-h recall, interviewed (54)	≥ 80 g/d vs none (4)	0.7 (0.4–1.1)	$p = 0.001$	Age, smoking	Case–cohort, incidence All cohort: 8006
Kneller *et al.*, 1991, USA	75/17 633, M 20 y	FFQ, self-administered (35)	Highest vs lowest (4)	0.9 (0.48–1.78)	NS	Age, cigarette smoking	Mortality
Kato *et al.*, 1992, Japan	57/9753, M, F 6 y	FFQ, self-administered (25)	Green-yellow veg.: Daily vs < 1–2/wk (3) Other veg.: Daily vs < 1–2/wk (3)	1.54 (0.77–3.11) 1.15 (0.59–2.27)	$p = 0.23$ $p = 0.57$	Age, sex	Mortality Rural population

Table 24 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Guo *et al.*, 1994, China	538/2695, M, F 5 y	FFQ, interviewed	Fresh veg.: ≥ 60 vs ≤ 30 times/mo (3)	1.1 (0.8–1.4)		Matched by age and sex. Adjusted for years of smoking and cancer history in first-degree relatives	Incidence Nested case–control in randomized controlled trial
Inoue *et al.*, 1996, Japan	69/972, M, F 6 y	FFQ, self-administered	Raw veg.: Daily vs rare (3) Green-yellow veg.: Daily vs rare (3)	0.67 (0.29–1.57) 0.74 (0.17–3.20)		Sex, age	Incidence Similar findings in subjects with atrophic gastritis
Botterweck *et al.*, 1998, Netherlands	264/2953 (subcohort), M, F 6.3 y	FFQ (150, 17 veg.)	≥ 286 vs ≤ 103 g/d (5)	0.86 (0.58–1.26)	$p = 0.25$	Age, sex, smoking, education, stomach disorders, family history of gastric cancer, total fruit consumption	Incidence Case–cohort analysis. All cohort: 120 852
Galanis *et al.*, 1998, Hawaii (Japanese)	108/11 907, M, F 14.8 y	FFQ (13), interviewed	Raw veg.: ≥ 7 vs < 7/wk (2)	0.8 (0.5–1.2)		Age, education, Japanese place of birth, gender (analyses among men; also smoking and alcohol)	Incidence
McCullough *et al.*, 2001, USA	910/436 654, M 439/533 391, F 14 y	FFQ (32), self-administered	M: ≥ 13 vs < 8 d/wk (3) F: > 14 vs < 9 d/wk (3)	M: 0.89 (0.76–1.05) F: 1.25 (0.99–1.58)	$p = 0.17$ $p = 0.06$	Age, education, smoking, BMI, multivitamin and vitamin C use, aspirin use, race, family history	Mortality
Kasum *et al.*, 2002, USA	56 /34 351, F 14 y	FFQ (127), self-administered	Yellow/orange veg.: 3.5–106 vs 0–1 servings/wk (3)	0.63		Age, energy, alcohol, smoking	Incidence
Kobayashi *et al.*, 2002, Japan	404/39 903, M, F 10 y	FFQ (44), self-administered	Highest vs lowest (5)	0.75 (0.54–1.04)	$p = 0.17$	Age, sex, area, education, smoking, BMI, alcohol, vitamin A, C, E supplement use, energy, salted food, history of peptic ulcer, family history of gastric cancer	Incidence Similar finding when first two years' cases excluded. Significant inverse association only for differentiated histology type
Sauvaget *et al.*, 2003, Japan	617/38 540, M, F 17 y	FFQ (22), self-administered	Green-yellow veg.: Daily vs 0–1 d/wk (3)	0.91 (0.74–1.13)	$p = 0.35$	Age, sex, radiation dose, city, BMI, smoking alcohol, education	Mortality, atomic bombing survivors

*p for trend when applicable

Table 25. Case–control studies of vegetable consumption and risk of stomach cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Correa *et al.*, 1985, USA	Blacks 186/190, M, F	FFQ (+food preparation, preservation methods) (59), interviewed	Highest vs lowest (4)	0.50 (0.25–1.00)	$p < 0.05$	Matched by race, sex, and age (within 5 y). Adjusted for age, sex, respondent status, income, duration of smoking	Hospital-based Study also included whites, but association with veg. not reported for them
Risch *et al.*, 1985, Canada	246/246, M, F	Diet history (94), interviewed	Increase of 100 g/d	0.84 (0.72–0.96)	$p = 0.011$	Matched by sex, age, province of residence. Adjusted for total food intake, ethnicity, dietary fibre, nitrite, chocolate, carbohydrate, duration without refrigeration	Population-based
Jedrychowski *et al.*, 1986, Poland	110/110, M, F	FFQ, interviewed	Daily or almost daily vs less frequently (3)	[0.61 (0.25–1.49)]		Matched by sex and age. Adjusted for residence and smoking	Hospital-based
La Vecchia *et al.*, 1987b, Italy	206/474, M, F	FFQ (29), interviewed	Total green veg.: Highest vs lowest (3)	0.27	$p < 0.001$	Age, sex, education, areas of residence, other dietary factors	Hospital-based
Kono *et al.*, 1988, Japan	77/1583, M, F	FFQ, interviewed	Raw veg.: > 1/d vs < 3/mo (3) Green-yellow veg.: > 1/d vs < 3/mo (3)	0.8 1.3	$p > 0.05$ $p > 0.05$	Matched by age, sex and residence. Adjusted for occupational class	Hospital-based
You *et al.*, 1988, China	564/113, M, F	FFQ (85, 36 veg.), interviewed	Total fresh veg.: ≥ 156 vs ≤ 73 kg/y (4)	0.4 (0.3–0.6)		Matched by age and sex. Adjusted for sex, age and family income	Population-based
Buiatti *et al.*, 1989, Italy	1016/1159, M, F	FFQ (146), interviewed validated by pilot phase	Raw veg.: Highest vs lowest (3) Cooked veg.: Highest vs lowest (3)	0.6 1.1	$p < 0.001$ $p = 0.58$	Matched with age (5 y), sex, centre. Adjusted for sex, age, area, place of residence, migration from the south, socioeconomic status, familial gastric cancer history, Quetelet index	Population-based

Table 25 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
De Stefani *et al.*, 1990a, Uruguay	210/630, M, F	FFQ, interviewed	5–7 vs 2 or less times/wk (3)	[0.37 (0.23–0.59)]	$p < 0.001$	Matched by age and sex. Adjusted for age, sex, residence, smoking duration, wine ingestion, meat, salted meat, fruits and 'mate'	Hospital-based
Graham *et al.*, 1990, USA	186/181, M	FFQ, interviewed	Raw veg.: Highest monthly frequency vs less (2)	0.43 (0.23–0.78)		Matched by age, sex and neighbourhood. Adjusted for age, education	
Kato *et al.*, 1990, Japan	289/1247, M 138/1767 F	FFQ (10), self-administered	Raw veg.: Almost daily vs ≤ once or twice/mo (3)	M: 0.59(0.37–0.93) F: 0.84 (0.47–1.51)		Age and residence	Hospital-based Significant reduction for intestinal type in males
Boeing *et al.*, 1991a, Germany	143 /579, M, F	FFQ (74), interviewed	Highest vs lowest (3)	0.86 (0.54–1.36)	$p > 0.05$	Sex, age, hospital	Hospital-based
Gonzalez *et al.*,1991, Spain	354/354, M, F	Dietary history questionnaire (77), interviewed	Raw veg.: Highest vs lowest (4)	0.8	$p = 0.25$	Energy	Hospital-based Matched by age, sex, and area of residence
			Cooked veg.: Highest vs lowest (4)	0.6 (0.3–1.0)	$p = 0.12$	Energy and all groups of foods together	
Hoshiyama & Sasaba, 1992, Japan	216/483, M	FFQ (24), interviewed	Raw veg: ≥ 6 vs ≤ 1/wk (3)	0.6 (0.3–1.0)	$p < 0.04$	Age, smoking and other dietary variables	Population-based
			Green-yellow veg.: ≥ 8 vs ≤ 4/wk (3)	0.8 (0.4–1.4)	$p = 0.30$		
Jedrychowski *et al.*, 1992, Poland	741/741, M, F	FFQ, interviewed	Highest vs lowest (3)	0.60 (0.46–0.78)	$p < 0.001$	Matched by sex and age. Adjusted for age, sex, education, occupation of the index person and for residence, source of veg. and fruits, and status of the respondent (index person, other)	Hospital-based, multicentre Comparison based on dietary habits of case and control households

Table 25 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Mernik *et al.*, 1992, Turkey	117/609, M, F	FFQ	≥ 5 vs < 1/wk (3)	0.6 (0.31–1.23)	$p < 0.05$	Matched for age and sex	Population-based
Palli *et al.*, 1992, Italy	923/1159, M, F	FFQ (146), interviewed	Raw veg.: Highest vs lowest (3) Cooked veg.: Highest vs lowest (3)	0.4 (0.2–0.8)[1] 0.6 (0.3–0.8)[2] 1.5 (0.8–2.8)[1] 1.1 (0.9–1.4)[2] [1]Gastric cardia [2]All others		Age, sex, area, place of residence, migration from the south, socio-economic status, familial gastric cancer history, Quetelet index (tertile categories of weight/ height squared)	Population-based
Sanchez-Diez *et al.*, 1992, Spain	87/107, M, F	FFQ, interviewed	Daily vs none (2)	[0.70 (0.41–1.08)]		Matched by age, sex, municipality of residence	Population-based
Tuyns *et al.*, 1992, Belgium	449/3524, M, F	Diet history questionnaire	Cooked veg.: ≥ 1150 vs ≤ 600 g/wk (4) Raw veg.: ≥ 268 vs ≤ 80 g/wk (4)	0.33 0.4	$p < 0.001$ $p < 0.001$	Sex, age, province	Population-based
Hansson *et al.*, 1993, Sweden	338/669, M, F	FFQ (45), interviewed [1]Diet in adolescence [2]Diet consumed 20 years before interview	> 15 vs < 2.1 times/mo (4) Semi-continuous variables (effect per category)	[1]0.58 (0.37–0.89) [2]0.50 (0.32–0.78) [1]0.89 (0.77–1.03) [2]0.81 (0.70–0.94)	$p = 0.011$ $p = 0.005$	Age, gender, and socioeconomic status Age, gender, socio-economic status, consumption of a food item during adolescence and 20 years before interview	Population-based
Ramon *et al.*, 1993, Spain	117/234, M, F	FFQ (89), interviewed	Highest vs lowest (4)	0.66	$p > 0.05$	Matched by sex, age, telephone possession. Adjusted for sex, age	Population-based
Inoue *et al.*, 1994, Japan	668/668, M, F	FFQ, self-administered	Fresh veg.: ≥ 3 vs < 3/w (2)	0.70 (0.55–0.88)	$p < 0.05$	Matched by age, sex, time of hospital visit. Adjusted for sex	Hospital-based
Cornée *et al.*, 1995, France	92/128, M, F	FFQ (30, 9 fruits and veg.), interviewed	Highest vs lowest (3)	0.77 (0.37–1.60)	$p = 0.68$	Matched by age, sex (group matching) Adjusted for age, sex, occupation, energy	Hospital-based Veg. comprise all types except dried veg. and potatoes

Table 25 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Lee *et al.*, 1995, Korea	213/213, M, F	FFQ (64), interviewed	Fresh veg.: Highest vs lowest (3)	1.2 (0.8–1.9)	$p > 0.01$	Matched by age, sex. Adjusted for age, sex, education, economic status, residence	Hospital-based
Xu *et al.*, 1996, China	293/959, M, F	FFQ, interviewed	≥ 7.4 vs ≤ 5.4 g/d (3)	0.5 (0.4–0.8)		Matched by sex, age. Adjusted for age, smoking, education, fruit consumption, stomach disease, family stomach cancer	Iron and steel workers
Harrison, *et al.*, 1997, USA	91 (60 intestinal, 31 diffuse)/132, M, F	FFQ, self-administered	Increase in one standard deviation	Intestinal: 0.8 (0.5–1.3) Diffuse: 0.7 (0.4–1.2)		Energy, age, sex, race, education, smoking, alcohol, BMI	Hospital-based
La Vecchia *et al.*, 1997, Italy	746/2053, M, F	FFQ (29, 7 veg.) interviewed	≥ 7 vs ≤ 5 different types of veg./wk (4)	0.5 (0.4–0.7)	$p < 0.001$	Age, sex, area of residence, education, family history of gastric cancer, total number of serving, BMI, energy	Hospital-based Data relate to diversity of types of veg. consumed, rather than number of all veg. items
Muñoz *et al.*, 1997, Italy	88/103, M, F	FFQ (36), interviewed	≥ 8 vs ≤ 6/wk (3)	0.47 (0.22–1.03)	$p > 0.05$	Sex, age, area of residence, education	Hospital-based, subjects with family history. OR for subjects without family history 0.46
Ji *et al.*, 1998, China	770/819, M 354/632, F	FFQ (74), interviewed	≥ 263.5 vs ≤ 158.9 servings/mo (4)	M: 0.4 (0.3–0.5) F: 0.7 (0.5–1.1)	$p < 0.001$ $p > 0.05$	Matched by age and sex. Adjusted for age, income, education, smoking, alcohol	Population-based
Gao *et al.*, 1999, China	149/228, M, F	FFQ, interviewed	Raw veg.: Frequently vs almost never (3)	0.07 (0.04–0.13)		Matched by age, sex and neighbourhood. Adjusted for age and sex	Population-based
Ward & Lopez-Carrillo, 1999, Mexico	220/752, M, F	FFQ (70,13 veg.), interviewed	≥ 6 vs <4 times/d (4)	0.3 (0.1–0.6)	$p = 0.001$	Matched by age. Adjusted for age, sex, energy, chili pepper consumption, added salt, history of peptic ulcer, cigarettes, socioeconomic status	Population-based Similar findings by subtype

Table 25 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Ekström *et al.*, 2000, Sweden	(Cardia; 69, non-cardia 395)/1061, M, F	FFQ (45), dietary habits 20 years before interview	≥ 2/d vs ≤ 5/w (4)	Cardia: 0.5 (0.3–1.1) Non-cardia: 0.7 (0.5–1.0)	$p = 0.05$ $p = 0.02$	Matched by age, sex. Adjusted for energy, smoking, BMI, area, number of siblings, socioeconomic status, number of meals/day, multi-vitamin supplements, table salt use, urban environment	Population-based Similar findings by histology
Huang *et al.*, 2000, Japan	111/26 996, M, F	FFQ, self-administered	Raw veg.: ≥ 3 times/wk vs ≤ 3 times/mo	Gastric cancer family history (+): 0.52 (0.27–0.99) Gastric cancer family history (–): 0.95 (0.64–1.41)	$p < 0.05$ $p > 0.05$	Age, sex, smoking, drinking, pickled veg., fruit, raw veg., carrots, lettuce, pumpkin	Hospital-based
Mathew *et al.*, 2000, India	194/305, M, F	FFQ, interviewed	> 9 vs ≤ 3/w (3)	1.1 (0.2–5.0)	$p = 0.08$	Matched by age, sex, religion, residential area. Adjusted for age, sex, religion, income, smoking, alcohol	Hospital-based
De Stefani *et al.*, 2001, Uruguay	160/320, M, F	FFQ (64,13 veg.), interviewed	≥ 128.8 g/d vs ≤ 71.6 g/d (3)	0.83 (0.49–1.43)	$p = 0.54$	Matched with sex, age, residence and urban/rural status. Adjusted for age, sex, residence, urban/rural status, education, BMI, energy, fruit	Hospital-based Tubers and legumes excluded
Chen *et al.*, 2002a, USA	124/449, M, F	Short FFQ (54), interviewed, validated against full questionnaire	Highest vs lowest (4)	1.7 (0.77–3.7)	$p > 0.05$	Matched with age, sex and vital status. Adjusted for sex, age, energy, respondent type, BMI, alcohol, tobacco, education, family history, vitamin supplement use	Population-based

Table 25 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Kim *et al.*, 2002, Korea	136/136, M, F	FFQ (109), interviewed	Highest vs lowest (3) Green veg.: Daily vs < 1d/wk (4)	0.64 (0.31–1.32) 0.9 (0.4–1.9)	$p = 0.025$ $p = 0.73$	Matched by sex and age. Adjusted for sex, age, socio-economic status, family history, refrigerator use	Hospital-based
Hamada *et al.*, 2002, Brazil	96/192, M, F	FFQ (30), interviewed	Yellow veg.: Daily vs < 1d/wk(4) Other veg.: Daily vs < 1d/wk(4)	0.5 (0.1–1.5) 0.9 (0.3–3.0)	$p = 0.47$ $p = 0.45$	Matched by gender, age. Adjusted for country of birth	Hospital-based and population-based Japanese
Nishimoto *et al.*, 2002, Brazil	236/236, M, F	FFQ (30), interviewed	Green veg.: Daily vs <1 d/wk (4) Yellow veg.: Daily vs <1 d/wk (4) Other veg.: Daily vs < 1 d/wk (4)	0.7 (0.4–1.3) 0.5 (0.6–0.99) 0.5 (0.3–0.97)	$p = 0.33$ $p = 0.28$ $p = 0.02$	Matched by gender, age. Adjusted for race, education, smoking, other veg./fruit intake	Hospital-based, non-Japanese
Ito *et al.*, 2003 Japan	508/36 490, F	FFQ, self-administered	Raw veg.: Every day vs almost never (4)	0.50 (0.36–0.71)	$p < 0.001$	Age, year, season of visit, smoking, family history of gastric cancer	Hospital-based Similar findings for histological subtype

*p for trend when applicable

Table 26. Cohort studies of total fruit and vegetable consumption and risk of stomach cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Botterweck *et al.*, 1998, Netherlands	264/3123, M, F subcohorts 6.3 y	FFQ (150, 17 veg., 8 fruits)	≥ 544 vs ≤ 190 g/d (5)	0.72 (0.48–1.10)	$p = 0.14$	Age, sex, smoking, education, stomach disorders, family history of gastric cancer	Incidence Case–cohort analysis All cohort: 120 852
Galanis *et al.*, 1998, Hawaii (Japanese)	108/11 907, M, F 14.8 y	FFQ (13), interviewed	Fresh fruit and raw veg.: ≥ 14 vs < 8/wk (3)	0.5 (0.3–0.8)	$p = 0.02$	Age, education, Japanese place of birth, gender (analyses among men; also smoking, alcohol)	Incidence
Terry *et al.*, 1998, Sweden	116/11 546, M, F 25 y	FFQ (23), self-administered	High vs none/very little (4)	[0.18 (0.05–0.60)]	$p < 0.05$	Sex, age, smoking, BMI at 25 y, childhood socioeconomic status, alcohol	Incidence Twin study

*p for trend when applicable

Table 27. Case-control studies of total fruit and vegetable consumption and risk of stomach cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Boeing *et al.*, 1991b, Poland	741/741, M, F	FFQ (43, 8 fruits and 12 veg.), Fruit and veg. score	Highest vs lowest (5)	0.53 (0.37–0.75)	$p = 0.01$	Age, sex, occupation, education, residence	Hospital-based Similar results for intestinal and diffuse type
Hansson *et al.*, 1993, Sweden	338/669, M, F	FFQ (45), interviewed	Highest vs lowest (4)	0.38 (0.21–0.67)		Age, gender, socioeconomic status, consumption of a food item during adolescence and 20 years before interview	Population-based
De Stefani *et al.*, 2001, Uruguay	160/320, M, F	FFQ (64, 22 fruits and veg.), interviewed	≥ 321.1 vs ≤ 192.1 g/d (3)	0.33 (0.19–0.56)	$p < 0.001$	Matched by sex, age, residence and urban/rural status. Adjusted for age, sex, residence, urban/rural status, education, BMI, energy, tubers, legumes	Hospital-based Tubers and legumes excluded

*p for trend when applicable

Table 28. Cohort studies of fruit consumption and risk of colorectal cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata *et al.*, 1992, USA	105/11 580, F 9 y	FFQ (59, 23 fruits), self-administered	F ≥ 3.7 vs < 2.4 servings/day (3) M ≥ 3.5 vs < 2.2 servings/d (3)	Colon: 0.50 (0.31–0.80) 1.12 (0.69–1.81)	$p < 0.05$ NS	Age, smoking	Incidence Californian retirement community residents
Steinmetz *et al.*, 1994, USA	212/ 41 837, F 5 y	FFQ (127) at baseline, self-administered	> 17.4 vs < 7.5 servings/wk (4)	Colon: 0.86 (0.58–1.29)	$p > 0.05$	Age, energy	Incidence Iowa Women's Health Study
Kato *et al.*, 1997, USA	100/14 727, F average 7.1 y	FFQ at baseline, self-administered	Highest vs lowest (4)	Colorectum: 1.49 (0.82–2.70)	$p = 0.08$	Age, energy, enrolment site, education	Incidence NY University cohort
Hsing *et al.*, 1998a, USA	120 colon, 25 rectum/17 633, M (white) 11.5 y	FFQ (35) at baseline, self-administered	> 67.0 vs < 29.3 times/mo (4)	Colorectum: 1.6 (0.9– 2.8) Colon: 1.6 (0.9–2.9)	$p = 0.04$ $p = 0.05$	Age, energy, smoking, alcohol	Mortality Lutheran Brotherhood cohort
Pietinen *et al.*, 1999, Finland	185/26 926, M average 8 y	FFQ (276) at baseline, self-administered	216 vs 30 g/d (median values) (4)	Colorectum: 1.1 (0.8–1.7)	$p = 0.64$	Age, intervention group, years smoking, BMI, alcohol, education, physical activity, calcium	Incidence ATBC cohort, vitamin supplement trial
Michels *et al.*, 2000, USA	569 colon, 155 rectum/88 764, F 16 y 368 colon, 89 rectum/47 325, M 10 y	FFQ (61, 6 fruits expanded to 15)	≥ 5 vs ≤ 1 servings/d (5)	F, Colon: 0.80 (RR for 1 additional serving/d: 0.96 (0.89–1.03)) Rectum: 0.66 (RR for 1 additional serving/d: 0.96 (0.83–1.11)) M, Colon: 1.35 (RR for 1 additional serving/d: 1.08 (1.00–1.16)) Rectum: 2.04 (RR for 1 additional serving/d: 1.09 (0.94–1.26))		Age, family history of colorectal cancer, sigmoidoscopy, height, BMI, smoking, alcohol, physical activity, aspirin, vitamin supplement use, energy (standard), red meat	Incidence Nurses' Health Study or Health Professional Study Pooled estimates for M and F not made because of heterogeneity

Table 28 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Voorrips *et al.*, 2000a, Netherlands	331 colon, 215 rectum/58 279, M 6.3 y 280 colon, 119 rectum/ 62 573, F 6.3 y	FFQ (150) at baseline, self-administered	M 286 vs 34 g/d (median values) (5) F: 343 vs 65 g/d (median values) (5)	Colon:1.33 (0.90–1.97) Rectum: 0.85 (0.55–1.32) Colon: 0.73 (0.48–1.11) Rectum: 0.67 (0.34–1.33)	0.22 0.29 0.12 0.44	Age, family history, alcohol	Incidence Netherlands cohort
Terry *et al.*, 2001a, Sweden	291 colon, 259 rectum/ 61 463, F 9.6 y	FFQ (67) at baseline, self-administered	> 2 vs < 1 servings/d (4)	Colorectum: 0.68 (0.52–0.89) Colon: 0.76 (0.55–1.06) Rectum: 0.54 (0.33–0.89)	$p = 0.009$ $p = 0.23$ $p = 0.01$	Age, red meat, dairy food, energy	Incidence. Swedish mammography cohort
Bueno de Mesquita *et al.*, 2002, Europe	773/405 667, M, F M: 3.3 y, F: 4.4 y	FFQs country specific. Interviewed or self-administered	Highest vs lowest (5)	Colorectum: 0.83 (CI includes 1.0)	$p = 0.88$	Stratified by age and centre. Adjusted for gender, weight, height, smoking, physical activity, energy, alcohol, veg.	Incidence EPIC cohort Excludes potatoes
Flood *et al.*, 2002, USA	485/45 490, F Average 8.5 y	FFQ (62, 5 fruits) at baseline, self-administered	≥ 0.38 vs < 0.1 servings/day/ 1000 kJ (median values) (5)	Colorectum: 1.15 (0.86–1.53)		Age, energy (nutrient density), multivitamin supplement use, BMI, height, NSAIDs, smoking, education, physical activity, grains, red meat, calcium, vitamin D, alcohol, veg.	Incidence Breast Cancer Detection Demonstration Project cohort
Sauvaget *et al.*, 2003, Japan	226/38 540, M 17 y	FFQ (22), self-administered	Daily vs 0–1 day/wk (3)	Colorectum: 0.97 (0.73–1.29)	$p = 0.81$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors
McCullough *et al.*, 2003, USA	298/62 609, M 210/70 554, F 6 y	FFQ (68), self-administered	≥ 6.2 vs < 1.2 servings/d (5) ≥ 6.0 vs < 1.2 servings/d (5)	Colon: 1.11 (0.76–1.62) Colon: 0.74 (0.47–1.16)	$p = 0.52$ $p = 0.47$	Age, education, exercise, aspirin, smoking, family history of colorectal cancer, BMI, energy, multivitamin use, total calcium, red meat, HRT use	Incidence Cancer Prevention Study II Nutrition Cohort

Table 29. Case–control studies of fruit consumption and risk of colorectal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Manousos *et al.*, 1983, Greece	100/100, M, F	Dietary history (80), interviewed	Highest vs lowest (3)	Colorectum No difference in consumption between cases and controls		Age, sex	Hospital-based
Pickle *et al.*, 1984, USA	Colon 58, rectum 28/176, M, F	Dietary history (57), interviewed	> 11.8 servings/wk versus less (2)	M: Colon: 1.12 Rectum: 0.97 F: Colon: 0.97 Rectum: 1.21		Age, sex, ethnic group, residence	Hospital-based Rural area
Macquart-Moulin *et al.*, 1986, France	354/399, M, F	FFQ, interviewed	Highest vs lowest (4)	Colorectum: 0.74	NS	Age, sex, weight, energy	Hospital-based
Kune *et al.*, 1987, Australia	Colon 392, rectum 323/727	Dietary history (> 300)	> 2440 vs < 610 g/wk (5)	M [0.74] F [0.61]	$p = 0.01$ in men	Age, sex	Population-based
La Vecchia *et al.*, 1988c, Italy	Colon 339, rectum 236/778, M, F	FFQ (29)	Fresh fruit: Highest vs lowest (3)	Colon: 0.85 Rectum: 1.18	NS	Age, sex	Hospital-based
Slattery *et al.*, 1988, USA	M, 112/185 F, 119/206	FFQ (99), interviewed	M: > 374 vs ≤ 158 g/d (4) F: > 431 vs ≤ 169 g/d (4)	Colon: M: 0.3 (0.1–0.6) F: 0.6 (0.3–1.3)		Age, BMI, religion, energy	Population-based
Tuyns *et al.*, 1988, Belgium	Colon 453, rectum 365/2851, M, F	FFQ (extensive list), interviewed	Fresh fruit: > 1538 vs < 300 g/wk (4)	Colon: 0.91 Rectum: 0.87	$p = 0.19$ $p = 0.24$	Age, sex, province	Population-based
Benito *et al.*, 1990, Spain	286/295, M, F	FFQ (99), interviewed	Fresh fruit: > 89 vs < 44 times/mo (4)	Colorectum: 1.09	NS	Age, sex, weight 10 years before	Population-based
Bidoli *et al.*, 1992, Italy	Colon 123, rectum 125/699, M, F	FFQ, interviewed	Fresh fruit: Highest vs lowest (3)	Colon: 1.0 Rectum: 0.7	NS	Age, sex, social status	Hospital-based
Iscovich *et al.*, 1992, Argentina	110/220	FFQ (140) interviewed		Colon: No association		Matched by age, sex, residence	Population-based, neigbour-hood controls
Peters *et al.*, 1992, USA	746/746, M, F	Semi-quantitative FFQ (116), interviewed	Risk increase per 10 servings/mo	Colon: 1.00 (0.97–1.03)	NS	Age, sex, neighbourhood, fat, protein, carbohydrates, alcohol, calcium, family history, weight, physical activity, if female, pregnancy history	Population-based

Table 29 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Steinmetz & Potter, 1993, Australia	M 121/241 F 99/197	FFQ (141, 14 fruits), self-administered, previously validated	M: ≥ 28 vs ≤ 8 servings/wk (4) F: ≥ 34 vs ≤ 12 servings/wk (4)	Colon M: 1.74 (0.88–3.46) F: 0.90 (0.38–2.11)		Age, sex, occupation, Quetelet index, alcohol, protein intake, age at first live birth for women	Population-based
Centonze *et al.*, 1994, Italy	Colorectal 119/119, M, F	FFQ (70), interviewed	≥ 480 vs ≤ 305 g/d (3)	Colorectum: 1.02 (0.53–1.95)	$p = 0.96$	Age, sex, smoking, education, changes in diet	Population-based
Kampman *et al.*, 1995, Netherlands	M 130/136 F 102/123	FFQ (289), interviewed	M: > 269 vs < 100 g/d (3) F: > 327 vs < 143 g/d (3)	Colon: M: 1.00 (0.49–2.03) F: 0.54 (0.23–1.23)	$p = 0.88$ $p = 0.13$	Age, urbanization, energy, alcohol, cholecystectomy, family history	Population-based
Kotake *et al.*, 1995, Japan	Colon 187, rectum 176/363 screening and hospital controls, M, F	FFQ (10)	Daily vs 1–2 times/wk (4)	Colon: 0.8 (0.27–2.41) Rectum: 0.7 (0.21–2.08)		Age, sex	Hospital-based
Shannon *et al.*, 1996, USA	M 238/224 F 186/190	Semiquantitative FFQ (71), interviewed by telephone	M: > 17 vs ≤ 0.46 servings/d (4) F: > 2.1 vs ≤ 0.69 servings/d (4)	Colon: M: 0.77 (0.44–1.36) F: 0.44 (0.24–0.82)	$p = 0.21$ $p = 0.007$	Age, energy	Population-based
Franceschi *et al.*, 1997, Italy	Colon 1225 Rectum 728/4154, M, F	FFQ (79), interviewed	Diversity of consumption: ≥ 6 vs ≤ 3 servings/wk (3)	Colon: 0.80 (0.63–1.01) Rectum: 0.94 (0.70–1.25)	NS $p = 0.36$	Age, sex, centre, education, energy, physical activity, veg., number of servings	Hospital-based
Boutron-Ruault *et al.*, 1999, France	171/309, M, F	Dietary history, interviewed	M: > 273.2 vs < 130 g/d (4) F: > 286.4 vs < 137.4 g/d (4)	Colorectum: 1.0 (0.6–1.6)	$p = 0.34$	Age, sex, energy	Population-based
Levi *et al.*, 1999, Switzerland	Colon 119, rectum 104/491, M, F	FFQ (79), interviewed	Citrus fruit: OR for an increase of one serving/d Other fruit: OR for an increase of one serving/d	Colorectum: 0.86 (0.78–0.96) Colorectum: 0.85 (0.75–0.96)		Age, sex, education, tobacco, alcohol, BMI, energy, physical activity	Hospital-based

Table 29 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Murata *et al.*, 1999, Japan	Colon 265 Rectum 164/794, M, F	FFQ, self-administered	Daily vs rare (4)	Colon: 0.94 (0.78–1.13) Rectum: 0.98 (0.79–1.22)		Age, alcohol, tobacco, sex, eating attitude, other foods	Hospital-based
Deneo-Pellegrini *et al.*, 2002, Uruguay	Colon: 260, Rectum: 224/ 1452	FFQ (64, 10 fruits), interviewed	Highest vs lowest (4)	Colorectum: 0.7 (0.5–0.9)	$p = 0.04$	Age, sex, residence, urban/rural status, education, family history of colon cancer, BMI, energy, red meat intake	Hospital-based

*p for trend when applicable

Table 30. Cohort studies of vegetable consumption and risk of colorectal cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata, *et al.*, 1992, USA	105 F, 97 M/ 11 580 9 y	FFQ (59) at baseline, self-administered	F ≥ 4.8 vs < 3.2 servings/ d (3) M ≥ 4.5 vs < 3 servings/ d (3)	Colon: 0.72 (0.45–1.16) 1.39 (0.84–2.30)	NS NS	Age, smoking	Incidence California retirement community residents Includes potatoes
Thun *et al.*, 1992, USA	539 F, 611, M/ 5746 6 y	FFQ (32) at baseline	Highest vs lowest (5)	Colon: F 0.66 M 0.80		Matched by age, race, sex	Mortality ACS Cancer Prevention II cohort: 426 838 F, 337 505 M Nested case–cohort design Inclusion of potatoes not specified
Steinmetz, *et al.*, 1994, USA	212/41 837, F 5 y	FFQ (127) at baseline, self-administered	> 30.4 vs < 15.1 servings/wk (4)	Colon: 0.73 (0.47–1.13)	$p > 0.05$	Age, energy	Incidence Iowa Woman's Health Study Includes potatoes

Table 30 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Kato, *et al.*, 1997, USA	100/14 727, F Average 7.1 y	FFQ at baseline, self-administered	Highest vs lowest (4)	Colorectum: 1.63 (0.92–2.89)	$p = 0.40$	Age, energy, enrolment site, education	Incidence NY University cohort Excludes potatoes
Hsing, *et al.*, 1998a, USA	125 colon, 25 rectum/17 633, M (white) 11.5 y	FFQ (35) at baseline, self-administered	> 4.5 vs < 1.2 times/mo	Colorectum: 1.3 (0.8–2.4) Colon: 1.5 (0.8–2.8)	$p = 0.3$ $p = 0.3$	Age, energy (standard), smoking, alcohol	Mortality Lutheran Brotherhood cohort Includes potatoes
Pietinen, *et al.*, 1999, Finland	185/26 926, M Average 8 y	FFQ (276) at baseline, self-administered	191 vs 44 g/d (median values) (4)	Colorectum: 1.2 (0.8–1.9)	$p = 0.46$	Age, intervention group, years smoking BMI, alcohol, education, physical activity, calcium	Incidence ATBC cohort, vitamin supplement trial. All smokers Inclusion of potatoes not specified
Michels, *et al.*, 2000, USA	368 colon, 89 rectum/47 325, M 569 colon; 155 rectum/88 764, F M 10 y, F 16 y	FFQ (61, 11 veg., expanded to 28)	≥ 5 vs ≤ 1 servings/d (5)	Colon: 1.00 (0.72–1.38) (RR for 1 additional serving/day: 1.03 (0.97–1.09)) Rectum: 1.17 (0.63–2.18) (RR for 1 additional serving/day: 1.02 (0.92– 1.14))		Age, family history of colorectal cancer, sigmoidoscopy, height, BMI, smoking, alcohol, physical activity, menopausal status, hormone replacement therapy, aspirin, vitamin supplement use, energy, red meat	Incidence Nurses' Health Study or Health Professional Study Excludes potatoes Pooled estimates for M and F
Voorrips *et al.*, 2000a, Netherlands	312 colon, 199 rectum/58 279, M 266 colon, 115 rectum/62 573, F 6.3 y	FFQ (150) at baseline, self-administered	M 285 vs 100 g/d (median values) (5) F 293 vs 107 g/d (median values) (5)	Colon: 0.85 (0.57–1.27) Rectum: 0.88 (0.55–1.41) Colon: 0.83 (0.54–1.26) Rectum: 1.78 (0.94–3.38)	$p = 0.45$ $p = 0.58$ $p = 0.31$ $p = 0.09$	Age, family history, alcohol	Incidence Netherlands cohort Excludes potatoes

Table 30 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Terry *et al.*, 2001a, Sweden	291 colon, 159 rectum/61 463, F 9.6 y	FFQ (67) at baseline, self-administered	> 2 vs < 1 servings/d (4)	Colorectum: 0.84 (0.65–1.09) Colon: 0.90 (0.66–1.24) Rectum: 0.71 (0.45–1.12)	$p = 0.25$ $p = 0.43$ $p = 0.29$	Age, red meat, dairy food, energy	Incidence Swedish Mammography cohort Includes potatoes
Bueno de Mesquita *et al.*, 2002, Europe	773/405 667, M, F M 3.3 y, F 4.4 y	FFQs country specific, interviewed or self-administered	Highest vs lowest (5)	Colorectum: 0.71 (CI does not include 1.0)	$p = 0.37$	Stratified by age and centre. Adjusted for gender, weight, height, smoking, physical activity, energy, alcohol, fruit	Incidence EPIC cohort Excludes potatoes
Flood *et al.*, 2002, USA	485/45 490, F Average 8.5 y	FFQ (62, 5 fruits) at baseline, self-administered	≥ 0.79 vs < 0.33 servings/d 1000 kJ (5)	Colorectum: 0.95 (0.71–1.26)		Age, energy (nutrient density), multivitamin supplement use, BMI, height, NSAIDs, smoking, education, physical activity, grains, red meat, calcium, vitamin D, alcohol, fruits	Incidence Breast Cancer Detection Demonstration Project cohort Includes potatoes
Sauvaget *et al.*, 2003, Japan	226/38,540, M, F 17 y	FFQ (22), self-administered	Green-yellow veg.: Daily vs 0–1 d/wk (3)	Colorectum: 1.10 (0.82–1.47)	$p = 0.52$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors
McCullough *et al.*, 2003, USA	298/62 609, M 210/70 554 F 6 y	FFQ (68), self-administered	≥ 3.3 vs < 1.3 servings/d (5)	Colon: 0.69 (0.47–1.03) Colon: 0.91 (0.56–1.48)	$p = 0.10$ $p = 0.56$	Age, education, exercise, aspirin, smoking, family history of colorectal cancer, BMI, energy, mullti-vitamin use, total calcium, red meat, HRT use	Incidence Cancer Prevention Study II Nutrion cohort Excludes potatoes

*p for trend when applicable

Table 31. Case–control studies of vegetable consumption and risk of colorectal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Graham *et al.*, 1978, USA	Colon 183/611 Rectum 243/492, M (white)	Interview (19 veg.)	> 61 vs ≤ 20 times/mo (4)	Colon: 1.76 Rectum: 1.60	$p = 0.02$ $p = 0.012$		Population-based
Manousos *et al.*, 1983, Greece	100/100, M, F	Dietary histories (80), interviewed	Highest vs lowest (4)	Colorectum: cases less frequent consumption of veg. than controls	$p < 0.05$	Age, sex	Hospital-based
Miller *et al.*, 1983, Canada	Colon 348 (171 M, 177 F), rectum 194 (114 M, 80 F)/ 535 hospital and 542 neighbourhood controls	FFQ (150), interviewed	M > 468 vs < 291 g/d (3) F > 395 vs < 251 g/d (3)	M, Colon: 0.8 Rectum: 1.1 F, Colon: 0.7 Rectum: 1.2	$p = 0.19$ $p = 0.43$ $p = 0.06$ $p = 0.28$	Age, sex, saturated fat, other foods	Hospital-based and population-based
Pickle *et al.*, 1984, USA	Colon 58, rectum 28/17, M, F	Dietary history (57), interviewed	> 8.9 servings/wk vs less (2)	Colon: 1.77 Rectum: 1.43		Age, sex, ethnic group, residence	Hospital-based Rural area
Macquart-Moulin *et al.*, 1986, France	399/399, M, F	FFQ, interviewed	Highest vs lowest (4)	Colorectum: Veg. with 1 g veg./100 g fibre: 0.42 Veg. with 2.8 g veg./100 g fibre: 0.58	$p < 0.001$ $p = 0.004$	Age, sex, energy, weight	Hospital-based
Kune *et al.*, 1987, Australia	Colon 392, rectum 323/727, M, F	Dietary history (+300)	> 2370 vs < 1180 g/wk (4)	Colorectum: M [0.38] F [0.48]	$p < 0.001$ $p < 0.001$		Population-based
La Vecchia *et al.*, 1988c, Italy	Colon 339, rectum 236/778, M, F	FFQ (29)	Green veg.: Highest vs lowest (3)	Colon: 0.50 Rectum : 0.51	$p < 0.01$ $p < 0.01$	Age, sex, education, area, other foods	Hospital-based
Slattery *et al.*, 1988	M 112/185, F 119/206	FFQ (99), interviewed	M > 400.1 vs ≤ 220.5 g/d (4) F > 456 vs ≤ 231.2 g/d (4)	Colon: M 0.6 (0.3–1.3) F 0.3 (0.1–0.9)		Age, BMI, religion, energy	Population-based
Tuyns *et al.*, 1988, Belgium	Colon 453, rectum 365/2851, M, F	FFQ (extensive list), interviewed	Cooked veg.: > 1375 vs < 800 g/wk (4) Raw veg.: > 268 vs < 80 g/wk (4)	Colon : 0.71 Rectum: 0.36 Colon: 0.37 Rectum: 0.49	$p < 0.01$ $p < 0.013$ $p < 0.0001$ $p < 0.0001$	Age, sex, province	Population-based

Table 31 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Young & Wolf, 1988, USA	353/618, M, F (white)	FFQ (25) Diet over age 35 y	Miscellaneous veg.: 20 times/mo vs 1/mo (5)	Colon: 0.72 (0.48–1.07)		Age, sex	Population-based
Lee *et al.*, 1989, Singapore	Colon 131, Rectum 71/426, M, F	FFQ (116), interviewed	Highest vs lowest (3)	Colon: 0.79 (0.48–1.28) Rectum: 0.51 (0.27–0.98) Colorectum: 0.69 (0.45–1.05)	NS $p < 0.05$ NS	Age, sex, dialect, education, occupation	Hospital-based
Benito *et al.*, 1990, Spain	265/267, M, F	FFQ (99), interviewed	> 117 vs < 64 times/mo (4)	Colorectum: 0.71	NS	Age, sex, weight 10 years prior	Population-based
Hu *et al.*, 1991, China	Colon 111, rectum 225/336, M, F	FFQ (25)	> 193 vs < 75.5 kg/y (3)	[0.18 (0.05–0.61)]	$p = 0.003$	Age, sex, residence	Hospital-based
Bidoli *et al.*, 1992, Italy	Colon 123, rectum 125/699, M, F	FFQ, interviewed	Highest vs lowest (3)	Colon: 0.7 Rectum : 0.6	NS	Age, sex, social status	Hospital-based
Iscovich *et al.*, 1992, Argentina	110/220,	FFQ (140)	> 1281 vs < 483 times/y (4)	Colon: 0.075 (0.02–0.3)	$p < 0.001$	Age, sex, residence, other foods	Population-based, neighbourhood controls
Peters *et al.*, 1992, USA	746/746, M, F	Semiquantitative FFQ (116), interviewed	Other non-cruciferous veg.: Risk increase per 10 servings/mo	1.01 (0.97–1.04)		Age, sex, neighbourhood, fat, protein, carbohydrates, alcohol, calcium, family history, weight, physical activity, if female, pregnancy history	Population-based
Steinmetz & Potter, 1993	M 121/241, F 99/197	FFQ (141, 48 veg.), self-administered, previously validated	M ≥ 32 vs < 15 servings/wk (4) F ≥ 38 vs < 19 servings/wk (4)	Colon: M 1.29 (0.67–2.51) F 1.11 (0.50–2.45)		Age, sex, occupation, Quetelet index, alcohol, protein intake, age at first live birth for women	Population-based

Table 31 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Centonze *et al.*, 1994, Italy	119/119. M, F	FFQ (70), interviewed	> 329 vs ≤ 236 g/d (3)	Colorectum: 0.51 (0.25–1.04)	$p = 0.07$	Age, sex, smoking, education, changes in diet, cereals, dairy products, dried fruits, foods contained refined sugar, coffee, wine	Population-based
Kampman *et al.*, 1995, Netherlands	232/259. M, F	FFQ (289), interviewed	> 247 vs < 142 g/d (4)	Colon: 0.40 (0.23–0.69)	$p = 0.0004$	Age, sex, urbanization, energy, alcohol, cholecystectomy, family history	Population-based
Kotake *et al.*, 1995, Japan	Colon 187, rectum 176/363, screening and hospital controls	FFQ (10)	Daily vs 1–2 wk (4)	Colon: 1.01 (0.24–4.22) Rectum: 0.5(0.12–1.96		Age, sex	Hospital-based
Shannon *et al.*, 1996, USA	M 238/224 F 186/190	Semiquantitative FFQ (71), interviewed by telephone	M: > 3.5 vs < 1.2 servings/d (4) F: > 3.9 vs < 1.5 servings/d (4)	Colon: M 0.78 (0.45–1.35) F 0.51 (0.28–0.93)	$p = 0.46$ $p = 0.02$	Age, energy	Population-based
Franceschi *et al.*, 1997, Italy	Colon 1225, rectum 728/4154, M, F	FFQ (79), interviewed	Diversity of consumption: ≥ 8 vs ≤ 5 servings/wk (3)	Colon: 0.77 (0.62–0.95) Rectum: 0.85 (0.65–1.09)	$p < 0.05$ NS	Age, sex, centre, education, energy, physical activity, fruits, number of servings	Hospital-based
Boutron-Ruault *et al.*, 1999, France	171/309, M, F	Dietary history, interviewed	M: > 251.8 vs < 130.8 g/d (4) F: > 243.4 vs < 120 g/d (4)	Colorectum: 0.7 (0.4–1.3)	$p = 0.19$	Age, sex, energy	Population-based
Levi *et al.*, 1999, Switzerland	Colon 119, rectum 104/491, M, F	FFQ (79), interviewed	Raw veg.: OR for an increase of one serving per day Cooked veg.: OR for an increase of one serving	Colorectum: 0.85 (0.74–0.98) Colorectum: 0.69 (0.57–0.83)		Age sex, education, tobacco, alcohol, BMI, energy, physical activity	Hospital-based

Table 31 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
La Vecchia *et al.*, 1999, Italy	Colon 1225 (688 M, 537 F)/4154 (2073 M, 2081 F)	FFQ (78), validated	Highest vs lowest (3)	Colon: M [0.74 (0.59–0.91)] F [0.43 (0.32–0.56)]	NS $p < 0.01$	Age, sex, centre, education, physical activity, energy, meal frequency, family history	Hospital-based
Murata *et al.*, 1999, Japan	Colon 265, rectum 164/794	FFQ, self-administered	Green veg,: Daily vs rare (4)	Colon: 0.87 (0.67–1.12) Rectum: 0.84 (0.62–1.14)		Age, alcohol, tobacco, sex, eating attitude, other foods	Hospital-based
Deneo-Pellegrini *et al.*, 2002, Uruguay	Colon 260, rectum 224/1452 (882 M, 570 F)	FFQ (64, 18 veg.), interviewed	Highest vs lowest (4)	Colorectum: 0.7 (0.5–0.9)	$p = 0.04$	Age, sex, residence, urban/rural status, education, family history of colon cancer, BMI, energy, red meat	Hospital-based

*p for trend when applicable

Table 32. Cohort studies on fruit and vegetable consumption and risk of colorectal cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata *et al.*, 1992, USA	905 F, 97 M/ 11 580 9 y	FFQ (52, 23 fruits and 21 veg.) at baseline, self-administered	F ≥ 8.3 vs < 5.9 servings/d (3) M ≥ 7.09 vs < 5.5 servings/d (3)	Colon: F 0.63 (0.40–1.00) M 1.50 (0.91–2.46)	$p < 0.05$ NS	Age, smoking	Incidence California retirement community residents Includes potatoes
Steinmetz *et al.*, 1994, USA	212/41 837, F 5 y	FFQ (127) at baseline, self-administered	> 47 vs < 24.6 servings/wk (4)	Colon: 0.89 (0.57–1.40)	$p > 0.05$	Age, energy	Incidence Iowa Women's Health Study Includes potatoes

Table 32 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Michels *et al.*, 2000, USA	569 colon, 155 rectum/88 764, F 16 y 368 colon, 89 rectum/ 47 325, M 10 y	FFQ (61, 6 fruits and 11 veg. expanded to 15 fruits and 28 veg.)	≥ 6 vs ≤ 2 servings/d (5)	Colon: 1.08 (0.84–1.38) (RR for 1 additional serving/d: 1.02 (0.98–1.05)) Rectum: 0.99 (0.62–1.56) (RR for 1 additional serving/d: 1.02 (0.95–1.09))		Age, family history of colorectal cancer, sigmoidoscopy, height, BMI, smoking, alcohol, physical activity, aspirin, vitamin supplement use, energy (standard), red meat	Incidence Nurses' Health Study (F) and Health Professional Study (M) Pooled estimates for M and F
Voorrips *et al.*, 2000a, Netherlands	312 colon, 199 rectum/ 58 279, M 266 colon, 115 rectum/ 62 573, F 6.3 y	FFQ (150) at baseline, self-administered	M 519 vs 177 g/d (median values) (5) F 578 vs 208 g/d (median values) (5)	Colon: 0.95 (0.64–1.41) Rectum: 0.88 (0.56–1.37) Colon: 0.66 (0.44–1.01) Rectum: 1.17 (0.63–2.17)	$p = 0.90$ $p = 0.90$ $p = 0.10$ $p = 0.84$	Age, family history, alcohol	Incidence Netherlands cohort Excludes potatoes
Terry *et al.*, 2001a, Sweden	291 colon, 159 rectum/61 463, F 9.6 y	FFQ (67) at baseline, self-administered	> 5 vs < 2.5 servings/d (4)	Colorectum: 0.73 (0.56–0.96) Colon: 0.81 (0.59–1.13) Rectum: 0.60 (0.38–0.96)	$p = 0.03$ $p = 0.36$ $p = 0.02$	Age, red meat, dairy food, energy	Incidence Swedish mammography cohort
Bueno de Mesquita *et al.*, 2002, Europe	773/405 667, M, F M 3.3 y F 4.4 y	FFQ country-specific, interviewed or self-administered	Highest vs lowest (5)	Colorectum: 0.74 (CI does not include 1)	$p = 0.45$	Stratified by age and centre. Adjusted for gender, weight, height, smoking, physical activity, energy, alcohol, veg.	Incidence EPIC cohort Excludes potatoes

*p for trend when applicable

Table 33. Case–control studies of total fruit and vegetable consumption and risk of colorectal cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Pickle *et al.*, 1984, USA	58 colon, 28 rectum/176, M, F	Dietary history (57), interviewed	> 21.3 servings/wk vs less (2)	Colon 0.97 Rectum 1.21		Age, sex, ethnic group, residence	Hospital-based, rural area
Peters *et al.*, 1989, USA	147/147 M white	Questionnaire, interviewed	Fresh fruit: or raw veg.: ≥ 5 vs ≤ 1 times/wk (3)	Colorectum: 0.6 (0.2–1.4)		Education, age	Population-based, neighbourhood controls
Steinmetz & Potter, 1993, Australia	M 121/141 F 99/197	FFQ (141, 14 fruits, 48 veg.), previously validated, self-administered	M: ≥ 59 vs ≤ 28 servings/wk (4) F: ≥ 70 vs ≤ 36 servings/wk (4)	Colon: M 1.39 (0.72–2.71) F 0.76 (0.33–1.76)		Age, sex, occcupation, Quetelet index, alcohol, protein intake, age at first live birth for women	Population-based
Shannon *et al.*, 1996, USA	M 238/224 F 186/190	Semiquantitative FFQ (71), interviewed by telephone	M: > 5 vs 1.8 servings/d (4) F: > 5.7 vs < 2.4 servings/d (4)	0.93 (0.52–1.64) 0.48 (0.26–0.86)	$p = 0.61$ $p = 0.02$	Age, energy	Population-based
Deneo-Pellegrini *et al.*, 2002, Uruguay	260 colon, 224 rectum/1452	FFQ (64, 10 fruits, 18 veg.), interviewed	Highest vs lowest (4)	Colorectum: 0.7 (0.5–0.9)	$p = 0.01$	Age, sex, residence, urban/rural status, education, family history of colon cancer, BMI, energy, red meat	Hospital-based

*p for trend when applicable

Table 34. Cohort study of fruit consumption and risk of adenomatous polyps

Author, year, country	Cases/cohort size gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Platz *et al.*, 1997, USA	690/16 448, M 9 y	FFQ (131)	> 8.4 vs < 1.3 g/d (5)	0.81 (0.59–1.11)	$p = 0.03$	Age, endoscopy before 1986, family history of colorectal cancer, BMI, pack-years smoking, physical activity, regular aspirin use, energy, alcohol, red meat, folate and methionine intake	Subjects who had endoscopy (left-sided adenomas)

*p for trend when applicable

Table 35. Case–control studies of fruit consumption and risk of adenomatous polyps

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Macquart-Moulin *et al.*, 1987, France	252/238	FFQ, interviewed	Highest vs lowest (4)	Colorectum: 0.70		Age, sex, energy, weight	Hospital-based
Sandler *et al.*, 1993, USA	M 105/165 F 131/244	FFQ (>100), interviewed by telephone, previously validated	M > 19.9 vs < 6.3 servings/wk (5) F ≥ 22.3 vs < 8.4 servings/wk (5)	Colorectum: M 0.60 (0.24–1.52) F 0.44 (0.20–0.95)	$p = 0.50$ $p = 0.03$	Age, alcohol, BMI, energy	Hospital-based
Witte *et al.*, 1996, USA	488/488, M, F	Semiquantitative FFQ (129), interviewed	≥ 25 vs < 2.5 servings/wk (5)	Colorectum: 0.92 (0.52–1.63)	$p = 0.99$	Race, BMI, physical activity, smoking, energy, saturated fat, fibre, folate, β-carotene, vitamin C	Asymptomatic screened controls
Lubin *et al*, 1997, Israel	196/196, M, F	FFQ (180), interviewed	Fruit/fresh juices > 478 vs < 283 g/d (3)	1.1 (0.6–1.9)	$p = 0.78$	Matched by age, sex, country of origin, follow-up. Adjusted for energy, physical activity	Asymptomatic screened controls
Almendinge *et al.*, 2001, Norway	87/35 hospital and 35 healthy controls, M, F	Dietary record	Fruits and berries: > 321 vs < 110 g/d (3)	Hospital: 5.5 (1.3–23.1) Population: 2.9 (0.6–14.5)	$p = 0.01$ $p = 0.2$	Sex, age, BMI, history of colorectal cancer, energy, fat, fibre, smoking	Hospital-based and population-based
Smith-Warner *et al.*, 2002b USA	564/535, M, F	Semi-quantitative FFQ (153, 59 fruits and veg.)	M > 27.9 vs < 2.1 servings/wk (5) F > 27.5 vs < 3.3 servings/wk (5)	Colorectum: M 0.75 (0.41–1.35) F 0.68 (0.32–1.43)	$p = 0.44$ $p = 0.29$	Age, energy, fat intake BMI, smoking, alcohol, use of NSAIDs, multivitamins, hormone replacement therapy	Population-based

*p for trend when applicable

Table 36. Cohort study of vegetable consumption and risk of adenomatous polyps

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Platz *et al.*, 1997, USA	690/16 448, M 9 y	FFQ (131)	> 11.5 vs < 3.2 g/d (5)	0.93 (0.67–1.30)	$p = 0.33$	Age, endoscopy before 1986, family history of colorectal cancer, BMI, pack-years smoking, physical activity, regular aspirin use, energy, alcohol, red meat, folate and methionine intake	Subjects who had endoscopy (left-sided adenomas)

*p for trend when applicable

Table 37. Case–control studies of vegetable consumption and risk of adenomatous polyps

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Macquart-Moulin *et al.*, 1987, France	252/238, M, F	FFQ, interviewed	Veg. (low fibre): Highest vs lowest (4) Veg.: Highest vs lowest (4)	Colorectum: 0.78 1.24		Age, sex, energy, weight	Hospital-based
Witte *et al.*, 1996, USA	488/488, M, F	Semiquantitative FFQ (129), interviewed	≥ 45.5 vs ≤ 9 servings/wk (5)	Colorectum: 0.90 (0.49–1.68)	$p = 0.27$	Race, BMI, physical activity, smoking, energy, sarurated fat, fibre, folate, β-carotene, vitamin C	Asymptomatic screened controls
Lubin *et al.*, 1997, Israel	196/196, M, F	FFQ (180), interviewed	> 460 vs < 290 g/d (3)	0.9 (0.6–1.6)	$p = 0.838$	Matched by age, sex, country of origin, follow-up. Adjusted for energy, physical activity	Asymptomatic screened controls
Sandler *et al.*, 1993, USA	M 105/165 F 131/244	FFQ (> 100), interviewed by telephone, previously validated	M: ≥ 23.9 vs < 11.1 servings/wk (5) F: ≥ 24.8 vs < 11.2 servings/wk (5)	Colorectal adenomas: M 1.20 (0.49–2.93) F 0.74 (0.35–1.57)	 $p = 0.72$ $p = 0.69$	Age, alcohol, BMI, energy	Hospital-based

Table 37 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Almendingen *et al.*, 2001, Norway	87/35 hospital and 35 healthy controls, M, F	Dietary record	≥ 181 vs < 80 g/d (3)	Hospital: 0.4 (0.1–1.8) Population: 1.1 (0.2–5.1)	$p = 0.2$ $p = 0.82$	Sex, age, BMI, history of colorectal cancer, energy, fat, fibre, smoking	Hospital-based and population-based
Smith-Warner *et al.*, 2002b, USA	564/535, M, F	Semiquantitative FFQ (153, 59 fruits and veg.)	M ≥ 44.7 vs ≤ 8.8 servings/wk (5) F ≥ 51.4 vs ≤ 10.1 servings/wk (5)	Colorectal adenomas: M 0.55 (0.30–0.98) F 1.40 (0.67–2.92)	$p = 0.16$ $p = 0.24$	Age, energy, fat, BMI, smoking, alcohol, use of NSAIDs, multivitamins, hormone replacement therapy	Population-based

*p for trend when applicable

Table 38. Case–control studies of fruit and vegetable consumption and risk of adenomatous polyps

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Smith-Warner *et al.*, 2002b, USA	564/535, M, F	Semiquantitative FFQ (153, 59 fruits and veg.)	M: ≥ 75.9 vs ≤ 16.5 servings/wk (5) F: ≥ 82.8 vs ≤ 18.4 servings/wk	Colorectal adenoma: M 0.60 (0.32–1.12) F 0.76 (0.34–1.66)	$p = 0.20$ $p = 0.86$	Age, energy, fat, BMI, smoking, alcohol, use of NSAIDs, multivitamins, hormone replacement therapy	Population-based

*p for trend when applicable

Table 39. Cohort study of fruit consumption and risk of liver cancer

Author, year, country	Cases/ cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Sauvaget *et al.*, 2003, Japan	555/38 540, M 17 y	FFQ (22), self-administered	Daily vs 0–1 d/wk (3)	0.96 (0.78–1.19)	$p = 0.81$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors

*p for trend when applicable

Table 40. Case–control studies of fruit consumption and risk of liver cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
La Vecchia *et al.*, 1988b, Italy	151 HCC/1051, M, F	FFQ	Fresh fruit: Highest vs lowest (3)	0.76	NS	Age, sex, area of residence, education, history of hepatitis, alcohol, smoking, other dietary factors	Hospital-based
Parkin *et al.*, 1991, Thailand	93 cholangiocarcinoma/103 hospital or visitor, M, F	FFQ (54)	Fresh fruit: ≥ 3/month vs < 3/month (2)	0.5 (0.3–0.9)		Matched by sex, age, residence	Hospital-based
Hadziyannis *et al.*, 1995, Greece	65 HCC/65 metastatic liver cancer, 65 hospital, M, F	Semiquantitative FFQ (115)		No association			Hospital-based Response rate for cases 89%, for metastatic liver cancer controls 90% and for hospital controls 93%
Kuper *et al.*, 2000, Greece	97 HCC/128, M, F	Semiquantitative FFQ (~ 120)	One quintile increment	1.00 (0.71–1.41)	$p = 0.99$	Age, gender, schooling, HBV/HCV infection, alcohol, tobacco, energy, other food groups	Hospital-based

*p for trend when applicable

Table 41. Cohort studies of vegetable consumption and risk of liver cancer

Author, year, country	Cases/cohort size, gender, (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hirayama, 1990, Japan	1251/265 118, M, F 17 y	FFQ (7)	Green-yellow veg.: daily vs non-daily (2)	0.91 (90% CI 0.82–1.01)		Not reported	Mortality Census-based cohort in seven prefectures
Yu *et al.*, 1995, Taiwan	50/8436, M 54 y	FFQ	≥ 6 veg-containing meals/wk vs < 6	[0.4 (0.2–0.8)]	$p = 0.006$	Age, HBsAg carrier status, cigarette smoking, habitual alcohol consumption, history of liver disease	Incidence Cohort recruited primarily for a study of biological markers of HCC
Sauvaget *et al.*, 2003, Japan	555/38 540, M 17 y	FFQ (22), self-administered	Green-yellow veg.: Daily vs 0–1 d/wk (3)	0.75 (0.60–0.95)	$p = 0.009$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors

*p for trend when applicable

Table 42. Case–control studies of vegetable consumption and risk of liver cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Lam *et al.*, 1982, Hong Kong	106/107, M, F	FFQ	Yellow veg.: weekly vs less Green veg.: daily vs less	0.6 1.0			Hospital-based Response rate for cases 72%
La Vecchia *et al.*, 1988b, Italy	151/1051, M, F	FFQ	Green veg.: Highest vs lowest (3)	0.58	$p < 0.05$	Age, sex, area of residence, education, history of hepatitis, alcohol, smoking, other dietary factors	Hospital-based
Srivatanakul *et al.*, 1991, Thailand	65/65 matched hospital or visitor, M, F	FFQ (54)	"Other" fresh veg.: ≤ twice a day vs less (2)	0.2 (0.04–1.0)	$p < 0.05$	HBsAg status, alcohol, betel-nut chewing, shrimp paste and powdered peanut consumption	Hospital-based. 'Other' fresh veg. consumption excludes cucumber and cabbage (Parkin *et al.*, 1991)

Table 42 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Fukuda *et al.*, 1993, Japan	368/485, M, F	FFQ (12)		No difference in consumption between cases and controls			Hospital-based Response rates high, only 7 cases not interviewed, and 3 controls excluded with incomplete information
Hadziyannis *et al.*, 1995, Greece	65/65 controls with metastatic liver cancer, 65 hospital controls, M, F	Semiquantitative FFQ (115)		No association			Hospital-based Response rate for cases 89%, for metastatic liver cancer controls 90% and for hospital controls 93%
Kuper *et al.*, 2000, Greece	97/128, M, F	Semiquantitative FFQ (~ 120)	One quintile increment	1.21 (0.80–1.82)	$p = 0.36$	Age, gender, schooling, HBV/HCV infection, alcohol, tobacco, energy, other food groups	Hospital-based

*p for trend when applicable

Table 43. Case–control study of fruit and vegetable consumption and risk of liver (hepatocellular cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95%)	Stat. sign.*	Adjustment for confounding	Comments
Braga *et al.*, 1997a, Italy	320/1408, M, F	FFQ	Fresh fruit, green veg. and carrots combined: Highest vs lowest (3)	[0.46 (0.32–0.67)]		Age, sex, area of residence, smoking history, diabetes, liver cirrhosis	Hospital-based. This is an extension of La Vecchia *et al.* (1988b). Attributable risk estimated to be 40% (26–54%), 44% for males (28–60%) and 32% for females (4–60%)

*p for trend when applicable

Table 44. Cohort study of fruit consumption and risk of gallbladder cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Sauvaget *et al.*, 2003, Japan	157/38 540, M 17 y	FFQ (22), self-administered	Daily vs 0–1 d/wk (3)	0.85 (0.57–1.25)	$p = 0.53$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors

*p for trend when applicable

Table 45. Cohort study of vegetable consumption and risk of gallbladder cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hirayama, 1990, Japan	530/265 118, M, F 17 y	FFQ (7)	Green-yellow veg.: Daily vs non-daily (2)	1.06 (90% CI 0.90–1.24)		Not reported	Mortality Census-based cohort in seven prefectures
Sauvaget *et al.*, 2003, Japan	157/38 540, M 17 y	FFQ (22), self-administered	Green-yellow veg.: Daily vs 0–1 d/wk (3)	1.09 (0.73–1.74)	$p = 0.73$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors

*p for trend when applicable

Table 46. Case–control study of fruit and vegetable consumption and risk of gallbladder cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Kato *et al.*, 1989, Japan	109/218, M, F	FFQ (~ 46)	Daily vs less than daily (2)	0.26 (0.13–0.50)		Marital status, other food items	Population-based Response rates 84% for cases, virtually 100% for controls

*p for trend when applicable

Table 47. Cohort studies of fruit consumption and risk of pancreas cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Mills *et al.*, 1988, USA	40/34 000, M, F 7 y	FFQ		Protective, non-significant effect of fresh citrus fruits and fresh winter fruits			Mortality Cohort of Seventh-Day Adventists
Zheng *et al.*, 1993, USA	57/17 633, M 20 y	FFQ (35), self-administered		No association			Mortality Cohort of insurance policy holders
Shibata *et al.*, 1994, USA	65/13 979, M, F 9 y	FFQ (59, 23 fruits)	≥ 3.6 vs < 2.4 servings/d (3)	0.89 (0.49–1.62)	NS	Sex, age, cigarette smoking	Incidence Cohort of a retirement community
Appleby *et al.*, 2002, UK	39/10 741, M, F 25 y	FFQ	Daily consumption of fresh fruit vs less than daily (2)	0.83 (0.38–1.80)	$p > 0.05$	Age, sex, smoking, other foods	Mortality Cohort of health-food shoppers
Stolzenberg-Solomon *et al.*, 2002, Finland	163/27 111, M 13 y	FFQ (over 200), self-administered	Highest vs lowest (5)	0.85 (0.53–1.35)	$p = 0.52$	Age, years of smoking, energy	Incidence Cohort of smokers based on baseline data in a randomized trial
Sauvaget *et al.*, 2003, Japan	177/38 540, M 17 y	FFQ (22), self-administered	Daily vs 0–1 d/wk (3)	0.81 (0.55–1.20)	$p = 0.23$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors

*p for trend when applicable

Table 48. Case–control studies of fruit consumption and risk of pancreas cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Norell *et al*, 1986, Sweden	99/163 hospital and 138 population controls, M, F	FFQ	Fruit juices: Almost daily vs seldom (3) Citrus fruit: Almost daily vs seldom (3)	0.6 (90% CI 0.3–1.2) 0.3 (90% CI 0.1–0.6)		Stratified by sex, age (two groups) and hospital	Hospital- and population-based Response rates 82% for cases Similar finding for population controls, and after adjustments for other risk factors
Voirol *et al.*, 1987, Switzerland	88/336, M, F	Semiquantitative FFQ, interviewed	Average consumption: 88.6 g vs 40 g		Significant		Population-based Response rate 64% for controls
Falk *et al.*, 1988, USA	363/1234, M, F	FFQ (59)	(2)	0.63 (0.49–0.82)	Significant	Sex, age, cigarette smoking, income, residence, Cajun ancestry, respondent type, history of diabetes	Hospital-based Similar finding when fruit juices were included When RR stratified for Cajun/non-Cajun ethnicity, associations were stronger for Cajuns for fruits and juices
Olsen *et al.*, 1989, USA	212/220, M	FFQ	Fruit and juices: ≥ 53 vs ≤ 21 times/mo (3)	0.88 (0.48–1.62)		Age, education, history of diabetes, smoking, alcohol, meat	Population-based Data obtained on 81% of cases ascertained Similar finding for spouse interviews
Farrow & Davis, 1990, USA	148/188 (by random digit dialling), M	FFQ (135), interviewed by telephone		No significant difference in consumption between cases and controls			Population-based Interviews with case spouses

Table 48 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Howe *et al*, 1990, Canada	249/505, M, F	Quantitative FFQ (over 200)	Highest vs lowest (4)	0.92 (0.74–1.14)		Fibre, energy, lifetime cigarette consumption	Population-based 547 cases ascertained 1636 potential controls approached 78% cases and 38% controls interviewed by proxy
La Vecchia *et al.*, 1990a, Italy	247/1089, M, F	FFQ (14)	Fresh fruit: Highest vs lowest (3)	0.68 (0.41–0.98)	$p < 0.05$	Age, sex	Hospital-based
Baghurst *et al.*, 1991, Australia	104/253, community controls, M, F	FFQ (179)		No difference in consumption between cases and controls			Population-based Response rate 62% for male and 63% for female cases, and 57% and 51% for controls, respectively
Bueno de Mesquita *et al.*, 1991, Netherlands	164/480, M, F	Semi-quantitative FFQ (116)	Highest vs lowest (5)	1.09		Age, gender, response status (direct/proxy), smoking, energy	Population-based Overall response rate 72%. More than half of the cases directly interviewed
Lyon *et al.*, 1993, USA	M 85/192 F 60/171	FFQ directed to period 20 y before interview (32)	Highest vs lowest (3)	M 0.81 (0.40–1.62) F 0.37 (0.18–0.81)	$p = 0.26$ $p < 0.05$	Age, cigarette smoking, coffee, alcohol	Population-based Response rate for cases 88%; for controls 77% All data derived from interviews of next of kin
Ji *et al.*, 1995, China	451/1552, M, F	FFQ (86), interviewed	Highest vs lowest (4)	M 0.66 (0.43–1.01) F 0.58 (0.34–1.00)	$p = 0.02$ $p = 0.08$	Age, income, smoking, green tea drinks (females only) and response status	Population-based Deceased cases excluded (19%) Relatives assisted with interviews

Table 48. (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Silverman *et al.*, 1998, USA	436/2003, M, F	FFQ (60), interviewed	Highest vs lowest (4)	M: 0.9 F: 1.1		Age at diagnosis, race, study area, energy, diabetes mellitus, BMI, cholecystectomy, smoking, alcohol, income (men), marital status (women)	Population-based Multicentre study 1153 cases identified 78% ascertained potential controls interviewed
Mori *et al.*, 1999, India	79 pancreatic ductal adenocarcinoma/146 visitor or friend control,	FFQ, interviewed	Every day vs seldom (3)	0.07 (0.02–0.21)	$p < 0.001$		Hospital-based 23 additional cases with chronic calcific pancreatitis and cancer showed no association with fruit consumption

*p for trend when applicable

Table 49. Cohort studies of vegetable consumption and risk of pancreas cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Mills *et al.*, 1988, USA	40/34 000, M, F 7 y	FFQ		Non-significant increase of risk for consumption of cooked green veg. and green salad			Mortality Cohort of Seventh-Day Adventists
Hirayama, 1990, Japan	679/265 118, M, F 17 y	FFQ (7)	Green-yellow veg.: daily vs non-daily (2)	1.11 (90% CI 0.96–1.29)		Not reported	Mortality Census-based cohort in seven prefectures
Zheng *et al.*, 1993, USA	57/17 633, M 20 y	FFQ (35), self-administered		No association			Mortality Cohort of insurance policy holders
Shibata *et al.*, 1994, USA	65/13 979, M, F 9 y	FFQ (59, 21 veg.), self-administered	≥ 4.7 vs < 3.2 servings/d (3)	0.82 (0.44–1.51)	NS	Sex, age, cigarette smoking	Mortality Cohort of members of a retirement community

Table 49 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Stolzenberg-Solomon *et al.*, 2002, Finland	163/27111, M 13 y	FFQ (over 200), self-administered	Highest vs lowest (5)	0.77 (0.47–1.27)	$p = 0.32$	Age, years of smoking, energy	Incidence Cohort based on baseline data in a randomized trial. Potatoes and legumes excluded
Sauvaget *et al.*, 2003, Japan	177/38 540 M 17 y	FFQ (22), self-administered	Green-yellow veg.:daily vs 0–1 d/wk (3)	0.82 (0.54–1.24)	$p = 0.36$	Age, sex, radiation dose, city, BMI, smoking, alcohol, education	Mortality, atomic bombing survivors

*p for trend when applicable

Table 50. Case–control studies of vegetable consumption and risk of pancreas cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Norell *et al.*, 1986, Sweden	99/163 hospital and 138 population controls, M, F	FFQ	Almost daily vs seldom (3)	0.5 (90% 0.3–1.1)		Stratified by sex, age (two groups) and hospital	Hospital- and population-based Response rates 82% for cases. Similar finding for population controls, for raw veg. and after adjustment for other risk factors.
Voirol *et al.*, 1987, Switzerland	88/336, M, F	Semiquantitative FFQ, interviewed	Average consumption: 230 g vs 156.6 g	0.47	Significant		Population-based Response rate for controls 64%
Falk *et al.*, 1988, USA	363/1234, M, F	FFQ (59)	(2)	0.88 (0.68–1.14)	NS	Sex, age, smoking, income, residence, Cajun ancestry, respondent type, history of diabetes	Hospital-based

Table 50 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Olsen *et al.*, 1989, USA	212/220, M	FFQ	Non-cruciferous veg: ≥ 32 vs ≤16 times/mo (3)	0.95 (0.52–1.73)		Age, education, history of diabetes, smoking, alcohol, meat	Population-based Data obtained on 81% of cases ascertained Similar finding for spouse interviews.
Howe *et al.*, 1990, Canada	249/505, M, F	Quantified FFQ (over 200)	Highest vs lowest (4)	1.03 (0.79–1.34)		Fibre, energy, lifetime cigarette consumption	Population-based 547 cases ascertained 1636 potential controls approached 78% cases and 38% controls interviewed by proxy
Farrow & Davies, 1990, USA	148/188 (by random digit dialling), M	FFQ (135), interviewed by telephone		No significant difference in consumption between cases and controls			Population-based Interviews with case spouses
La Vecchia *et al.*, 1990a, Italy	247/1089, M, F	FFQ (14)	Green veg.: Highest vs lowest (3)	0.84 (0.58–1.22)		Age, sex	Hospital-based
Baghurst *et al.*, 1991, Australia	104/253, M, F	FFQ (179)		No difference in consumption between cases and controls			Population-based Response rate 62% for male and 63% for female cases, and 57% and 51% for controls, respectively
Bueno de Mesquita *et al.*, 1991, Netherlands	164/480, M, F	Semi-quantitative FFQ (116)	Highest vs lowest (5)	0.34	$p < 0.05$	Age, gender, response status (direct/proxy), smoking, energy	Population-based Overall response rate 72%. More than half of the cases directly interviewed

Table 50 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Lyon *et al.*, 1993, USA	M 87/191, F 60/169	FFQ directed to period 20 y before interview (32)	Highest vs lowest (3)	M 0.99 (0.50–2.01) F 0.32 (0.13–0.74)	$p = 0.80$ $p = 0.01$	Age, cigarette smoking, alcohol, coffee consumption	Population-based Response rate 88% for cases and 77% for controls. All data derived from interviews of next of kin
Ji *et al.*, 1995, China	451/1552, M, F	FFQ (86), interviewed	Highest vs lowest (4)	M 0.63 (0.45–1.03) F 0.67 (0.39–1.14)	$p = 0.03$ $p = 0.15$	Age, income, smoking, green tea drinks (females only), response status	Population-based Deceased cases excluded (19%) Relatives assisted with interviews.
Silverman *et al.*, 1998, USA	436/2003, M, F	FFQ (60), interviewed	Highest vs lowest (4)	M 0.6 F 0.9	$p = 0.035$	Age at diagnosis, race, study area, energy, cholecystectomy, diabetes mellitus, BMI, cigarette smoking, alcohol, income (men), marital status (women)	Population-based. Multicentre study. 1153 cases identified 78% ascertained potential controls interviewed
Mori *et al.*, 1999, India	79 pancreatic ductal adenocarcinoma/146 visitor or friend control, M, F	FFQ, interviewed	Every day vs seldom or sometimes (3)	0.42 (0.24–0.74)	$p < 0.01$		Hospital-based 23 additional cases with chronic calcific pancreatitis and cancer showed similar, non-significant association with veg. consumption

*p for trend when applicable

Table 51. Case-control studies of fruit and vegetable consumption and risk of pancreas cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Gold *et al.*, 1985, USA	201/201 hospital (H) and 201 population (P) controls, M, F	FFQ, interviewed	Raw fruits and veg.: ≥ 5 vs < 5 times/wk (2)	H: 0.58 (0.37–0.90) P: 0.55 (0.34–0.91)	$p \leq 0.02$	Matched by age, race, sex	Hospital- and population-based Response rates for cases 70%, for hospital controls 54% and for population controls 50% (random digit dialling)
Mack *et al.*, 1986, USA	326/363 neighbourhood controls, M, F	FFQ in broad groups, interviewed	Fresh fruit and veg.: ≥ 5 vs < 5 times/wk (2)	0.7 (0.5–0.9)		Matched by age, sex, race, neighbourhood	Population-based Response rate 66% for cases Direct interviews of 124 pairs, proxy interviews of the remainder

*p for trend when applicable

Table 52. Case–control studies of fruit consumption and risk of larynx cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
De Stefani *et al.*, 1987, Uruguay	107/290, M	FFQ, interviewed, frequency	Daily vs never (4)	[0.37 (0.19–0.77)]	$p < 0.05$	Age	Hospital-based No control for smoking and alcohol
Notani & Jayant, 1987, India	80/215 hospital controls, 177 population control, M	FFQ, interviewed, frequency	≥ once/wk vs < once/wk (2)	Hospital controls: [0.65 (0.33–1.25)] Population controls: [0.50 (0.24–1.0)]		Age, tobacco habits	Hospital-based and population-based
La Vecchia *et al.*, 1990b, Italy	110/833, M	FFQ (17), interviewed, frequency	Fresh fruits: Highest vs lowest (3)	0.3	$p < 0.01$	Age, residence, education, smoking, intake of fish, green veg., alcohol	Hospital-based No interaction with tobacco or with alcohol
Zheng *et al.*, 1992b, China	201/414, M, F	FFQ (41, 5 fruits), interviewed, frequency, portion size	Highest vs lowest (3)	M: 0.7 F: 0.5 (0.2–1.5)	M: $p = 0.21$	Age, education, smoking pack-years	Population-based No control for alcohol
Guo *et al.*, 1995, China	100/100, M, F	FFQ, interviewed	Insufficient vs sufficient	0.44	$p = 0.03$	Age, number of cigarettes, mental factors, using firewood in winter, smoke in environment	Hospital-based No control for alcohol Unclear presentation
Estève *et al.*, 1996, France, Switzerland, Spain, Italy	727 endolarynx/ 2736, M	Diet history, interviewed, frequency, portion size	> 250 vs ≤ 70 g/d (5)	[0.72 (0.53–0.96)]	$p < 0.05$	Age, study centre, smoking, alcohol, energy	Population-based Similar finding for epilarynx and hypopharynx
Maier & Tisch, 1997, Germany	164/656, M	FFQ, interviewed, frequency	Fresh fruit: ≥ once/wk vs less (2)	0.7 (0.4–1.1)	$p = 0.08$	Age, smoking, alcohol	Hospital-based Includes incident and prevalent cases
De Stefani *et al.*, 1999, Uruguay	34/393, M, F	FFQ (64, 8 fruits), interviewed, frequency, portion size	Highest vs lowest (3)	0.8 (0.5–1.3)		Age, sex, residence, urban/rural, education, BMI, smoking pack-years, alcohol, energy	Hospital-based Part of larger case–control study on aero-digestive cancers

Table 52 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
De Stefani *et al.*, 2000a, Uruguay	148/444, M	FFQ (62, 8 fruits), interviewed, frequency, portion size	≥ 204 vs ≤ 69.8 g/d (4)	0.38 (0.20–0.72)	$p = 0.001$	Age, residence, urban/rural, education, BMI, smoking pack-years, alcohol, energy	Hospital-based
Bosetti *et al.*, 2002a, Switzerland, Italy	527/1297, M, F	FFQ (78), interviewed, frequency, portion size	≥ 24.8 vs < 8.9 servings/wk (5)	0.52 (0.35–0.77)	$p < 0.001$	Age, sex, centre, education, smoking, alcohol and non-alcohol energy intake	Hospital-based OR weaker in subgroups of age, alcohol, smoking and for supra-glottis, epiglottis or others

*p for trend when applicable

Table 53. Case–control studies of vegetable consumption and risk of larynx cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
De Stefani *et al.*, 1987, Uruguay	107/290, M	FFQ, interviewed, frequency	Daily vs infrequent (1–3 d/mo) (3)	[0.59 (0.34–1.11)]	NS	Age	Hospital-based No control for smoking and alcohol
Notani & Jayant, 1987, India	80/215 hospital controls, 177 population controls, M	FFQ, interviewed, frequency	Daily vs not daily (2)	Hospital controls:[0.78 (0.42–1.43)] Population controls: [0.36 (0.19–0.71)]		Age, tobacco habits	Hospital-based and population-based
La Vecchia *et al.*, 1990b, Italy	110/833, M	FFQ (17), interviewed, frequency	Green veg.: Highest vs lowest (3)	0.4	NS	Age, residence, education, smoking, fish, fresh fruit, alcohol	Hospital-based No total veg.
Zheng *et al.*, 1992b, China	201/414, M, F	FFQ (41, 26 veg.), interviewed, frequency, portion size	Highest vs lowest (3)	M: 1.2 F: 1.1 (0.4–3.2)	M: $p = 0.61$	Age, education, smoking pack-years	Population-based No control for alcohol

Table 53 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Guo *et al.*, 1995, China	100/100, M, F	FFQ, interviewed	Sufficient vs insufficient	0.37	$p = 0.03$	Age	Hospital-based No control for alcohol
Estève *et al.*, 1996, France, Italy, Spain, Switzerland	727 endolarynx/ 2736, M	Diet history, interviewed, frequency, portion size	> 350 vs ≤ 170 g/d (5)	[0.61 (0.45–0.81)]	$p < 0.05$	Age, study centre, smoking, alcohol, energy	Population-based Similar finding for epilarynx and hypopharynx
De Stefani *et al.*, 1999, Uruguay	34/393,. M, F	FFQ (64, 14 veg.), interviewed, frequency, portion size	Highest vs lowest (3)	0.9 (0.6–1.6)		Age, sex, residence, urban/rural, education, BMI, smoking pack-years, alcohol, energy	Hospital-based Part of larger case–control study on aerodigestive cancers
De Stefani *et al.*, 2000a, Uruguay	148/444, M	FFQ (62, 11 veg.), interviewed, frequency, portion size	≥ 120.4 vs ≤ 54.1 g/d (4)	0.57 (0.30–1.08)	$p = 0.18$	Age, residence, urban/rural, education, BMI, smoking pack-years, alcohol, energy	Hospital-based
Bosetti *et al.*, 2002a, Switzerland, Italy	527/1297, M, F	FFQ (78), interviewed, frequency, portion size	≥ 18.1 vs < 8.6 servings/wk (5)	0.17 (0.11–0.27)	$p < 0.001$	Age, sex, centre, education, smoking, alcohol and non-alcohol energy intake	Hospital-based OR similar for subgroups of age, alcohol, smoking and for supraglottis, epiglottis or others

Table 54. Case–control studies of fruit and vegetable consumption and risk of larynx cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Zatonski *et al.*, 1991, Poland	249/965, M	FFQ (30), interviewed, frequency	Highest vs lowest (3)	0.34 (0.18–0.64)		Age, residence, education, smoking, alcohol	Population-based
De Stefani *et al.*, 2000a, Uruguay	148/444, M	FFQ (62, 8 fruits and 11 veg.), interviewed, frequency, portion size	≥ 320.7 vs ≤ 143.0 g/d (4)	0.30 (0.15–0.59)	$p < 0.001$	Age, residence, urban/rural, education, BMI, smoking pack-years, alcohol, energy	Hospital-based

*p for trend when applicable

Table 55. Cohort studies of fruit consumption and risk of lung cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95 % CI)	Stat. sign.*	Adjustment for confounding	Comments
Kvale *et al.*, 1983, Norway	168/13 785, M 11.5 y	FFQ (31, 9 fruits), self-administered, frequency	≥ 50 vs < 20 times/mo (4)	1.10	$p = 0.90$	Age, cigarette smoking, region, urban/rural residence	Incidence RR = 0.71 (NS) for squamous and small-cell carcinomas
Wang & Hammond 1985, USA	671/136 28, M 10 y	FFQ (16), self-administered, frequency	Fruit/fruit juice: 5–7 vs 0–2 d/wk (3)	[0.57]		Age	Mortality No control for smoking. RR = 0.52 in those taking vitamin pills; RR = 0.65 in heavy smokers
Fraser *et al.*, 1991, USA	61/34 198, M, F 6 y	FFQ (51, 5 fruits), self-administered, frequency	≥ 2 times/d vs < 3 times/wk (3)	0.26 (0.10–0.70)	$p = 0.006$	Age, sex, smoking history	Incidence Seventh-Day Adventists RR = 0.28 in never-smokers, RR= 0.22 in ever-smokers. Similar finding for adenocarcinoma and tumours of other cell types
Chow *et al.*, 1992, USA	219/17 633, M 20 y	FFQ (35), self-administered, frequency	> 90 vs < 31 times/mo (4)	0.7 (0.4–1.3)		Age, smoking status, occupation	Mortality Lutheran Brotherhood Significant association only for oranges
Shibata *et al.*, 1992, USA	164 (94 M, 70 F)/11 580 9 y	FFQ (59, 23 fruits), self-administered, frequency	M: ≥ 3.5 vs < 2.2 servings/d (3) F: > 3.7 vs < 2.4 servings/d (3)	0.99 (0.59–1.66) 0.68 (0.37–1.24)	NS NS	Age, smoking	Incidence Retirement community
Steinmetz *et al.*, 1993, USA	138/2814, F 4 y	FFQ (127, 15 fruits), self-administered, frequency, portion size; validated	≥ 18 vs ≤ 7 servings/wk (4)	0.75 (0.44–1.23)	$p = 0.08$	Age, pack-years of smoking, energy	Incidence Nested case–control; total cohort = 34 977 Strongest effect in large-cell carcinoma and in ex-smokers, but small numbers
Key *et al.*, 1996, UK	59/10 771, M, F 17 y	FFQ (5), self-administered, frequency	Fresh fruit: Daily vs less than daily (2)	SMR: 0.59 (0.34–1.02)		Age, sex, smoking	Mortality Vegetarians and health-conscious people

Table 55 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95 % CI)	Stat. sign.*	Adjustment for confounding	Comments
Ocké *et al.*, 1997a, Netherlands	54/561. M 20 y	Dietary history, spouse interview, frequency and portion size	> 33rd vs ≤ 33rd percentile (2)	0.40 (0.18–0.87)		Age, pack-years of cigarette smoking, energy	Incidence RR for stable dietary habits. Weaker RR for average habits
Breslow *et al.*, 2000, USA	154/20 004, M, F 8.5 y	FFQ (59, 5 fruits), self-administered, frequency, portion size; validated	> 11.5 vs < 3 servings/wk (4)	0.9 (0.5–1.6)	$p < 0.489$	Age, sex, smoking duration, packs/day smoked	Mortality
Feskanich *et al.*, 2000, USA	F 519/77 823 M 274/47 778 F: 12 y M: 10 y	FFQ (116, 15 fruits), self-administered, frequency, portion size; validated	F > 3.1 vs < 1.7 servings/d (5) M > 3.3 vs ≤ 1.7 servings/d (5)	0.76 (0.56–1.02) 1.22 (0.80–1.87)		Age, follow-up cycle, smoking status, years since quitting, cigarettes/day, age at start smoking, energy	Incidence In females, effect strongest in never-smokers; effect similar in Kreyberg I and II In males, protective effect only in never-smokers, and in Kreyberg I
Voorrips *et al.*, 2000b, Netherlands	1010/2953 (subcohort), M, F 6.3 y	FFQ (150, 8 fruits), self-administered, frequency , portion size; validated	Highest (median 325 g/d) vs lowest (median 46 g/d) (5)	0.8 (0.6–1.1)	$p < 0.001$	Age, sex, family history of lung cancer, education, current smoker (y/n), years of smoking, cig./day	Incidence Total cohort = 120 852 Protective effect only in smokers (current and ex), and in all cell types
Jansen *et al.*, 2001, Finland, Italy, Netherlands	149/1578, M, smokers 25 y	Dietary history, interviewed, frequency and portion size	Highest vs lowest (3)	0.69 (0.46–1.02)	$p = 0.05$	Age, cig./day, country, energy, veg.	Mortality. Protective effect only in heavy smokers (20+ cig/day) Effects less strong in Italy

Table 55 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95 % CI)	Stat. sign.*	Adjustment for confounding	Comments
Holick *et al.*, 2002, Finland	1644/ 27 084, M, smokers 14 y	FFQ (276), self-administered, frequency, portion size; validated	> 188 vs < 45 g/d (5)	0.87 (0.74–1.02)	$p = 0.01$	Age, years smoked, cig./ day, interven-tion (α-tocopherol/β-carotene), previ-ous supplement use (β-carotene and vitamin A), energy, choles-terol, fat	Incidence ATBC trial
Sauvaget *et al.* 2003, Japan	563/38 540, M, F 18 y	FFQ (22), self-administered, frequency; vali-dated	Highest vs lowest (3)	0.80 (0.65–0.98)	$p = 0.035$	Age, sex, radia-tion dose, city, BMI, smoking status, alcohol, education	Mortality Atomic bombing survivors Strongest effect in never and cur-rent smokers No effect in women
Miller *et al.* 2003, 10 European countries	860/478 021, M, F 0–14 (mean 6 y)	FFQ (~300), self-adminis-tered or inter-viewed, fre-quency, portion size; calibration study	Highest vs lowest (5)	0.60 (0.46–0.78)	$p = 0.01$	Age, sex, weight, height, centre, smoking intensity and duration	Incidence Strongest effects in never- and current smokers
Neuhouser *et al.*, 2003, USA	Intervention arm: 414/7072, M, F Placebo arm: 326/7048, M, F 12 y	FFQ, self-administered (45 items relating to fruit and veg.)	Intervention arm: Highest vs lowest (5) Placebo arm: Highest vs lowest (5)	0.79 (0.57–1.11) 0.56 (0.39–0.81)	$p = 0.13$ $p = 0.003$	Sex, age, smoking status, total pack-years of smoking, asbestos expo-sure, race/ ethnicity, enrol-ment centre	Follow-up of participants in CARET trial in smokers and asbestos workers
Smith-Warner *et al.*, 2003, pooled analy-sis of 8 cohorts	3206/430 281 (8 cohorts), M, F 6–16 y	FFQ self-administered, frequency, portion size; validated	Highest vs lowest (5)	0.77 (0.67–0.87)	$p < 0.001$	Age, education, BMI, alcohol, energy, smoking status, duration, amount smoked	Incidence Effect strongest in never-smokers; significant effect only in current smokers; stronger effects in squa-mous-cell and adenocarcinoma than small-cell carcinoma Citrus fruit in-versely associated

*p for trend when applicable

Table 56. Case–control studies of fruit consumption and risk of lung cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Ziegler *et al.*, 1986, USA	763/900, M	FFQ (44, 12 fruits), interviewed, frequency	Highest vs lowest (4)	1.0	$p = 0.35$	Age, smoking	Population-based Small effect in current and recent smokers
Fontham *et al.*, 1988, USA	1253/1274, M, F	FFQ (59), interviewed, frequency	Highest vs lowest (3)	0.66 (0.54–0.82)	Significant	Age, sex, race, pack-years cig., family income, ethnic group, respondent status, veg. intake	Hospital-based Somewhat stronger effect in squamous and small-cell than in adenocarcinoma
Koo, 1988, China	88/137, F, never-smokers (< 20 cig. in past)	FFQ, interviewed, frequency	Fresh fruit: Highest vs lowest (3)	[0.42 (0.19–0.92)]	$p = 0.002$	Age, no. of live births, schooling	Population-based RR = 0.65 in adenocarcinoma and large cell; RR = 0.43 in squamous and small-cell carcinoma
Jain *et al.*, 1990, Canada	839/772, M, F	Diet history (81), interviewed, frequency, portion size; validated	> 378 vs < 110 g/d (4)	1.10	$p = 0.76$	Age, sex, residence, cumulative cig. smoking	Population-based
Kalandidi *et al.*, 1990, Greece	91/120, F, never-smokers (lifelong)	FFQ (47), interviewed, frequency	Highest vs lowest (4)	0.33 (0.13–0.68)	$p = 0.02$	Age, years of education, interviewer, energy	Hospital-based ORs similar in adenocarcinoma and other types
Candelora *et al.*, 1992, USA	124/263, F never-smokers (< 100 cig. in lifetime)	FFQ (60), interviewed, frequency, portion size	Highest vs lowest (4)	0.6 (0.3–1.1)	$p = 0.04$	Age, education, energy	Population-based
Forman *et al.*, 1992, China	183/183, M tin miners	FFQ (27), interviewed, frequency	Highest vs lowest (4)	[1.10 (0.57–2.08)]		Age, cumulative tobacco intake (water pipe), pack-years cig., height, number of meals/day at home, socioeconomic status, radon and arsenic exposure	Population-based

Table 56 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Swanson *et al.*, 1992, China	425/1007, M, tin mining community	FFQ (31), interviewed, frequency	Fresh fruit: > 3.9 vs < 1.1 times/mo (4)	0.94	$p = 0.31$	Age, respondent type, study site, smoking, family income, education, occupation	Population-based Associations for tin miners and mining community
Alavanja *et al.*, 1993, USA	429/1021, F, not current smokers	FFQ (60, 16 fruits), self-administered, frequency, portion size	≥ 22.1 vs ≤ 9.2 servings/wk (5)	1.14	$p = 0.99$	Age, smoking history, pre-vious lung disease, interview type, energy	Population-based
Dorgan *et al.*, 1993, USA	1951 (355 blacks)/1238 (217 blacks), M, F	FFQ (44, 8 fruits), interviewed, frequency	≥ 37 vs ≤ 18 servings/mo (3)	WM: [0.95 (0.70–1.30)] WF: [0.56 (0.40–0.79)] BM: [2.04 (1.11–3.70)] BF: [1.30 (0.44–3.85)]	NS $p < 0.01$ $p < 0.05$ NS	Age, education, occupation, residence, smoking, passive smoking, study phase	Population-based Extension to females and blacks from Ziegler *et al.* (1986)
Gao *et al.*, 1993, Japan	282/282, M, smokers	FFQ, interviewed, frequency	Daily vs < sometimes (3)	0.45 (0.30–0.67)		Age, smoking status	Hospital-based Stronger effect in squamous and adenocarcinoma and in current smokers
Suzuki *et al.*, 1994, Brazil	123/123, M, F	FFQ, interviewed, frequency	Daily vs < once/wk (3)	1.2 (0.4–3.1)	$p = 0.57$	Age, sex, race, pack-years, smoking, income	Hospital-based
Mayne *et al.*, 1994, USA	413/413, M, F, not current smokers	FFQ (26), interviewed, frequency	Fresh fruit: Highest vs lowest (4)	0.44	$p < 0.01$	Age, sex, prior cig. use, religion, education, BMI, income	Population-based
Axelsson *et al.*, 1996, Sweden	308/504, M	FFQ (80), interviewed, frequency	Fruit index: Almost daily vs < 1–2/mo (3)	0.73 (0.43–1.23)	$p = 0.014$	Age, cig./day, years smoked, marital status, socioeconomic job class	Population-based OR lower for 'other fruits and berries'. OR fruit = 1.02 when veg. index in model

Table 56 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Lei *et al.*, 1996, China	792/792, M, F	FFQ, spouse interview, frequency	≥ almost daily vs never (3)	M: 0.79 (0.56–1.11) F: 0.87 (0.51–1.47)		Age	Population-based No control for smoking Deceased cases and controls; info. from spouses or cohabiting relatives
Xu *et al.*, 1996, China	610/959, M iron and steel workers	FFQ, interviewed, frequency	≥ 55 vs 0 'jing'/y (4)	0.6 (0.5–0.9)		Age, smoking (pack-years), income, education, tea intake, pulmonary disease, family history of lung cancer	Population-based
Agudo *et al.*, 1997, Spain	103/206, F	FFQ (33, 8 fruits), interviewed, frequency, portion size	Fresh fruit: Highest vs lowest (3)	1.20 (0.56–2.56)	$p = 0.66$	Age, residence, hospital, smoking status, pack-years	Hospital-based
Hu *et al.*, 1997, China	227/227, M, F	FFQ (50, 4 fruits), interviewed, frequency	≥ 15 vs 0 kg/y (4)	0.7 (0.4–1.2)	$p = 0.10$	Age, sex, residence, cig./day, smoking, duration, income	Hospital-based OR = 0.9 in smokers, OR = 0.6 in non-smokers
Ko *et al.*, 1997, Taiwan, China	105/105, F non-smokers	FFQ (12), interviewed, frequency, portion size	Daily vs 0–6/wk (2)	1.0 (0.5–1.7)		Age, date of interview, education, socio-economic status, residential area	Hospital-based
Pawlega *et al.*, 1997, Poland	176/341, M	FFQ, self-administered, frequency	>1 vs < 1 times/wk (3)	0.42 (0.23–0.77)	$p < 0.05$	Age, education, residence, pack-years smoking, occupational exposure	Population-based OR = 1.67 among drinkers of vodka above average
Pillow *et al.*, 1997, USA , Sweden	137/187, M, F	FFQ (100), self-administered, frequency, portion size	Continuous variable	0.56 (0.31–0.99)	$p = 0.05$	Age, sex, ethnicity, pack-years smoking, energy	Population-based Increment is unclear

Table 56 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Nyberg *et al.*, 1998, Sweden	124/235, M, F never-smokers	FFQ (19), interviewed, frequency	Fruit index: Highest vs lowest (3)	0.67 (0.33–1.36)		Age, sex, urban residence, occasional smoking, occupation, passive smoking, carrots	Population-based
Brennan *et al.*, 2000, European centres	506/1045, M, F (never-smokers, < 400 cig. in life-time)	FFQ, interviewed, frequency	2–7/wk vs < 1/mo (3)	1.0 (0.6–1.5) SqCC 0.7 SmCC 0.9 ADC 0.9	$p = 0.81$	Age, sex, centre	Population-based Items differed per centre
Alavanja *et al.*, 2001, USA	360/574, F	FFQ (70, 6 fruits), self-administered, frequency	Fruit and fruit juice: Highest vs lowest (5)	0.4 (0.3–0.6)	$p < 0.001$	Age, energy	Population-based No control for smoking
Takezaki *et al.*, 2001, Japan	1045/4153, M, F	FFQ (24), self-administered, frequency	Daily vs almost never (4)	M, ADC: 0.98 (0.61–1.58) M, SqSC + SmCC: 0.61 (0.40– 0.95) F, ADC: 0.68 (0.27–1.70) F, SqCC + SmCC: 0.49 (0.11–2.13)	$p = 0.383$ $p = 0.007$ $p = 0.536$ $p = 0.668$	Age, year of visit, occupation, prior lung diseases, smoking, meat, green veg.	Hospital-based
De Stefani *et al.*, 2002, Uruguay	1032/1030, M, F	FFQ (11), interviewed, frequency, portion size	> 364 vs ≤ 52 servings/y (4)	0.84 (0.62–1.13)	$p = 0.14$	Age, sex, residence, urban/rural, education, year of diagnosis, smoking status, years since quitting, smoking intensity, age at start, energy	Hospital-based Strongest effects in large-cell carcinoma, in never- and current smokers

Table 56 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Kreuzer *et al.*, 2002, Germany	234/535, F (never-smokers, < 400 cig. in lifetime)	FFQ (15) interviewed, frequency	Daily vs ≤ once/wk (3)	0.66 (0.37–1.19)	$p = 0.94$	Age, region	Population-based
Marchand *et al.*, 2002, New Caledonia	134/295, M, F	FFQ (89), interviewed, frequency, portion size	Highest vs lowest (3)	M: 0.7 (0.4–1.5)	$p = 0.09$	Age, ethnicity, pack-years smoking	Population-based No significant association in women ('data not shown')
Rachtan, 2002a, Poland	242/352, F	FFQ (17), self-administered, frequency	Daily vs rarely (2)	0.49 (0.32–0.74)	$p = 0.001$	Age, pack-years	Population-based
Seow *et al.*, 2002, Singapore	303/765, F	FFQ (39, 12 fruits), interviewed, frequency, portion size	≥ 9.7 vs < 3.8 servings/wk (3)	Smokers: 0.63 (0.28–1.44) Non-smokers: 0.60 (0.39–0.93)	$p = 0.4$ $p = 0.03$	Age, date of admission, place of birth, family history of cancer, (for smokers: duration, cig./day)	Hospital-based

*p for trend when applicable

ADC, adenocarcinoma; SqCC, squamous-cell carcinoma; SmCC, small-cell carcinoma

Table 57. Cohort studies of vegetable consumption and risk of lung cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95 % CI)	Stat. sign.*	Adjustment for confounding	Comments
Kvale *et al.*, 1983, Norway	168/13 785, M 11.5 y	FFQ (31, 8 veg.), self-administered, frequency	Veg. index: ≥ 50 vs < 20 times/mo (4)	0.74	$p = 0.37$	Age, sex, cig. smoking, region, urban/rural residence	Incidence RR = 0.54 (NS) for squamous and small cell carcinomas
Fraser *et al.*, 1991, USA	61/34 198, M, F 6 y	FFQ (51), self-administered, frequency	Cooked green veg.: ≥ 7 vs < 3 times/wk (3)	1.09 (0.41–2.87)	$p = 0.50$	Age, sex, cig. smoking status (never, ex, current)	Potatoes excluded Incidence Seventh-Day Adventists No information on total veg.
Chow *et al.*, 1992, USA	219/17 633, M 20 y	FFQ (35), self-administered, frequency	> 160 vs < 46 times/mo (4)	1.2 (0.6–2.3)		Age, smoking status, occupation	Mortality Lutheran Brotherhood

Table 57 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95 % CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata *et al.*, 1992, USA	164 (94 M 70 F)/11 580 9 y	FFQ (59, 21 veg.), self-administered, frequency	M: ≥ 4.5 vs < 3 servings/d (3) F: ≥ 4.8 vs < 3.2 servings/d (3)	1.37 (0.74–2.25) 0.58 (0.32–1.05)	NS NS	Age, smoking	Incidence Retirement community
Steinmetz *et al.*, 1993, USA	138/2814, F 4 y	FFQ (127, 29 veg.), self-administered, frequency, portion size; validated	≥ 31 vs ≤ 14 servings/wk (4)	0.50 (0.29–0.87)	$p = 0.01$	Age, pack-years of smoking, energy	Incidence Nested case–control; total cohort 34 977 Strongest effect in large-cell carcinoma, and in ex-smokers, but small numbers
Ocké *et al.*, 1997a, Netherlands	54/561, M 20 y	Dietary history, spouse interview; frequency and portion size	> 33rd vs ≤ 33rd percentile (2)	0.47 (0.21–1.03)		Age, pack-years of cig. smoking, energy	Incidence RR for stable dietary habits Weaker RR for average habits
Breslow *et al.*, 2000, USA	158/20 004, M, F 8.5 y	FFQ (59, 12 veg.), self-administered, frequency, portion size; validated	> 13.6 vs < 5.2 servings/wk (4)	0.9 (0.5–1.5)	$p < 0.786$	Age, sex, smoking duration, packs/day smoked	Mortality
Feskanich *et al.*, 2000, USA	519/77 823, F 274/47 778 M F 12 y M 10 y	FFQ (116, 23 veg.), self-administered, frequency, portion size; validated	F: > 4.3 vs ≤ 2.5 servings/d (5) M: > 4.1 vs ≤ 2.3 servings/d (5)	0.68 (0.51–0.90) 1.04 (0.69–1.57)		Age, follow-up cycle, smoking status, years since quitting, cig./day, age at start smoking, energy	Incidence Excludes beans and lentils, potatoes For females, effect strongest in current smokers, and in Kreyberg I For males protective effect only in never-smokers, and in Kreyberg I
Voorrips *et al.*, 2000b, Netherlands	1010/2953 (sub-cohort), M, F 6.3 y	FFQ (150, 21 veg.), self-administered, frequency, portion size; validated	Highest (median 286 g/d) vs lowest (103 g/d) (5)	0.7 (0.5–1.0)	$p = 0.001$	Age, sex, family history of lung cancer, education, current smoker, years of smoking, cig./day	Incidence Total cohort = 120 852 Protective effect only in current and ex smokers, and in Kreyberg I (men)

Table 57 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95 % CI)	Stat. sign.*	Adjustment for confounding	Comments
Jansen *et al.*, 2001, Italy, Netherlands	149/1578, M, smokers 25 y	Dietary history, interviewed, frequency and portion size	Highest vs lowest (3)	0.90 (0.61–1.33)	$p = 0.59$	Age, cig./day, country, energy, fruit	Mortality Protective effect only in heavy smokers (20+ cig./day), effects less strong in Italy
Ozasa *et al.*, 2001, Japan	572/98 248, M, F 9 y	FFQ (32), self-administered, frequency	Green leafy veg.: Almost daily vs ≤ 1–2/wk (3)	M: 0.76 (0.59–0.98) F: 1.19 (0.75–1.90)	$p = 0.035$ $p = 0.45$	Age, family history of lung cancer, smoking status, cigts/day x duration, time since quitting	Mortality No information on total veg. Effects stronger in male ex-smokers and female non-smokers
Holick *et al.*, 2002, Finland	1644/27 084, M, smokers 14 y	FFQ (276), self-administered, frequency, portion size; validated	> 156 vs < 52 g/d (5)	0.75 (0.63–0.88)	$p < 0.0001$	Age, years smoked, cig./day, intervention (α-tocopherol/β-carotene), previous supplement use (β-carotene and vitamin A), energy, cholesterol, fat	Incidence ATBC trial
Miller *et al*, 2003, 10 European countries	860/ 478,021, M, F (0–14 mean 6 y)	FFQ (300), self-administered or interviewed, frequency, portion size; calibration study	Highest vs lowest (5)	1.00 (0.76–1.30)	$p = 0.85$	Age, sex, weight, height, centre, smoking	Incidence No association in never-, current and ex-smokers
Neuhouser *et al.*, 2003, USA	Intervention arm: 414/7072, M, F Placebo arm: 326/7048, M, F 12 y	FFQ, self-administered (45 items relating to fruit and veg.)	Intervention arm: Highest vs lowest (5) Placebo arm: Highest vs lowest (5)	0.81 (0.65–1.21) 0.82 (0.59–1.14)	$p = 0.46$ $p = 0.39$	Sex, age, smoking status, pack-years of smoking, asbestos exposure, race/ethnicity, enrolment centre	Follow up of participants in CARET trial in smokers and asbestos workers

Table 57 (contd)

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Sauvaget *et al.*, 2003, Japan	563/38 540, M, F 18 y	FFQ (22), self-administered, frequency; validated	Green-yellow veg.: Highest vs lowest (3)	0.95 (0.76–1.19)	$p = 0.676$	Age, sex, radiation dose, city, BMI, smoking status, alcohol, education	Mortality Atomic bombing survivors No information on total veg. No association in smoking subgroups
Smith-Warner *et al*, 2003, pooled analysis	3206/430 281 (8 cohorts), M, F 6–16 y	FFQ, self-administered, frequency, portion size; validated	Highest vs lowest (5)	0.88 (0.78–1.00)	$p = 0.12$	Age, education, BMI, alcohol, energy, smoking status, duration, amount smoked	Incidence No difference between smoking status categories, or between morphological categories

*p for trend when applicable

Table 58. Case–control studies of vegetable consumption and risk of lung cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
MacLennan *et al.*, 1977, Singapore	233/300, M, F	FFQ (8 veg.), interviewed, frequency	Veg. index: Highest vs lowest (2)	[0.45 (0.30–0.67)]		Age, sex, dialect, smoking, socio-economic status	Hospital-based
Ziegler *et al.*, 1986, USA	763/900, M	FFQ (44, 16 veg.), interviewed, frequency	Highest vs lowest (4)	[0.71]	$p = 0.01$	Age, smoking	Population-based Strongest effect for squamous-cell carcinoma Effect limited to current and recent smokers
Fontham *et al.*, 1988, USA	1253/1274, M, F	FFQ (59), interviewed, frequency	Highest vs lowest (3)	0.90 (0.74–1.11)	NS	Age, sex, race, pack-years cig., family income, ethnic group, respondent status, fruit intake	Hospital-based No difference between cell types
Le Marchand *et al.*, 1989, USA	332/865, M, F	FFQ (>130, 22 veg.), interviewed, frequency, portion size; validated	Highest vs lowest (4)	M: [0.31 (0.17–0.56)] F: [0.18 (0.06–0.53)]	$p = 0.001$ $p = 0.001$	Age, ethnicity, smoking status, pack-years cig., cholesterol intake (M only), total vitamin C and folic acid intake	Population-based Effect most apparent in current and recent ex-smokers in M, and in never/ex-smokers in F Effect somewhat stronger for squamous- and small-cell in M
Jain *et al.*, 1990, Canada	839/772, M, F	Diet history (81), interviewed, frequency, portion size; validated	> 308 vs < 129 g/d (4)	0.60 (0.40–0.88)	$p = 0.01$	Age, sex, residence, cumulative cig. smoking	Population-based
Kalandidi *et al.*, 1990, Greece	91/120, F, never-smokers (lifelong)	FFQ (47), interviewed, frequency	Highest vs lowest (4)	1.09 (0.44–2.68)	$p = 0.86$	Age, years of education, interviewer, energy	Hospital-based
Candelora *et al.*, 1992, USA	124/263, F (never-smokers, < 100 cig. in lifetime)	FFQ (60), interviewed, frequency, portion size	Highest vs lowest (4)	0.3 (0.1–0.5)	Significant	Age, education, energy, fruit consumption	Population-based ORs higher for self-reports than for next of kin interviews

Table 58 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Forman *et al.*, 1992, China	183/183, M, tin miners	FFQ (27), interviewed, frequency	Highest vs lowest (4)	[0.60 (0.30–1.18)]		Age, cumulative tobacco intake (water pipe), pack-years cig. smoking, height, number of meals/day at home, socio-economic status, radon and arsenic exposure	Population-based Stronger protective effect for yellow-light green veg.
Alavanja *et al.*, 1993, USA	429/1021, F, not current smokers	FFQ (60; 28 veg.), self-administered, frequency, portion size	≥ 25 vs ≤ 13 servings/wk (5)	0.99	$p = 0.89$	Age, smoking history, previous lung disease, interview type, energy	Population-based Includes potatoes
Dorgan *et al.*, 1993, USA	1951 (355 blacks)/1238 (217 blacks), M, F	FFQ (44, 16 veg.), inter-viewed, frequency	≥ 66 vs ≤ 41 servings/mo (3)	WM: [0.80 (0.58–1.10)] WF: [0.59 (0.42–0.82)] BM: [1.10 (0.59–2.04)] BF: [0.67 (0.23–1.96)]	NS $p < 0.01$ NS NS	Age, education, occupation, resi-dence, smoking, passive smoking, study phase	Population-based Extension to females and blacks from Ziegler *et al.* (1986) Effects stronger in squamous- and small-cell than adenocarcinoma Effect limited to current and ex cig. smokers
Sankaranara-yanan *et al.*, 1994, India	261/1190, M	FFQ (45, 12 veg.), inter-viewed, frequency	Highest vs lowest (4)	0.32 (0.13–0.78)	$p = 0.02$	Age, smoking, education, religion	Population-based Onions most pro-tective (RR = 0.03)
Mayne *et al.*, 1994, USA	413/413, M, F, not current smokers	FFQ (26), inter-viewed, frequency	Highest vs lowest (4)	M: 0.55 F: 0.47	NS $p < 0.025$	Age, prior cig. use, religion, education, BMI, income	Population-based

Table 58 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Axelsson *et al.*, 1996, Sweden	308/504, M	FFQ (80), interviewed, frequency	Veg. index: Almost daily vs < 1–2/mo (3)	0.37 (0.23–0.61)	$p < 0.001$	Age, cig./day, years smoked, marital status, socio-economic job class	Population-based OR lower for cabbage, green pepper. OR=0.37 in current smokers; Lowest in 30+ y smokers Consistent low OR for all 4 hist. types
Agudo *et al.*, 1997, Spain	103/206, F	FFQ (33, 11 veg.), interviewed, frequency, portion size	Highest vs lowest (3)	0.65 (0.32–1.31)	$p = 0.23$	Age, residence, hospital, smoking status, pack-years	Hospital-based Includes potatoes. Same OR in ADC and never smokers (only subgroups)
Hu *et al.*, 1997, China	227/227, M, F	FFQ (50, 20 veg.), interviewed, frequency	Fresh veg.: > 138 vs < 77 kg/y (4)	0.8 (0.4–1.3)	$p = 0.65$	Age, sex, residence, cig./day, smoking duration, income	Hospital-based OR=1.0 in smokers, OR=0.6 in non-smokers
Ko *et al.*, 1997, Taiwan	105/105, F, non-smokers	FFQ (12), interviewed, frequency, portion size	Daily vs 0–6 times/wk (2)	0.4 (0.2–0.8)		Age, date of interview, education, residential area	Hospital-based
Pawlega *et al.*, 1997, Poland	176/341, M	FFQ, self-administered, frequency	Boiled veg: > 3 vs < 3 times/wk (3)	0.22 (0.11–0.43)	$p < 0.05$	Age, education, residence, pack-years smoking, occupational exposure	Population-based OR=0.08 among drinkers of vodka above average
Pillow *et al.*, 1997, USA	137/187, M, F	FFQ (100), self-administered, frequency, portion size	Continuous variable	1.49 (0.84–2.63)	$p = 0.17$	Age, sex, ethnicity, pack-years smoking, energy	Population-based Increment is unclear

Table 58 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Nyberg *et al.*, 1998, Sweden	124/235 M, F (never-smokers)	FFQ (19), interviewed, frequency	Veg. index: Highest vs lowest (3)	0.57 (0.29–1.13)	$p = 0.35$	Age, sex, urban residence, occasional smoking, occupation, passive smoking, non-citrus fruit	Population-based
Brennan *et al.*, 2000, 8 European centres	506/1045, M, F (never smokers, < 400 cigs in lifetime)	FFQ, interviewed, frequency	Fresh veg.: 7/wk vs < 1/wk (3)	0.7 (0.5–1.0)	$p = 0.09$	Age, sex, centre	Population-based Items differed per centre. Effect only seen in adenocarcinoma
Kubik *et al.*, 2001, Czech Republic	282/1120, F	FFQ (9), interviewed, frequency	> several times/wk vs. 'never' (4)	0.84 (0.6–1.3)		Age, residence, education, pack-years smoking	Hospital-based Effect only (OR=0.55) in squamous +small + large cell carcinoma
De Stefani *et al.*, 2002, Uruguay	1032/1030, M, F	FFQ (11), interviewed, frequency, portion size	> 156 vs < 52 servings/y (4)	0.72 (0.54–0.97)	$p = 0.008$	Age, sex, residence, urban/rural, education, year of diagnosis, smoking status, years since quitting, smoking intensity, age at start, energy	Hospital-based Strongest effects in squamous-, small- cell carcinoma, in current and ex- smokers
Marchand *et al.*, 2002, New Caledonia	134/295, M, F	FFQ (89), interviewed, frequency, portion size	Highest vs lowest (3)	M: 1.4 (0.7–2.9)	$p = 0.72$	Age, ethnicity, pack-years smoking	Population-based No significant association in women ('data not shown')

Table 58 (contd)

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Rachtan, 2002b Poland	242/352, F	FFQ (17), self-administered, frequency	Veg. other than carrots: Daily vs. rarely (2)	0.24 (0.11–0.52)		Age, pack-years of smoking, passive smoking, consumption of beer and vodka, siblings with cancer, tuberculosis, place of residence, occupational exposures	Population-based
Seow *et al.*, 2002, Singapore	303/765, F	FFQ (39, 19 veg.), interviewed, frequency, portion size	> 26.4 vs. < 14.3 servings/wk (3)	Smokers: 0.48 (0.23–1.00) Non-smokers: 0.78 (0.51–1.20)	$p = 0.04$ $p = 0.3$	Age, date of admission, place of birth, family history of cancer, (for smokers: duration, cig./day)	Hospital-based

*p for trend when applicable
ADC, adenocarcinoma, SqCC, squamous-cell carcinoma; SmCC, small-cell carcinoma

Table 59. Cohort studies of fruit and vegetable consumption and risk of lung cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata *et al.*, 1992, USA	164 (94 M, 70 F)/ 11 580, 9 y	FFQ (59, 21 veg.), self-administered, frequency	M: ≥ 7.9 vs < 5.5 servings/d (3) F: ≥ 8.3 vs < 5.9 servings/d (3)	1.22 (0.72–2.07) 0.58 (0.32–1.04)	NS NS	Age, smoking	Incidence Retirement community
Steinmetz *et al.*, 1993, USA	138/ 2814, F 4 y	FFQ (127, 15 fruits, 29 veg.), self-administered, frequency, portion size; validated	> 48 vs ≤ 24 servings/wk (4)	0.49 (0.28–0.86)	$p = 0.02$	Age, pack-years of smoking, energy	Incidence Nested case–control; total cohort 34 977 Strongest effect in large-cell carcinoma, and in ex-smokers, but small numbers

Table 59 (contd)

Author, year, country	Cases/ cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Feskanich *et al.*, 2000, USA	F 519/77 823, 12 y M 274/ 47 778, 10 y	FFQ (116, 15 fruits, 23 veg.), self-administered, frequency, portion size; validated	F > 7.2 vs ≤ 4.5 servings/d (5) M > 7.2 vs ≤ 4.3 servings/d (5)	0.79 (0.59–1.06) 1.12 (0.74–1.69)		Age, follow-up cycle, smoking status, years since quitting, cig./day (current smokers), age at start smoking, energy	Incidence. Excludes beans and lentils, potatoes For females, effect strongest in never-smokers, and in Kreyberg I. For males, protective effect only in never-smokers, and in Kreyberg I
Voorrips *et al.*, 2000b, Netherlands	1010/2953, (subcohort). M, F 6.3 y	FFQ (150, 8 fruits, 21 veg.), self-administered, frequency, portion size; validated	Highest (median 554 g/d) vs lowest (191 g/d) (5)	0.7 (0.5–1.0)	$p < 0.001$	Age, sex, family history of lung cancer, education, current smoker (yes/no), years of smoking, cig./day	Incidence Total cohort 120 852
Holick *et al.*, 2002, Finland	1644/27 084, M, smokers 14 y	FFQ (276), self-administered, frequency, portion size; validated	> 332 vs < 116 g/d (5)	0.73 (0.62–0.86)	$p < 0.001$	Age, years smoked, cig./day, intervention (α-tocopherol/β-carotene), previous supplement use (β-carotene and vitamin A), energy, cholesterol, fat	Incidence ATBC trial
Neuhouser *et al.*, 2003, USA	Intervention arm: 414/ 7072, M, F Placebo arm: 326/ 7048, M, F 12 y	FFQ, self-administered (45 items relating to fruits and veg.)	Intervention arm: Highest vs lowest (5) Placebo arm: Highest vs lowest (5)	0.76 (0.55–1.06) 0.73 (0.51–1.04)	$p = 0.13$ $p = 0.21$	Sex, age, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, enrolment centre	Follow up of participants in CARET trial in smokers and asbestos workers
Smith-Warner *et al.*, 2003, pooled analysis	3206/430 281 (8 cohorts), M, F 6–16 y	FFQ, self-administered, frequency, portion size; validated	Highest vs lowest (5)	0.79 (0.69–0.90)	$p = 0.001$	Age, education, BMI, alcohol, energy, smoking status, duration, amount smoked	Incidence. Effect strongest in never-smokers; significant effect only in current smokers; stronger effects in SqCC and ADC than SmCC

*p for trend when applicable
ADC, adenocarcinoma, SqCC, squamous-cell carcinoma; SmCC, small-cell carcinoma

Table 60. Case–control studies of fruit and vegetable consumption and risk of lung cancer

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Ziegler *et al.*, 1986, USA	763/900, M	FFQ (44, 12 fruits, 16 veg.), interviewed, frequency	Highest vs lowest (4)	[0.77]	$p = 0.04$	Age, smoking	Population-based
Fontham *et al.*, 1988, USA	1253/1274, M, F	FFQ (59), interviewed, frequency	Highest vs lowest (3)	0.70 (0.55–0.91)	$p = 0.004$	Age, sex, race, pack-years cig., family income, ethnic group, respondent status	Hospital-based Somewhat stronger effect (RR = 0.65) for SqCC and SmCC; RR = 0.77 for ADC
Mayne *et al.*, 1994, USA	413/413, M, F, not current smokers	FFQ (26), interviewed, frequency	Raw: Highest vs lowest (4) Processed: Highest vs lowest (4)	M: 0.41 F: 0.40 M: 1.02 F: 0.69	$p < 0.005$ $p < 0.005$ NS NS	Age, prior cig. use, religion, education, BMI, income	Population-based
De Stefani *et al.*, 2002, Uruguay	1032/1030, M, F	FFQ (11), interviewed, frequency, portion size	> 494 vs ≤ 156 servings/y (4)	0.62 (0.45–0.84)	$p = 0.002$	Age, sex, residence, urban/rural, education, year of diagnosis, smoking status, years since quitting, intensity smoking, age at start, energy	Hospital-based Strongest effects for SqCC, in current and ex-smokers

*p for trend when applicable

SqCC, Squamous-cell carcinoma; SmCC, small-cell carcinoma

Table 61. Cohort studies of fruit consumption and risk of breast cancer in women

Author, year, country	Cases/cohort size (years follow-up)	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata *et al.*, 1992, USA	219/11 580 9 y	Mean 74 y	FFQ (59, 23 fruits, self-administered, estimated frequency	≥ 3.7 vs < 2.4 servings/d (3)	0.82 (0.60–1.12)	NS	Age, smoking	Incidence Retirement community
Rohan *et al.*, 1993, Canada	519/1182 6 y	40–59 y	Diet history (86), self-administered, estimated frequency and amount	≥ 491 vs < 189 g/d (5)	0.81 (0.57–1.14)	$p = 0.174$	Age, age at menarche, surgical menopause, age at first live birth, education, family history of breast cancer, history of benign breast disease, other contributors to total food intake	Incidence Nested in the Canadian Breast Screening Cohort (56 837 women) No statistically significant difference by menopausal status
Verhoeven *et al.*, 1997a, Netherlands	519/ 62 573 4.3 y	55–69 y, only postmenopausal	Semi-quantitative FFQ, past year (150), self-administered, estimated frequency; validity assessed	Highest vs lowest (5) (median values 343.1 g/d vs 64.9 g.d)	0.76 (0.54–1.08)	$p = 0.10$	Age, energy, alcohol, history of benign breast disease, maternal breast cancer, breast cancer in sister(s), age at menarche, age at menopause, age at first birth, parity	Incidence
Zhang *et al.*, 1999, USA	2697 (784 premenopausal, 1913 postmenopausal)/ 83 234 15 y	33–60 y	Semiquantitative FFQ, past year (61–126), estimated frequency; validity and reliability assessed	≥ 5.0 vs < 2 servings/d (5)	Premenopausal: 0.74 (0.45–1.24) Postmenopausal: 0.84 (0.64–1.09) Postmenopausal, current HRT user: 0.57 (0.33–1.00)	$p = 0.13$ $p = 0.10$	Age, length of follow-up, energy, parity, age at first birth, age at menarche, history of breast cancer in mother or sister, history of benign breast disease, alcohol, BMI at age 18, weight change from age 18, height, age at menopause, HRT use	Incidence Nurses' Health Study
Gandini *et al.*, 2000	10 case–control; 2 cohort ($n = 9429$ cases) Studies publ. 1982–97			≥ 1 portion/d vs ≤ 3–4 portions/wk 6 vs 1 portion/wk	0.94 (0.79–1.11) 0.83 (0.79–0.87)			Meta-analysis of published literature p for heterogeneity < 0.001

Table 61 (contd)

Author, year, country	Cases/cohort size (years follow-up)	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Smith-Warner *et al.*, 2001	7377 cases from eight cohort studies with total baseline population of 351 825 women Follow-up 1976–96			Highest vs lowest (4) Increment = 100 g/d	All: 0.93 (0.86–1.00) All:0.99 (0.98–1.00). Premenopausal: 0.98 (0.94–1.02) Postmenopausal: 0.99 (0.98–1.01)	$p = 0.8$		Pooled analysis Study-specific RRs were calculated using the primary data and then combined using the random effects model Similar finding when fruit juices were excluded from total fruits p for heterogeneity: 0.89–0.94
Appleby *et al.*, 2002, UK 25 y	90/6416 25 y	≥16 y	FFQ (5); estimated frequency	Fresh fruit Daily vs < daily (2)	0.66 (0.38–1.14)	NS	Age, smoking, other foods	Mortality Cohort of health food shoppers
Maynard *et al.*, 2002, UK 64 y	82 incident, 36 fatal/1959 64 y	Mean 8 y	7-day household inventory	Highest (mean = 88.4 g/d) vs lowest (mean = 0.6 g/d) (4)	Incidence: 1.08 (0.52–2.25). Mortality: 1.25 (0.40–3.92)	$p = 0.61$ $p = 0.73$	Age, energy, food expenditure, Townsend score, season	Incidence and mortality Survey conducted at the household level 78% of the 4999 boys and girls originally identified were included in the cohort
Riboli & Norat, 2003	8 case–control, 10 cohort studies, publ. 1973–2001			Increment = 100 g/d	Cohort: 0.99 (0.98–1.00) Case–control: 0.92 (0.84–1.01) All: 0.99 (0.98–1.00)	p for heterogeneity = 0.99 p for heterogeneity < 0.01 p for heterogeneity = 0.88		Meta-analysis of published literature
Sauvaget *et al.*, 2003, Japan	76/23 667 18 y	34–103 y	FFQ, past year (22), self-administered, estimated frequency	Daily vs ≤1/wk (3)	0.91 (0.48–1.72)	0.71	Age, radiation dose, city, BMI, smoking, alcohol, education	Mortality Atomic bombing survivors

*p for trend when applicable; HRT, hormone replacement therapy

Table 62. Case–control studies of fruit consumption and risk of breast cancer in women

Author, year, country	Cases/ controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Katsouyanni *et al.*, 1986, Greece	120/120	Mean 55 y for cases	FFQ, before onset of disease (120), interviewed, estimated frequency	Highest vs lowest (5)	[0.59]	$p = 0.10$	Age, interviewer, years of schooling	Hospital-based Response rate 92% for cases
Iscovich *et al.*, 1989, Argentina	150/150 hospital controls, 150 neighbourhood controls	Mean = 56 y for cases	FFQ, 5 y up to 6 mo before inter-view (147, 13 fruits), interviewed, estimated frequency	Highest vs lowest (4)	Citrus fruit Hospital controls: 0.75 Neighbourhood controls: 0.58 Other than citrus: Hospital controls: 0.55 Neighbourhood controls: 0.41	NS $p < 0.05$ $p < 0.05$ $p < 0.05$	Age, education, husband's occupation, age at first pregnancy, parity, obesity index	Hospital-based and population-based Response rate 98% for cases
Toniolo *et al.*, 1989, Italy	250 (70 premenopausal, 180 postmenopausal)/ 499	< 75 y	Interviewer-administered dietary history (70); estimated frequency and amount	Highest vs lowest (4)	1.1		Age, energy	Population-based Response rate 91% for cases, 79% for controls
Van't Veer *et al.*, 1990, Netherlands	133/238	25–44, 55–64 y	Diet history, 12 mo before diagnosis (236), interviewed, estimated frequency and amount; validity and reliability assessed	Highest vs lowest (4)	0.55	$p = 0.35$	Age, history of benign breast disease, first and second degree of family history, number of cigarettes smoked daily, education, ever-use of oral contraceptives, age at menarche, age at first full-term pregnancy, BMI, energy, alcohol	Population-based Response rate 80% for cases, 53% for controls
Ingram *et al.*, 1991, Australia	99/209	22–86 y	FFQ, current intake (179), self-administered	Highest vs lowest (2)	0.9 (0.5–1.6)	NS	Age, residence	Population-based Response rate 100% for cases

Table 62 (contd)

Author, year, country	Cases/ controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Negri *et al.*, 1991, Italy	2860/3625	<75 y	FFQ (14–37 depending on cancer site)	Highest vs lowest (3)	1.1 (1.0–1.3)	$p < 0.01$	Age, area of residence, education, smoking, veg.	Hospital-based Data from a network of case–control studies Response rate >97%
Franceschi *et al.*, 1995, Italy	2569/2588	20–74 y	FFQ, 2 y before diagnosis (79, 10 fruits), interviewed, estimated weekly frequency; validity assessed	Citrus fruit: > 7.3 vs < 1.3 servings/wk (5) Other fruit: > 20.5 vs < 7.6 (5)	1.06 (0.89–1.28) 0.89 (0.73–1.07)	NS NS	Age, study centre, education, parity, energy, alcohol	Hospital-based Response rate 96% No significant interaction by study centre, age group, menopausal status, education, parity and BMI
Zaridze *et al.*, 1991, Russia	139 (58 premenopausal, 81 postmenopausal)/ 139		FFQ, year before diagnosis (145), interviewed, estimated frequency	Increased vs decreased intake in last 10 years	Premenopausal: [0.82 (0.13–5.26)] Postmenopausal: [1.82 (0.46–7.14)]	NS NS	Age at menarche, age at first birth, education	Hospital-based Response rate 99% for cases, 94% for controls
Levi *et al.* 1993b, Switzerland	107/318	≤ 75 y	Questionnaire (50, 4 fruits), interviewed, estimated frequency	Fresh fruit: Highest vs lowest (3)	0.8		Age	Hospital-based Response rate > 85%
Holmberg *et al.*, 1994, Sweden	265 (55 ≤ 50 y, 210 > 50 y)/432 screening controls	40–74 y	FFQ, past 6 mo (60), interviewed, estimated frequency	Highest vs lowest (4)	All: 1.4 (0.9–2.3) ≤ 50 years: 0.7 (0.3–2.1) > 50 years: 1.7 (1.0–3.0)		Age, county of residence, month of mammography	Population-based Response rate for cases 70%, for controls 82% Effect modification by age group non-significant
Landa *et al.*, 1994, Spain	100/100	Mean 59 y	FFQ, before onset of disease (99), inteviewed, estimated frequency	Highest vs lowest (3)	[0.26]	$p < 0.05$	Age	Hospital-based

Table 62 (contd)

Author, year, country	Cases/ controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Qi *et al.*, 1994, China	244/244		Diet history starting from 1 y before diagnosis (40), interviewed, estimated frequency and amount		No association		Age, length of stay in Tianjin	Hospital-based
Hirose *et al.*, 1995, Japan	1052 (607 premenopausal, 445 postmenopausal)/ 23 163	≥ 20 y	Questionnaire before symptoms, self-administered	Daily vs ≤ 3–4/wk (2)	Premenopausal 0.95 (0.78–1.17) Postmenopausal: 1.05 (0.82–1.35)	NS NS	Age, first-visit year, BMI, age at menarche, delivery, smoking, physical activity, type of breakfast, milk, dietary control, bean curd, green-yellow veg., carrots, potato/sweet potato, chicken, ham/sausage	Hospital-based Response rate 98%
Trichopoulou *et al.*, 1995a, Greece	820 (270 premenopausal, 550 postmenopausal)/795 hospital controls, 753 visitor controls		Semi-quantitative FFQ, past year (115, 18 fruits, interviewed, estimated frequency, validated	Highest vs lowest (5) (Median 183 vs 42.5 times/mo)	0.65 (0.47–0.90)	$p = 0.004$	Age, place of birth, parity, age at first pregnancy, age at menarche, menopausal status, Quetelet index, energy	Hospital-based and population-based Response rate for cases 94%, for hospital controls 96%, for visitor controls 93% Confounding between fruits and veg. was limited Further adjustment for other food groups or fat did not change association No statistically significant effect modification by menopausal status ($p > 0.10$)

Table 62 (contd)

Author, year, country	Cases/ controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Freudenheim *et al.*, 1996, USA	297/311	≥ 40 y Only premenopausal	FFQ, past year 2 y before interview (172, 21 fruits), interviewed, estimated frequency and amount; validity and reliability assessed	≥ 484 vs ≤ 204 g/d (4)	0.67 (0.42–1.09)	$p = 0.05$	Age, education, age at first birth, age at menarche, first-degree relative with breast cancer, previous benign breast disease, BMI, energy	Population-based Response rate 66% for cases, 62% for controls
Thorand *et al.*, 1998, Germany	43/106	38–80 y All postmenopausal	Diet history, past year (201), interviewed, estimated frequency and amount; validity and reliability assessed; validated	Continuous variable, increment 206 g/d	0.82 (0.51–1.32)		Age, BMI, exogenous hormone use, age at menarche, nulliparity, smoking status, socioeconomic status	Population-based Response rate 75% for cases, 45% for controls
Potischman *et al.*, 1999, USA	568 *in situ* or invasive localized disease, did not report chemotherapy treatment)/ 1451	20–44 y	FFQ, past year (100/25 fruits, self-administered, estimated frequency and amount; validated	Fruit and fruit juice: > 11.2 vs < 3.5 times/wk (4) Fruit: ≥ 8.3 vs < 2.1 times/wk (4)	1.08 (0.8–1.4) 1.2 (0.8–1.4)		Age at diagnosis, study site, ethnicity, education, age at first birth, alcohol, years of oral contraceptive use, smoking status	Population-based Response rate 84% for cases, 70% for controls Results were similar when limited to the 353 cases with localized disease or who were interviewed within three months of diagnosis
Ronco *et al.*, 1999, Uruguay	400/405	20–89 y	FFQ (64, 9 fruits), interviewed; reliability assessed	> 7.9 vs < 3.5 servings/wk (4)	0.57 (0.36–0.89)	$p = 0.05$	Age, residence, urban/rural status, family history of breast cancer in a first-degree relative, BMI, age at menarche, parity, menopausal status, energy	Hospital-based. Response rate for cases 97%, for controls 94%. No effect modification by menopausal status

Table 62 (contd)

Author, year, country	Cases/ controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Terry *et al.* 2001c, Sweden	2832/2650	50–74 y All postmenopausal	FFQ, past year (65, 19 fruits and veg.), self-administered, estimated frequency	Highest vs lowest (4)	0.96 (0.79–1.17)	$p = 0.81$	Age, height, BMI, current smoking, socioeconomic status, alcohol, high-fibre grains and cereals, fatty fish, multivitamin use, parity, hormone replacement therapy, history of benign breast disease, family history of breast cancer, type of menopause, age at menopause, age at menarche, age at first birth	Population-based Response rate for cases 84%, for controls 82%
Dos Santos Silva *et al.*, 2002, UK	240/477	< 75 y	FFQ, 2–3 y before (108, 23 fruits), interviewed, estimated frequency and amount; validity assessed	≥ 4 vs ≤ 1 servings/d (4)	0.89 (0.50–1.57)	$p = 0.45$	Age, general practitioner, energy, age at menarche, age at first birth, parous, parity, breastfeeding, family history of breast cancer, menopausal status, time since menopause, education	Population-based Population: women of South Asian ethnicity who had migrated to England Response rate 79% for cases, 76% for controls

*p for trend when applicable

Table 63. Cohort studies of vegetable consumption and risk of breast cancer in women

Author, year, country	Cases/cohort size (years follow-up)	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata *et al.*, 1992, USA	219/11 580 9 y	Mean 74 y	FFQ (59, 21 veg.), self-administered, estimated frequency	> 4.8 vs < 3.2 servings/d (3)	0.96 (0.69–1.34)	NS	Age, smoking	Incidence Retirement community Includes potatoes
Rohan *et al.*, 1993, Canada	519/1182 6 y	40–59 y	Diet history (86), self-administered, estimated frequency and amount	> 433 vs < 203 g/d (5)	0.86 (0.61–1.23)	$p = 0.752$	Age, age at menarche, surgical menopause, age at first live birth, education, family history of breast cancer, history of benign breast disease, and other contributors to total food intake	Incidence Nested in the Canadian Breast Cancer Screening Cohort (56 837 women) No statistically significant difference by menopausal status
Järvinen *et al.*, 1997, Finland	88/4697 25 y	≥ 15 y	Diet history, interviewed, past year	Highest vs lowest (3)	No association		Age, BMI, parity, region, occupation, smoking	Incidence
Verhoeven *et al.*, 1997a, Netherlands	519/62 573 4.3 y	55–69 y Only postmenopausal women	Semi-quanti-tative FFQ, past year (150), self-administered, estimated frequency; validity assessed	Highest vs lowest (5) (Median values: 303 vs 108 g/d)	0.94 (0.67–1.31)	$p = 0.30$	Age, energy, alcohol, history of benign breast disease, maternal breast cancer, breast cancer in sister(s), age at menarche, age at menopause, age at first birth, parity	Incidence
Zhang *et al.*, 1999, USA	2697 (784 premenopausal, 1913 postmenopausal)/ 83 234 15 y	33–60 y	Semi-quantitative FFQ, past year (61–126), self-administered, estimated frequency, validity and reliability asssessed	> 5.0 vs < 2 servings/d (5)	Premenopausal: 0.64 (0.43–0.95) Postmenopausal: 1.02 (0.85–1.24) Postmenopausal, current HRT user: 0.87 (0.63–1.20)	$p = 0.10$ $p = 0.61$	Age, length of follow-up, energy, parity, age at first birth, age at menarche, history of breast cancer in mother or sister, history of benign breast disease, alcohol, BMI at age 18, weight change from age 18, height, age at menopause, HRT use	Incidence Nurses' Health Study

Table 63 (contd)

Author, year, country	Cases/cohort size (years follow-up)	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Gandini *et al.*, 2000	14 case–control, 3 cohort (n = 16 052 cases); Studies publ. 1982–97			≥ 1 portion/d vs ≤ 3–4 portion/wk 6 vs 1 portions/wk	0.75 (0.66–0.85) 0.79 (0.77–0.80)			Meta-analysis of published literature p for heterogeneity < 0.001
Smith-Warner *et al.*, 2001	7377 cases from 8 cohort studies with total baseline population of 351 825 women Follow-up: 1976–1996			Highest vs lowest (4) Increment = 100 g/d	All: 0.96 (0.89–1.04) All: 1.00 (0.97–1.02) Premenopausal: 0.99 (0.93–1.06) Postmenopausal: 1.00 (0.97– 1.02)	p = 0.54		Pooled analysis Study-specific RRs were calculated using the primary data and then were combined using the random effects model Excludes potatoes p for heterogeneity: 0.31–0.73
Maynard *et al.*, 2002, UK	82 incident, 36 fatal/1959 64 y	Mean 8 y	7-day household inventory	Highest vs lowest (4) (mean = 115.2 vs 23.1 g/d)	Incidence: 1.43 (0.70–2.92) Mortality: 0.86 (0.30–2.47)	p = 0.59 p = 0.35	Age, energy, food expenditure, Townsend score, season	Incidence and mortality Survey conducted at the household level 78% of the 4999 boys and girls originally identified were included in the cohort
Riboli & Norat, (2003)	10 case–control, 10 cohort studies publ. 1973–2001			Increment = 100 g/d	Cohort: 1.00 (0.97–1.02) Case–control: 0.86 (0.78–0.94) All: 0.96 (0.94–0.98)	p for heterogeneity =0.99 p for heterogeneity <0.01 p for heterogeneity =0.89		Meta-analysis of published literature
Sauvaget *et al.*, 2003, Japan	76/23 667 18 y	34–103 y	FFQ, past year (22), self-administered, estimated frequency	Green-yellow veg.: Daily vs ≤ 1/ wk (3)	1.28 (0.64–2.54)	0.54	Age, radiation dose, city, BMI, smoking, alcohol, education	Mortality Atomic bombing survivors

*p for trend when applicable; HRT, hormone replacement therapy

Table 64. Case–control studies of vegetable consumption and risk of breast cancer in women

Author, year, country	Cases/controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Zemla, 1984, Poland	328 (214 native upper Silesians, 114 migrants)/ 585	17–79 y	Questionnaire (5), interviewed	Raw veg. Rather regular vs none (3)	Upper Silesians 0.73 Migrants 1.57			Population-based, hospital visitor controls Response rate for cases 98%
Katsouyanni *et al.*, 1986, Greece	120/120	Mean 55 y for cases	FFQ, before onset of disease (120), interviewed, estimated frequency	Highest vs lowest (5)	0.09 (0.03–0.30)	$p < 0.001$	Age, interviewer, years of schooling, parity, age at first birth, marital status, menopausal status, age at menopause, age at menarche, place of residence	Hospital-based Response rate for cases 92% No interaction with age, years of schooling, menopausal status
Iscovich *et al.*, 1989, Argentina	150/150 hospital controls, 150 neighbourhood controls	Mean 56 y for cases	FFQ, 5 y up to 6 mo before interview (147, 12 veg., excluding potatoes, 4 pulses), interviewed, estimated frequency	Green leafy veg.: Highest vs lowest (4) All green veg.: Highest vs lowest (4)	Hospital controls: 0.32 Neighbourhood controls: 0.15 Hospital controls: 0.52 Neighbourhood controls: 0.40	$p < 0.05$ $p < 0.05$ $p < 0.05$ $p < 0.05$	Age, education, husband's occupation, age at first pregnancy, parity, obesity index	Hospital-based and population-based Response rate 98% for cases In multivariate analyses controlling for other food groups, the association with green vegetables remained
Toniolo *et al.*, 1989, Italy	250 (70 premenopausal, 180 postmenopausal)/499	< 75 y	Diet history (70), interviewed, estimated frequency and amount	Highest vs lowest (4)	1.2		Age, energy	Population-based Response rate for cases 91%, for controls 79%
Ewertz & Gill, 1990, Denmark	1474/1322	< 70 y	Semi-quantitative FFQ, year before diagnosis (21), estimated frequency and amount; included summary question on veg.	7 vs < 2 (7) times/wk	[1.05 (0.76–1.47)]		Age, residence	Population-based Response rate for cases 88%, for controls 79% Questionnaire completed one year after diagnosis

Table 64 (contd)

Author, year, country	Cases/controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Van't Veer *et al.*, 1990, Netherlands	133/238	25–44, 55–64 y	Diet history, 12 mo before diagnosis (236), interviewed, estimated frequency and amount; validity and reliability assessed	Highest vs lowest (4)	0.86	$p = 0.66$	Age, history of benign breast disease, first- and second-degree of family history, number of cigarettes daily, education, ever-use of oral contraceptives, age at menarche, age at first full-term pregnancy, BMI, energy, alcohol	Population-based Response rate for cases 80%, for controls 53%
Ingram, 1991, Australia	99/209	22–86 y	FFQ, current intake (179), self-administered	Highest vs lowest (2)	1.4 (0.8–2.4)	NS	Age, residence	Population-based Response rate for cases 100%
Negri *et al.*, 1991, Italy	2860/3625	< 75 y	FFQ; (14–37 depending on cancer site)	Green veg.: Highest vs lowest (3)	0.7 (0.6–0.8)	$p < 0.01$	Age, area of residence, education, smoking, fruit consumption	Hospital-based Data from a network of case–control studies Response rate > 97%
Richardson *et al.*, 1991, France	409/515	28–66 y	Diet history (55), interviewed, estimated frequency and amount		No difference in mean intake in cases (1092 g/wk) vs controls (1064 g/wk)		Age, menopausal status	Hospital-based Response rate > 98%
Zaridze *et al.*, 1991, Russia	139 (58 premenopausal, 81 postmenopausal)/139		FFQ, year before diagnosis (145); interviewed, estimated frequency	Increased vs decreased intake in last 10 y	Premenopausal: [0.31 (0.03–3.70)] Postmenopausal: [0.69 (0.10–4.54)]	NS NS	Age at menarche, age at first birth, education	Hospital-based Response rate for cases 99%, for controls 94%

Table 64 (contd)

Author, year, country	Cases/controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Pawlega, 1992, Poland	127 (33 < 50 y, 94 ≥ 50 y)/250	≥ 35 y	Questionnaire, 20 y ago (44)	Boiled veg.: > 3 vs ≤ 1/wk (3)	≥ 50 years: 0.4 (0.2–0.8)	$p = 0.01$	Age, education, social class, marital status, number of persons in household, years of smoking, BMI, drinking of vodka 20 years earlier	Population-based Data on boiled veg. among women < 50 years were not accepted because of low reproducibility
Levi *et al.*, 1993b, Switzerland	107/318	≤ 75 y	Questionnaire (50, 9 veg., 1 pulses, 1 potato), interviewed, estimated frequency	Green veg. Highest vs lowest (3)	0.4	$p < 0.01$	Age, education, energy	Hospital-based Response rate > 85%
Holmberg *et al.*, 1994, Sweden	265 (55 ≤ 50 y, 210 > 50 y)/432 screening controls	40–74 y	FFQ, past 6 mo (60), interviewed, estimated frequency	Highest vs lowest (4)	All: 0.7 (0.4–1.1) < 50 years: 1.6 (0.5–4.7) > 50 years: 0.6 (0.3–1.0)		Age, county of residence, month of mammography	Population-based Response rate for cases 70%, for controls 82% Potatoes excluded Effect modification by age group non-significant
Landa *et al.*, 1994, Spain	100/100	Mean 59 y	FFQ, before onset of disease (99), interviewed, estimated frequency	Highest vs lowest (3)	[0.52]	$p < 0.05$	Age	Hospital-based
Qi *et al.*, 1994, China	244/244		Diet history, starting from one year before diagnosis (40), interviewed, estimated frequency and amount	≥ 600 vs < 400 g (4)	0.26 (0.14–0.47)		Age, length of stay in Tianjin, age at menarche, age at menopause, age at first birth	Hospital-based

Table 64 (contd)

Author, year, country	Cases/controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Franceschi *et al.*, 1995, Italy	2569/2588	20–74 y	FFQ, 2 y before diagnosis (79, 11 veg., 2 potatoes), interviewed, estimated weekly frequency; validity assessed	Raw veg.: > 12.5 vs < 4.9 servings/wk (5) Cooked veg: > 7.5 vs < 3.1 servings/wk (5)	0.73 (0.60–0.88) 0.96 (0.79–1.16)	$p < 0.01$	Age, study centre, education, parity, energy, alcohol	Hospital-based Response rate 96% Cooked vegetable group includes pulses
Hirose *et al.*, 1995, Japan	1052 (607 premenopausal, 445 postmenopausal)/ 23 163	≥ 20 y	Questionnaire before symptoms, self-administered	Raw veg. Daily vs ≤ 3–4/wk (2)	Premenopausal: 1.00 (0.85-19) Postmenopausal: 0.99 (0.81–1.20)	NS NS	Age, first-visit year	Hospital-based Response rate 98%
Trichopoulou *et al.*, 1995a, Greece	820, (270 premenopausal, 550 postmenopausal)/ 795 hospital controls, 753 visitor controls		Semi-quantitative FFQ, past year (115, 26 veg., 1 potato, 5 pulses), interviewed, estimated frequency; validated	Highest vs lowest (5) (median 142 vs 47 times/mo)	0.54 (0.40–0.74)	$p = 0.0001$	Age, place of birth, parity, age at first pregnancy, age at menarche, menopausal status, Quetelet index, energy	Hospital and population-based Response rate for cases 94%, for hospital controls 96%, for visitor controls 93%. Confounding between fruit and veg. was limited. Potatoes excluded. Further adjustment for other food groups or fat did not change association. No statistically significant effect modification by menopausal status ($p > 0.10$).
Freudenheim *et al.*, 1996, USA	297/311	≥ 40 y, only premenopausal	FFQ, past year 2 y before interview (172, 31 veg.), interviewed, estimated frequency and amount; validity and reliability assessed	≥ 523 vs ≤ 276 g/d (4)	0.46 (0.28–0.74)	$p < 0.001$	Age, education, age at first birth, age at menarche, first-degree relative with breast cancer, previous benign breast disease, BMI, energy	Population-based. Response rate 66% for cases, 62% for controls. Potatoes excluded. Association attenuated after further adjustment for β-carotene (RR = 0.84, 0.43–1.63) and lutein/zeaxanthin (RR = 0.76, 0.41–1.44). No change in vegetable estimate after adjusting for vitamin C, α-tocopherol, folic acid, dietary fibre or α-carotene

Table 64 (contd)

Author, year, country	Cases/controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Thorand *et al.*, 1998, Germany	43/106	38–80 y, all postmenopausal	Diet history, past year (201), interviewed, estimated frequency and amount; validity and reliability assessed	Continuous variable, increment 260 g/d	0.86 (0.51–1.46)		Age, BMI, exogenous hormone use, age at menarche, nulliparity, smoking, status, socioeconomic status	Population-based Response rate 75% for cases, 45% for controls. Potatoes excluded. Similar finding when potatoes are included
Potischman *et al.*, 1999, USA	568 *in situ* or invasive localized disease, did not report chemotherapy treatment/1451	20–44 y	FFQ, past year (100, 34 veg.), self-administered, estimated frequency and amount, validated	≥ 18.2 vs < 8.4 times/wk (4)	0.86 (0.6–1.1)		Age at diagnosis, study site, ethnicity, education, age at first birth, alcohol, years of oral contraceptive use, smoking status	Population-based Response rate 84% for cases, 70% for controls Vegetable group included potatoes, olives, avocado, garlic. Results not changed after further adjustment for cereals and grains. Results similar when limited to the 353 cases with localized disease or who were interviewed within three months of diagnosis
Ronco *et al.*, 1999, Uruguay	400/405	20–89 y	FFQ (64, 15 veg.), interviewed, reliability assessed	> 16.3 vs< 9 servings/wk (4)	0.41 (0.26–0.65)	$p = 0.004$	Age, residence, urban/rural status, family history of breast cancer in a first-degree relative, BMI, age at menarche, parity, menopausal status, energy	Hospital-based Response rate for cases 97%, for controls 94% Vegetable group includes garlic and legumes, excludes potatoes. No effect modification by menopausal status. RR remained significant after further adjustment for other nutrient but became non-significant after further adjustment for lycopene

Table 64 (contd)

Author, year, country	Cases/controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Tavani *et al.*, 1999, Italy	579/668	22–39 y	FFQ (78); estimated weekly frequency; validated	Raw veg.: > 8 servings/wk vs less (2)	0.57 (0.33–0.98)		Study centre, year of recruitment, age, education, BMI, family history of breast cancer, parity, age at first birth	Hospital-based Subset of studies by Franceschi *et al.*, 1995, Negri *et al.*, 1991 Response rate generally > 96%
Dos Santos Silva *et al.*, 2002, UK	240/477	< 75 y	FFQ, 2–3 y before (108, 40 veg., 21 pulses, lentils, dhals), interviewed, estimated frequency and amount; validity assessed	Veg. dishes: ≥ 4 vs ≤ 1 g/d (4)	0.48 (0.27–0.85)	$p = 0.005$	Age, general practitioner, energy, age at menarche, age at first birth, parous, parity, breast feeding, family history of breast cancer, menopausal status, time since menopause, education	Population-based Population: women of South Asian ethnicity who had migrated to England Response rate for cases 79%, for controls 76% Risk was attenuated after further adjustment for type of diet or meat consumption

*p for trend when applicable

Table 65. Cohort studies of total fruit and vegetable consumption and risk of breast cancer in women

Author, year, country	Cases/cohort size (years follow-up)	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata *et al.*, 1992, USA	219/11 580 9 y	Mean 74 y	FFQ (59, 23 fruits, 21 veg.), self-administered, estimated frequency	≥ 8.3 vs < 5.9 servings/d (3)	0.87 (0.63–1.21)	NS	Age, smoking	Incidence Retirement community Veg. group includes potatoes
Byrne *et al.* 1996, USA	53/6156 4 y	32–86 y	FFQ (93), interviewed; estimated frequency	> 3 vs ≤ 3 servings/d (2)	0.7 (0.4–1.5)		Age	Incidence
Zhang *et al.* 1999, USA	2697 (784 premenopausal, 1913 postmenopausal)/ 83 234 15 y	33–60 y	Semi-quantitative. FFQ, past year (61–126), self-administered, estimated frequency; validity and reliability assessed	≥ 5.0 vs < 2 servings/d (5)	Premenopausal: 0.77 (0.58–1.02) Premenopausal and positive family history: 0.29 (0.13–0.62) Premenopausal and drink ≥ 15 g/d of alcohol: 0.53 (0.27–1.04) Postmenopausal: 1.03 (0.81–1.31) Postmenopausal and current HRT user: 0.86 (0.54–1.39)	$p = 0.05$ $p = 0.003$ $p = 0.007$ $p = 0.73$	Age, length of follow-up, energy intake, parity, age at first birth, age at menarche, history of breast cancer in mother or sister, history of benign breast disease, alcohol, BMI at age 18, weight change from age 18, height, age at menopause, HRT use	Incidence Nurses' Health Study
Smith-Warner *et al.*, 2001	7377 cases from 8 cohort studies with total baseline population of 351 825 women Follow-up: 1976–96			Highest vs lowest (4) Increment = 100 g/d	All: 0.93 (0.86–1.00) All: 0.99 (0.98–1.00) Premenopausal: 0.99 (0.96–1.02) Postmenopausal: 1.00 (0.98–1.01)	$p = 0.12$		Pooled analysis Study-specific RRs were calculated using the primary data and then were combined using the random effects model Veg. group excludes potatoes p for heterogeneity 0.78–0.99

*p for trend when applicable. HRT, hormone replacement therapy

Table 66. Case–control studies of total fruit and vegetable consumption and risk of breast cancer in women

Author, year, country	Cases/ controls	Age, population subgroups	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Potischman *et al.*, 1998, USA	1647/1501	< 45 y	FFQ, 12–13 y of age (29, 2 fruits, 3 veg., 1 beans, 2 potatoes), interviewed, estimated frequency and amount; validity assessed	> 101 vs ≤ 54 times/mo (4)	0.89 (0.7–1.1)		Age, site, race, education, combination variable for age at first full-term birth and number of full-term births, oral contraceptive use, average lifetime exercise, exercise at ages 12–13 y, current alcohol consumption	Population-based Response rate for cases 86%, for controls 71% Veg. group includes potatoes, excludes beans Fruit group excludes juice. Results were similar when unreliable foods were removed from intake estimates. No effect modification by strata of adult fat or veg. intake
Potischman *et al.*, 1999, USA	568 *in situ* or invasive localized disease/ 1451	20–44 y	FFQ, past year (100, 25 fruits, 34 veg.), self-administered, estimated frequency and amount; validated	≥ 29.4 vs < 14 times/wk (4)	0.94 (0.7–1.2)		Age at diagnosis, study site, ethnicity, education, age at first birth, alcohol, years of oral contraceptive use, smoking status	Population-based Response rate for cases 84%, for controls 70%. Results were similar when limited to the 353 cases with localized disease or interviewed < 3 months after diagnosis
Ronco *et al.*, 1999, Uruguay	400/405	20–89 y	FFQ (64, 9 fruits, 15 veg.), interviewed, reliability assessed	Highest vs lowest (4)	0.42 (0.26–0.66)	$p = 0.005$	Age, residence, urban/ rural status, family history of breast cancer in a first-degree relative, BMI, age at menarche, parity, menopausal status, energy	Hospital-based Response rate for cases 97%, for controls 94% Veg. group includes garlic and legumes, excludes potatoes. No effect modification by menopausal status
Terry *et al.*, 2001c, Sweden	2832/2650	50–74 y All postmenopausal	FFQ, past year (65, 19 fruits and veg.), self-administered, estimated frequency	Highest vs lowest (4)	0.97 (0.80–1.18)	$p = 0.61$	Age, height, BMI, current smoking, socioeconomic status, alcohol, high-fibre grains and cereals, fatty fish, multivitamin use, parity, HRT, history of benign breast disease, family history of breast cancer, type of menopause, age at menopause, age at menarche, age at first birth	Population-based Response rate for cases 84%, for controls 82%

*p for trend when applicable. HRT, hormone replacement therapy

Table 67. Case–control studies of fruit and vegetable consumption and risk of breast cancer in men

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hsing *et al.*, 1998b, USA	178/512	Questionnaire, adult life (5), estimated frequency	Fruit: ≥ 7 vs < 1/wk (4) Veg.: ≥ 7 vs < 1/wk (4)	All respondents: 0.8 (0.4–1.3) Spouse respondents: 0.5 (0.2–1.2) All respondents: 0.5 (0.2–1.7) Spouse respondents: 0.3 (0.03–4.2)		Age at death, socioeconomic status	Mortality for cases and controls Questionnaire completed by next of kin
Rosenblatt *et al.*, 1999, USA	220/291	FFQ (125), self-administered	Citrus fruit: Highest vs lowest (4) Other fruit: Highest vs lowest (4) Green veg.: Highest vs lowest (4) Yellow veg.: Highest vs lowest (4)	1.7 (1.0–2.8) 1.1 (0.7–1.9) 1.0 (0.6–1.7) 0.8 (0.4–1.3)	$p = 0.032$ $p = 0.85$ $p = 0.44$ $p = 0.35$	Age, study site, energy	Population-based Response rate for cases 75%, for controls 45%
Johnson *et al.*, 2002, Canada	81/1905	FFQ (60), self-administered	Fruit and juice: ≥ 26 vs < 9.9 servings/wk (4) Fruit: ≥ 14.5 vs < 4.4 servings/wk (4) Veg.: ≥ 24 vs < 13 servings/wk (4) Veg. and veg. juice: ≥ 25 vs < 13.4 servings/wk (4)	2.26 (1.18–4.52) 1.15 (0.62–2.13) 0.70 (0.38–1.30) 0.75 (0.40–1.40)	$p = 0.02$ $p = 0.4$ $p = 0.33$ $p = 0.41$	Age, marriage status, coffee consumption, physical activity, BMI	Population-based Response rate for cases 68%, for controls 65%

*p for trend when applicable

Table 68. Case–control studies of fruit consumption and risk of invasive cervix cancer

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Verreault *et al.*, 1989, USA	189/227	FFQ, (66) average frequency of use, assumed standard portion size, interviewed by telephone	≥ 10.7 vs ≤ 3.4 servings/-wk (4)	1.3 (0.6–2.5)	$p = 0.68$	Age, education, smoking, frequency of Pap smears, oral and barrier contraceptive use, age at first intercourse, number of sexual partners, history of cervicovaginal infection	Population-based Response for cases 72%, for eligible controls 69% Interviews 2.8 years after diagnosis for cases
Ziegler *et al.*, 1990, USA	271/502	FFQ (75, 15 fruits and fruit juices), interviewed, open-ended frequency categories	≥ 19 vs ≤ 7.3 servings/wk (4)	[0.74]	$p = 0.26$	Matched on age, race and telephone exchange. Adjusted for number of sexual partners, age at first intercourse, cigarettes per day, oral contraceptive use duration, history of non-specific genital infection, years since last Pap smear, age, study centre	Population-based Response for cases 73%, for eligible controls 74%
Herrero *et al.*, 1991, four Latin American countries	748/1411	FFQ (58, 15 fruits), interviewed, frequency only, assumed average portion size	≥ 119 vs < 43 servings/mo (4)	0.86 (0.6–1.2)	$p = 0.44$	Age, study site, age at first intercourse, number of sexual partners, number of pregnancies, presence of HPV 16/18, time since last Pap smear, number of household facilities as measure of household socio-economic status	Hospital-based in two countries, hospital and community-based in other two countries Response for cases 99.1%, for controls 95.8% Controls with no sexual history excluded from analysis
Cuzick *et al.*, 1996, UK	121/241	Diet assessment tool not clear, interviewed	≥ 8 vs 0 pieces/wk (4)	0.67 (0.19–2.35)	$p = 0.33$	Number of partners and age at first intercourse	Hospital-based
Hirose *et al.*, 1996, Japan	556/26 751	Questionnaire on frequency of intake	Daily vs ≤ 3–4 servings/wk (2)	0.70 (0.59–0.83)	$p < 0.01$	Age and first visit year	Hospital-based 98% of first-visit patients completed questionnaire

*p for trend when applicable

Table 69. Case–control studies of vegetable consumption and risk of invasive cervical cancer

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
La Vecchia *et al.*, 1988a, Italy	392/392	FFQ (5), frequency only	Green veg.: ≥ 14 vs < 7 servings/wk (3)	[0.21 (0.10–0.45)	$p < 0.001$	Age, interviewer, marital status, education, parity, age at first intercourse, number of sexual partners, BMI, smoking, oral contraceptive use, other female hormone use	Hospital-based 98% response rate for cases and controls
Verreault *et al.*, 1989, USA	189/227	FFQ (66), interviewed by telephone, average frequency of use, assumed standard portion size	Dark green and yellow veg.: ≥ 5.3 vs < 2 servings/wk (4)	0.6 (0.3–1.1)	$p = 0.06$	Age, education, smoking, frequency of Pap smears, oral and barrier contraceptive use, age at first intercourse, number of sexual partners, history of cervico-vaginal infection	Population-based Response rate-for cases 72%, for eligible controls 69% Interviews 2.8 years after diagnosis for cases
			Light green veg.: ≥ 10.0 vs < 5.2 servings/wk (4)	0.9 (0.5–1.7)	$p = 0.43$		
Ziegler *et al.*, 1990, USA	271/502	FFQ, (75, 20 veg.) interviewed, open-ended frequency categories	≥ 26 vs ≤ 11 servings/wk (4)	[0.86]	$p = 0.43$	Matched on age, race and telephone, exchange. Adjusted for number of sexual partners, age at first intercourse, cigarettes per day, oral contraceptive use duration, history of non-specific genital infection, years since last Pap smear, age, study centre	Population-based Response rate for cases 73%, for eligible controls 74% Potatoes and legumes excluded
Herrero *et al.*, 1991, four Latin American countries	748/1411	FFQ (58, 16 veg.), interviewed, frequency only, assumed average portion size	≥ 207 vs < 121 servings/mo (4)	0.97 (0.7–1.3)	$p = 0.54$	Age, study site, age at first intercourse, number of sexual partners, number of pregnancies, presence of HPV 16/18, time since last Pap smear, number of household facilities as measure of household socio-economic status	Hospital-based in two countries, hospital and community-based in two other countries Response for cases 99.1%, for controls 95.8%. Controls with no sexual history excluded from analysis

Table 69 (contd)

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Cuzick *et al.*, 1996, UK	121/241	Diet assessment tool not clear, interviewed	≥ 7 vs ≤ 2 servings/wk (3)	Leafy veg.: 0.59 (0.24–1.48) Other veg.: 0.67 (0.23–1.98)	$p = 0.11$ $p = 0.39$	Number of partners, age at first intercourse	Hospital-based
Hirose *et al.*, 1996, Japan	556/26 751	Questionnaire on frequency of intake	Raw veg.: Daily vs ≤ 3–4 servings/wk (2) Green veg.: ≥ 5 vs ≤ 2 servings/wk (3)	0.88 (0.74–1.04) 0.56 (0.45–0.71)	NS $p < 0.01$	Age and first-visit year	Hospital-based 98% of first visit patients completed questionnaire

*p for trend when applicable

Table 70. Case–control studies of fruit and vegetable consumption and risk of cervical cancer

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Ziegler *et al.*, 1990, USA	271/502	FFQ (75, 15 fruits and fruit juices, 20 veg.), interviewed, open-ended frequency categories	≥ 44 vs ≤ 21 servings/wk (4)	[0.90]	$p = 0.34$	Matched on age, race and telephone exchange. Adjusted for number of sexual partners, age at first intercourse, cigarettes per day, oral contraceptive use duration, history of non-specific genital infection, years since last Pap smear, age, study centre	Population-based Response rate for cases 73%, for eligible controls 74%
Rajkumar *et al.*, 2003a, India	205/213	FFQ (21), interviewed	≥ 7 vs < 6 servings/wk (3)	0.48 (0.24–0.98)	$p = 0.04$	Age, residence, occupation, marital status, age at first marriage, number of pregnancies, husband's extramarital affairs, BMI, chewing habits	Hospital-based Little difference when only HPV-positive controls were considered

*p for trend when applicable

Table 71. Case–control study of fruit and/or vegetable consumption and risk of *in situ* cervical cancer

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Ziegler *et al.*, 1991, USA	229/502	FFQ, (75, 15 fruit and fruit juice, 20 veg.), interviewed, open-ended frequency categories	Fruit: ≥ 19 vs ≤ 7.3 servings/wk (4)	[0.61]	$p = 0.09$	Matched on age, race and telephone exchange. Adjusted for number of sexual partners, duration of cigarette use, oral contraceptive use duration, history of non-specific genital infection, years since last Pap smear, years of education, age, study centre	Population-based Limited to non-Hispanic whites Response for cases 78%, for eligible controls 74%
			Veg.: ≥ 26 vs ≤ 11 servings/wk (4)	[0.92]	$p = 0.48$		
			Fruit and veg.: ≥ 44 servings/wk vs ≤ 21 (4)	[0.74]	$p = 0.43$		

*p for trend when applicable

Table 72. Case–control study of fruit consumption and risk of cervical dysplasia

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
De Vet *et al.*, 1991, Netherlands	257/705	FFQ, self-administered, frequency of consumption and small, medium or large portion size	≥ 3 vs 0 servings/d (4)	0.29 (0.13–0.63)	$p = 0.06$	Demographic characteristics, season when questionnaire completed, marital status, education, smoking, parity, oral contraceptive use, age at first sexual intercourse, frequency of intercourse, number of sexual partners, frequency of Pap smears, consumption of other food groups	Population-based Cases were participants in a multi-centre trial; controls were drawn from population registries Response rate for cases 85%, for controls 67%

*p for trend when applicable

Table 73. Case–control studies of fruit consumption and risk of endometrium cancer

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
La Vecchia *et al.*, 1986, Italy	206/206	FFQ (10), frequency	Fresh fruit: ≥ 14 vs < 14 servings/wk (2)	0.57 (0.33–0.99)		Interviewer, age, marital status, years of education, BMI, parity, history of diabetes or hypertension, age at menarche, age at menopause, oral contraceptive use, other female hormone use	Hospital-based
Levi *et al.*, 1993a, Switzerland, northern Italy	274/572	FFQ (50), interviewed, frequency	Total fresh fruit: Highest vs lowest (3)	0.45	$p = 0.01$	Age, study centre, energy	Hospital-based
Potischman *et al.*, 1993, USA	399/296	FFQ (60, 7 fruits), interviewed, open-ended frequency of intake, one of three portion sizes	> 21.9 vs < 8.5 times/wk (4)	1.1 (0.6–1.9)		Age group, BMI, ever estrogen use, ever oral contraceptive use, number of births, current smoking, education, energy	Population-based Response rate among eligible cases 87%, among eligible controls 66%
Shu *et al.*, 1993, China	268/268	FFQ (63, 5 fruits), interviewed, open-ended usual intake frequency, portion per unit time	Highest vs lowest (4)	0.7	$p = 0.25$	Age, number of pregnancies, BMI, energy	Population-based Response rate for cases 91%, for controls 96%
Hirose *et al.*, 1996, Japan	145/26 751	Questionnaire, frequency of intake	Daily vs ≤ 3–4 servings/wk (2)	1.97 (1.37–2.82)	$p < 0.01$	Age and first-visit year	Hospital-based 98% of first-visit patients completed questionnaire
Tzonou *et al.*, 1996b, Greece	145/298	Semi-quantitative FFQ, (115, 19 fruits), interviewed	Highest vs lowest (4)	0.96 (0.76–1.21)	$p = 0.73$	Age, education, age at menopause, age at menarche, parity, miscarriages, abortions, oral contraceptive use, hormone replacement therapy, smoking, alcohol, coffee, height, energy, BMI	Hospital-based Response rate for cases 83%, for controls 88%

Table 73 (contd)

Author, year, country	Cases/control	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Goodman *et al.*, 1997, USA	332/511	FFQ (250), interviewed, open-ended usual intake frequency, portion size from pictures of three different portions	> 282 vs < 95 g/d (4)	0.5	$p = 0.004$	Pregnancy history, oral contraceptive usage, history of diabetes, BMI, energy	Population-based Response rate for cases 66%, for controls 73%
Jain *et al.*, 2000, Canada	552/563	Diet history, interviewed, usual frequency, usual amount in relation to food models	> 555 vs < 229 g/d (4)	1.29 (0.88–1.89)	$p = 0.41$	Energy, age, body weight, ever smoked, history of diabetes, oral contraceptive use, hormone replacement therapy use, university education, live births, age at menarche	Population-based Response rate for cases 50% of potentially eligible, 70% of eligible with MD approval, for controls 41%
McCann *et al.*, 2000, USA	232/639	Diet history (172, 18 fruits) self-administered, usual intake, portion size in relation to pictures	> 184 vs < 81 times/mo (4)	0.9 (0.5–1.7)	$p = 0.97$	Age, education, BMI, diabetes, hypertension, pack-years cigarette smoking, age at menarche, parity, oral contraceptive use, menopause status, hormone replacement therapy use, other food groups	Population-based Response rate for cases 51%, for controls 51%
Littman *et al.*, 2001, USA	679/944	FFQ (98, 16 fruits), interviewed, frequency five years previously, portion size relative to three categories	> 2.3 vs < 0.8 servings/d (5)	0.67 (0.47–0.95)	$p = 0.02$	Age, county of residence, energy, unopposed estrogen use, smoking, BMI	Population-based Response rate for cases 72%, for controls 73% among those found eligible
Terry *et al.*, 2002, Sweden	709/2887	FFQ, self-administered, nine frequency categories	> 21 vs < 2.5 servings/wk (median values (4)	0.9 (0.7–1.2)	$p = 0.35$	Age, BMI, smoking, physical activity, prevalence of diabetes, fatty fish consumption, quintiles of total food consumption, other dietary factors	Population-based Postmenopausal women with intact uterus, no history of endometrial or breast cancer Response rate for cases 75%

*p for trend when applicable

Table 74. Case–control studies of vegetable consumption and risk of endometrium cancer

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Zemla *et al.*, 1986, Poland	173/346	No information	Raw veg.: Frequent vs never (3)	0.43	$p < 0.001$	None	Hospital-based cases, control selection not clear
La Vecchia *et al.*, 1986, Italy	206/206	FFQ (10), frequency	Green veg.: ≥ 8 vs < 8 portions/wk (2)	0.24 (0.13–0.45)		Interviewer, age, marital status, years of education, BMI, parity, history of diabetes or hypertension, age at menarche, age at menopause, oral contraceptive use, other female hormone use	Hospital-based
Levi *et al.*, 1993a, Switzerland, northern Italy	274/572	FFQ (50) interviewed, frequencies	Highest vs lowest (3)	0.38	$p < 0.01$	Age, study centre, energy	Hospital-based
Potischman *et al.*, 1993, USA	399/296	FFQ (60, 13 veg.) open-ended frequency of intake, one of three portion sizes	> 21.0 vs < 11.1 times/wk (4)	1.0 (0.6–1.6)		Age-group, BMI, ever estrogen use, ever oral-contraceptive use, number of births, current smoking, education, energy	Population-based Response among eligible cases 87%, among eligible controls 66% Includes potatoes, pulses and legumes
Shu *et al.*, 1993, China	268/268	FFQ (63, 23 veg.), interviewed, open-ended usual intake frequency, portion per unit time, 23 veg. (includes four legumes)	Highest vs lowest (4)	1.4	$p = 0.39$	Age, number of pregnancies, BMI, energy	Population-based Response rate for cases 91%, for controls 96%
Hirose *et al.*, 1996, Japan	145/26 751	Questionnaire or frequency of intake	Raw veg.: Daily vs ≤ 3–4 servings/wk (2) Green veg.: > 5 vs ≤ 2 servings/wk (3)	1.54 (1.11–2.13) 1.12 (0.74–1.70)	$p < 0.05$ NS	Age and first-visit year	Hospital-based 98% of first-visit patients completed questionnaire

Table 74 (contd)

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Tzonou *et al.*, 1996b, Greece	145/298	Semi-quantitative FFQ, (115), 25 veg., interviewed	Highest vs lowest (4)	0.85 (0.66–1.11)	$p = 0.24$	Age, education, age at menopause, age at menarche, parity, miscarriages, abortions, oral contraceptive use, HRT, smoking, alcohol, coffee, height, BMI, energy	Hospital-based Response rate for cases 83%, for controls 88%
Goodman *et al.*, 1997, USA	332/511	FFQ, (250), interviewed, open ended usual intake frequency, portion size from pictures of three different portions	> 272 vs < 132 g/d (4)	0.5	$p = 0.02$	Pregnancy history, oral contraceptive usage, history of diabetes, BMI, energy	Population-based Response rate for cases 66%, for controls 73%
Jain *et al.*, 2000, Canada	552/563	Diet history, interviewed, usual frequency, usual amount in relation to food models	> 633 vs < 271 g/d (4)	0.65 (0.44–0.96)	$p = 0.04$	Energy, age, body weight, ever smoked, history of diabetes, oral contraceptive use, HRT, university education, live births, age at menarche	Population-based Response rate for cases 50% of potentially eligible, 70% of eligible with MD approval, for controls 41%
McCann *et al.*, 2000, USA	232/639	Diet history (172, 34 veg.), self-administered, usual intake portion size in relation to pictures	> 221 vs < 127 times/mo (4)	0.5 (0.3–0.9)	$p = 0.03$	Age, education, BMI, diabetes, hypertension, pack-years cigarette smoking, age at menarche, parity, oral contraceptive use, menopause status, HRT, other food groups	Population-based Response rate for cases 51%, for controls 51%
Littman *et al.*, 2001, USA	679/944	FFQ, (98, 19 veg.), frequency 5 y previous, portion size relative to three categories	> 3.1 vs < 1.5 servings/d (5)	0.69 (0.48–1.0)	$p = 0.07$	Age, county of residence, energy, unopposed estrogen usage, smoking, BMI	Population-based Response rate for cases 72%, for controls 73% among those found eligible Includes potatoes

*p for trend when applicable. HRT, hormone replacement therapy

Table 75. Cohort study of fruit and vegetable consumption and risk of endometrium cancer

Author, year, country	Cases/ cohort size (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Terry *et al.*, 1999, Sweden	133/11 659 25 y	Questionnaire (107, 1 fruit, 1 veg.), self-administered, four categories of contribution to total diet	Large vs very little or no part of the diet (4)	[0.32 (0.08–1.25)]	NS	Age, physical activity, weight at baseline, parity	Incidence Twin study

*p for trend when applicable

Table 76. Case–control studies of fruit and vegetable consumption and risk of endometrium cancer

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Goodman *et al.*, 1997, USA	332/511	FFQ (250), interviewed, open-ended usual intake frequency, portion size from pictures of three different portions	> 553 vs < 259 g (4)	0.6	$p = 0.02$	Pregnancy history, oral contraceptive use, history of diabetes, BMI, energy	Population-based Response rate for cases 66%, for controls 73%
Littman *et al.*, 2001, USA	679/944	FFQ, (98, 16 fruit 19 veg.), interviewed, frequency 5 y previously, portion size relative to three categories	> 5.2 vs < 2.3 servings/d (5)	0.73 (0.50–1.1)	$p = 0.13$	Age, county of residence, energy, unopposed estrogen use, smoking, BMI	Population-based Response rate for cases 72%, for controls 73% among those found eligible
Terry *et al.*, 2002, Sweden	709/2887	FFQ, self-administered , nine frequency categories	> 37 vs < 9.9 servings/wk (4) (median values	0.9 (0.7–1.2)	$p = 0.73$	Age, BMI, smoking, physical activity, prevalence of diabetes, fatty fish consumption, quintiles of total food consumption, other dietary factors	Population-based Postmenopausal women with intact uterus, no previous history of endometrial or breast cancer. Response rate among cases 75%, among controls 80%

*p for trend when applicable

Table 77. Cohort studies of fruit consumption and risk of ovary cancer

Author, year, country	Cases/ cohort size (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Kushi *et al.*, 1999, USA	139/29 083 10 y	Semi-quantitative FFQ (126), self-administered, nine frequency categories, validated	> 23 vs < 11 times/wk (4)	1.13 (0.66–1.93)	$p = 0.51$	Age, energy, number of live births, age at menopause, family history of ovarian cancer, hysterectomy/unilateral oophorectomy status, waist-to-hip ratio, physical activity, pack-years of smoking, education	Incidence Iowa Health Study
Fairfield *et al.*, 2001, USA	301/80 326 16 y	Semi-quantitative FFQ (126), self-administered, nine frequency categories, validated	≥ 3.2 vs < 1.1 servings/d (5)	1.27 (0.80–2.02)	$p = 0.20$	Age, energy, duration of oral contraceptive use, parity, tubal ligation, BMI, smoking, dietary fibre	Incidence Nurses' Health Study Limited to epithelial cancers

*p for trend when applicable

Table 78. Case–control studies of fruit consumption and risk of ovary cancer

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shu *et al.*, 1989, China	172/172	FFQ (63, 4 fruits), interviewed, open-ended usual intake frequency, portion per unit time	Highest vs lowest (4)	0.9	$p = 0.68$	Education	Population-based Response rate for eligible cases 89%, for controls 100%
McCann *et al.*, 2001, USA	496/1425	FFQ (44), self-administered, no portion size	Fruit and fruit juices: > 101 vs ≤ 48 times/mo (4)	0.85 (0.59–1.21)	$p = 0.40$	Age, education, region of residence, regularity of menstruation, family history of ovarian cancer, parity, age at menarche, oral contraceptive use, and remaining food groups	Hospital-based
Salazar-Martinez *et al.*, 2002, Mexico	84/629	FFQ (116), interviewed, frequency of fixed portion for 10 intake frequencies, validated	Highest vs lowest (3)	2.43 (1.02–5.75)	$p = 0.004$	Age, energy, number of live births, recent change in weight, physical activity, diabetes	Hospital-based
Zhang *et al.*, 2002b, China	254/652	FFQ (120), interviewed, portion size from eight categories, cooking method, vitamin and mineral supplements, validated	≥ 110.05 vs ≤ 32.60 kg/y (4)	0.36 (0.2–0.7)	$p < 0.001$	Age, education, area of residence, BMI five years previously, smoking, alcohol, tea, family income, marital status, menopausal status, parity, tubal ligation, oral contraceptive use, physical activity, family history of ovarian cancer, energy, other food groups	Hospital-based and population-based

* p for trend when applicable

Table 79. Cohort studies of vegetable consumption and risk of ovary cancer

Author, year, country	Cases/cohort size (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Kushi *et al.*, 1999, USA	139/29 083 10 y	Semi-quantitative FFQ (126), self-administered, nine frequency categories, validated	> 31 vs < 16 times/wk (4)	0.76 (0.42–1.37)	$p = 0.21$	Age, energy, number of live births, age at menopause, family history of ovarian cancer, hysterectomy/ unilateral oophorectomy status, waist-to-hip ratio, physical activity, pack-years of smoking, education	Incidence Iowa Health Study
Fairfield *et al.*, 2001, USA	301/80 326 16 y	Semi-quantitative FFQ (126), self-administered, nine frequency categories	> 4.4 vs < 1.8 servings/d (5)	0.77 (0.48–1.24)	$p = 0.30$	Age, energy, duration of oral contraceptive use, parity, tubal ligation, BMI, smoking, dietary fibre	Incidence Nurses' Health Study Limited to epithelial cancers

*p for trend when applicable

Table 80. Case–control studies of vegetable consumption and risk of ovary cancer

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shu *et al.*, 1989, China	172/172	FFQ (63, 18 veg.), interviewed, open-ended usual intake frequency, portion per unit time	Highest vs lowest (4)	0.8	$p = 0.45$	Education	Population-based Response rate for eligible cases 89%, for controls 100%
La Vecchia *et al.*, 1987b, Italy	455/1385	FFQ (10), interviewed, three categories of frequency	Green veg.: ≥ 8 vs < 7 times/wk (3)	0.61 (0.46–0.82)	$p < 0.001$	Age, interviewer, marital status, social class, education, parity, age at first birth, age at menarche, menopausal status, age at menopause, BMI, oral contraceptive use, other female hormone use, retinol, carotene, added fat, alcohol, other foods	Hospital-based

Table 80 (contd)

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Bosetti *et al.*, 2001, Italy	1031/2411	FFQ, (78), interviewed, frequency only	Raw veg.: > 11.5 vs < 4.0 servings/wk (5) Cooked veg.: > 5.0 vs < 1.8 servings/wk (5)	0.47 (0.34–0.64) 0.65 (0.48–0.87)	$p < 0.0001$ $p = 0.002$	Age, study centre, education, year of interview, parity, oral contraceptive use, energy	Hospital-based in four regions of Italy
McCann *et al.*, 2001, USA	496/1425	FFQ (44), self-administered, no portion size	> 66 vs ≤ 24 times/mo (4)	0.76 (0.52–1.10)	$p = 0.07$	Age, education, region of residence, regularity of menstruation, family history of ovarian cancer, parity, age at menarche, oral contraceptive use, and remaining food groups	Hospital-based
Salazar-Martinez *et al.*, 2002, Mexico	84/629	FFQ, (116), frequency of fixed portion for 10 intake frequencies, validated	Green leafy veg.: Highest vs lowest (3)	1.56 (0.67–3.64)	$p = 0.14$	Age, energy, number of live births, recent change in weight, physical activity, diabetes	Hospital-based
Zhang *et al.*, 2002b, China	254/652	FFQ (120), interviewed, portion size from eight categories, cooking method, vitamin and mineral supplements, validated	≥ 180.55 vs ≤ 89.25 kg/y (4)	0.24 (0.1–0.5)	$p < 0.001$	Age, education, area of residence, BMI five years previously, smoking, alcohol, tea, family income, marital status, menopausal status, parity, tubal ligation, oral contraceptive use, physical activity, family history of ovarian cancer, energy, other food groups	Hospital-based and population-based

*p for trend when applicable

Table 81. Cohort study of fruit and vegetable consumption and risk of ovary cancer

Author, year, country	Cases/cohort size (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Fairfield *et al.*, 2001, USA	301/80 325 16 y	FFQ (126), self-administered, nine frequency categories, validated	> 7.3 vs < 3.3 servings/d (5)	1.10 (0.64–1.90)	$p = 0.84$	Age, energy, duration or oral contraceptive use, parity, tubal ligation, BMI, smoking, dietary fibre	Incidence Nurses' Health Study Limited to epithelial cancers Inverse association with reported diet in adolescence

*p for trend when applicable

Table 82. Case–control study of fruit and vegetable consumption and risk of ovary cancer

Author, year, country	Cases/controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
McCann *et al.*, 2001, USA	496/1325	FFQ (44), self-administered, no portion size	> 164 vs ≤ 80 times/mo (4)	0.62 (0.42–0.92)	$p = 0.09$	Age, education, region of residence, regularity of menstruation, family history of ovarian cancer, parity, age at menarche, oral contraceptive use, remaining food groups	Hospital-based

*p for trend when applicable

Table 83. Cohort studies of fruit consumption and risk of prostate cancer

Author, year, country	Cases/cohort size (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Mills *et al.*, 1989, USA	180/14 000 6 y	FFQ (5 fruits)	≥ 60 vs < 12/mo (3)	1.07 (0.72–1.58)	NS	Age, education, other foods	Incidence Seventh-day Adventists
Severson *et al.*, 1989, USA	174/8006 21 y	FFQ (20), interviewed	≥ 5 vs ≤ 1/wk (3)	1.57 (0.95–2.61)		Age	Incidence Men of Japanese ancestry in Hawaii
Hsing *et al.*, 1990, USA	149/17 633 20 y	FFQ (35, 5 fruits), self-administered	> 67 vs < 29.3 times/mo (4)	0.9 (0.6–1.4)		Age, smoking	Mortality Policy holders
Shibata *et al.*, 1992, USA	208/11 580 (women included), 9 y	FFQ (59, 23 fruits), self-administered	≥ 3.5 vs < 2.2 servings/d (3)	1.04 (0.74–1.46)	NS	Age, smoking	Incidence Retirement community
Le Marchand *et al.*, 1994, USA	198/20 316 15 y	FFQ (13)	Fresh fruit: > 974 vs < 414 g/wk (4)	1.0 (0.7–1.6)	$p = 0.99$	Age, ethnicity, income	Incidence Men of various ethnicities in Hawaii
Giovannucci *et al.*, 1995, USA	773/47 894 7 y	FFQ (131, 46 fruits and veg.), self-administered, validated	> 4 vs < 1 serving/d	0.84 (0.59–1.84)	$p = 0.21$	Age, energy	Incidence Health professionals
Schuurman *et al.*, 1998, Netherlands	642/58 279 6.3 y	FFQ (150, 8 fruits), self-administered, validated	286.4 vs 34.0 g/d (median values) (5)	1.31 (0.96–1.79)	$p = 0.02$	Age, family history, socioeconomic status, veg.	Incidence Netherlands cohort study
Chan *et al.*, 2000, Finland	184/27 062 8 y	FFQ (276), self-administered, validated	230 vs 25 g/d (median values) (5)	1.3 (0.8–2.2)	$p = 0.13$	Supplementation group, education, age, BMI, energy, smoking	Incidence Smokers, ATBC study
Appleby *et al.*, 2002, UK	41/4325 25 y	FFQ	Fresh fruit: Daily vs < daily (2)	0.73 (0.35–1.50)	NS	Age, smoking, other foods	Mortality Cohort of health-food shoppers
Key *et al.*, 2003, European countries	1104/130 544 (mean, 4.8 y)	FFQ, validated self-administered or interviewed	Highest vs lowest (5)	1.06 (0.84–1.34)	$p = 0.74$	Age, centre, height, weight, energy	Incidence

*p for trend when applicable

Table 84. Case–control studies of fruit consumption and risk of prostate cancer

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Negri *et al.*, 1991, Italy	107/2522	FFQ (13–37 depending on cancer site)	Highest vs lowest (3)	0.4 (0.3–0.8)	$p < 0.01$	Age, area, education, smoking, vegetables	Hospital-based Data from a network of case–control studies Response rate > 97%
Talamini *et al.*, 1992, Italy	271/685	FFQ (14), interviewed	Fresh fruit: Highest vs lowest (3)	1.41 (0.96–2.07)	$p = 0.06$	Age, area, education, BMI	Hospital-based Response rate > 96%
De Stefani *et al.*, 1995, Uruguay	156/302	FFQ, interviewed	≥ 261 vs ≤ 96 times/y (3)	1.7 (1.1–2.8)	$p = 0.04$	Age, residence, education, tobacco, beer	Hospital-based Response rate for cases 98%, controls not given
Deneo-Pellegrini *et al.*, 1999, Uruguay	175/233	FFQ (64, 9 fruits), interviewed, not validated but reproducible	≥ 736 vs ≤ 270 times/y (4)	0.8 (0.4–1.4)	$p = 0.08$	Age, residence, urban/rural, education, family history, BMI, energy	Hospital-based Response rate for cases 92%, controls 97%
Hayes *et al.*, 1999, USA	932/1201	FFQ (60, 10 fruits), interviewed	Highest vs lowest (4)	1.1	$p = 0.48$	Age, study site, race	Population-based Response rate for cases 76%, controls 70%
Jain *et al.*, 1999, Canada	617/636	Diet history (1129), validated	> 514.4 vs < 183.3 g/d (4)	1.51 (1.14–2.01)	$p = 0.01$	Energy, vasectomy, age, smoking, marital status, area, BMI, education, multi-vitamins, other foods and nutrients	Population-based Response rate for cases 81%, controls 63%
Sung *et al.*, 1999, Taiwan	90/180	FFQ, interviewed	≥ 2 vs < 2/wk (2)	1.16 (0.57–2.35)		None	Hospital-based Response rate for cases 93%, controls 92%
Tzonou *et al.*, 1999, Greece	320/246	FFQ (120, 19 fruits), interviewed, validated	Quintile increment (median = 222.5 vs 64.5 times/mo)	0.98 (0.86–1.13)		Age, height, BMI, education, energy, other foods	Hospital-based Response rate for cases 86%, controls 80%

Table 84 (contd)

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Villeneuve *et al.*, 1999, Canada	1623/1623	FFQ (60), modified from validated FFQ, self-administered	Fruit and fruit juices ≥ 28 vs < 7/wk (4)	1.5 (1.1–1.9)	$p = 0.03$	Age, province, race, smoking, BMI, other foods, family history	Population-based Response rate for cases 69%, controls 69%
Cohen *et al.*, 2000, USA	628/602	FFQ (99, 12 fruits), self-administered	≥ 21 vs < 7 servings/wk (4)	1.07 (0.72–1.60)	$p = 0.96$	Fat, energy, race, age, family history, BMI, PSA in previous five years, education	Population-based Response rate for cases 82%, controls 75%
Kolonel *et al.*, 2000, USA and Canada	1619/1618	Diet history (147, 17 fruits), interviewed	> 360.9 vs ≤ 75.3 g/d (5)	1.01 (0.79–1.28)	$p = 0.48$	Age, education, ethnicity, geographical area, energy	Population-based, multicentre, multiethnic Response rate for cases 70%, controls 58%

*p for trend when applicable

Table 85. Cohort studies of vegetable consumption and risk of prostate cancer

Author, year, country	Cases/ cohort size, (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hirayama, 1990, Japan	183/265 118 17 y	FFQ (7)	Green yellow veg.: Daily vs non-daily (2)	0.95 (90% CI, 0.73–1.25)		Not reported	Mortality Census-based cohort in four prefectures
Hsing *et al.*, 1990, USA	149/17 633 20 y	FFQ (35, 10 veg.), self-administered	> 99.1 vs < 56.8 times/mo (4)	0.7 (0.4–1.2)		Age and tobacco	Mortality Policy-holders Include potatoes
Shibata *et al.*, 1992, USA	208/11 580 (women included) 9 y	FFQ (59, 21 veg.), self-administered	≥ 4.5 vs < 3.0 servings/d (3)	1.04 (0.74–1.46)	NS	Age and smoking	Incidence Retirement community
Le Marchand *et al.*, 1994	198/20 316 15 y	FFQ (13)	Raw veg.: > 302 vs < 82 g/wk (4)	1.1 (0.7–1.7)	$p = 0.69$	Age, ethnicity, income	Incidence Men of various ethnicities in Hawaii

Table 85 (contd)

Author, year, country	Cases/ cohort size, (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Giovannucci *et al.*, 1995, USA	773/47 894 7 y	FFQ (131, 46 fruits and veg.), self-administered, validated	> 5 vs < 2 servings/d	1.04 (0.81–1.34)	$p = 0.68$	Age and energy	Incidence Health professionals
Schuurman *et al.*, 1998, Netherlands	642/58 279 6.3 y	FFQ (150, 17 veg.), self-administered, validated	285 vs 100 g/d (median values) (5)	0.80 (0.57–1.12)	$p = 0.51$	Age, family history, socio-economic status, fruit	Incidence Netherlands cohort study
Chan *et al.*, 2000, Finland	184/27 062 8 y	FFQ (276), self-administered, validated	204 vs 40 g/d (median values) (5)	0.8 (0.5–1.3)	$p = 0.84$	Supplementation group, education, age, BMI, energy, smoking	Incidence Smokers, ATBC study
Key *et al.*, 2003, European countries	1104/130 544 (mean, 4.8 y)	FFQ, self-administered or interviewed, validated	Highest vs lowest (5)	1.00 (0.81–1.22)	$p = 0.74$	Age, centre, height, weight, energy	Incidence

* p for trend when applicable

Table 86. Case–control studies of vegetable consumption and risk of prostate cancer

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Mishina *et al.*, 1985, Japan	100/100	Questionnaire, interviewed	Green yellow veg. > occasionally vs ≤ occasionally (2)	0.5	NS	Matched by age	Mostly screening based
Oishi *et al.*, 1988, Japan	100/100	FFQ (31)	Highest vs lowest (3)	0.87 (0.43–1.76)		Matched by age	Hospital-based
Negri *et al.*, 1991, Italy	107/2522	FFQ (14–37 depending on cancer site)	Green veg.: Highest vs lowest (3)	0.3 (0.1–0.5)	$p < 0.01$	Age, area, education, smoking, fruit	Hospital-based Data from network of case–control studies Response rate > 97%
Talamini *et al.*, 1992, Italy	271/685	FFQ (14), interviewed	Highest vs lowest (3)	1.39 (0.88–2.17)	$p = 0.17$	Age, area, education, BMI	Hospital-based Response rate > 96%

Table 86 (contd)

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
De Stefani *et al.*, 1995, Uruguay	156/302	FFQ, interviewed	≥ 131 vs ≤ 51 times/y (3)	1.1 (0.6–1.9)	$p = 0.71$	Age, residence, education, tobacco, beer	Hospital-based Response rat for cases 98%, controls not given
Key *et al.*, 1997, UK	328/328	FFQ (83), interviewed, validated	Cooked veg.: > 1/d vs ≤ 4/wk (4)	0.71 (0.34–1.48)	$p = 0.415$	Matched by age. Adjusted for social class	Population-based Potatoes excluded Response rate for cases 77%, for controls 81%
Deneo-Pellegrini *et al.*, 1999, Uruguay	175/233	FFQ (64, 12 veg.), inteviewed, not validated but reproducible	≥ 697 vs ≤ 336 times/y (4)	0.6 (0.3–1.1)	$p = 0.02$	Age, residence, urban/rural, education, family history, BMI, energy	Hospital-based Response rate for cases 92%, for controls 97%
Hayes *et al.*, 1999, USA	932/1201	FFQ (60, 21 veg.), interviewed	Highest vs lowest (4)	1.0	$p = 0.89$	Age, study site, race	Population-based Includes potatoes Response rate for cases 76%, for controls 70%
Jain *et al.*, 1999, Canada	617/636	Diet history (1129), validated	> 594.6 vs < 286.5 g/d (4)	0.95 (0.68–1.33)	NS	Energy, vasectomy, age, smoking, marital status, area, BMI, education, multivitamins, other foods and nutrients	Population-based Response rate for cases 81%, for controls 63%
Tzonou *et al.*, 1999, Greece	320/246	FFQ (120, 26 veg.), interviewed, validated	Quintile increment (median = 121.3 vs 48 times/mo)	0.94 (0.81–1.10)		Age, height, BMI, education, energy, other foods	Hospital-based Potatoes excluded Response rate for cases 86%, for controls 80%
Villeneuve *et al.*, 1999, Canada	1623/1623	FFQ (60), modified from validated FFQ, self-administered	≥ 28 vs < 14/wk (4)	1.0 (0.8–1.3)	$p = 0.79$	Age, province, race, smoking, BMI, other foods, family history	Population-based Response rate for cases 69%, for controls 69%
Cohen *et al.*, 2000, USA	628/602	FFQ (99, 21 veg.), self-administered	≥ 28 vs < 14 servings/wk (4)	0.65 (0.45–0.94)	$p = 0.01$	Fat, energy, race, age, family history, BMI, PSA in previous 5 y, education	Population-based Response rate for cases 82%, for controls 75%
Kolonel *et al.*, 2000, USA, Canada	1619/1618	Diet history, 37 veg.	> 324.8 vs ≤ 101.3 g/d (5)	0.74 (0.58–0.96)	$p = 0.04$	Age, education, ethnicity, geographic area, energy	Population-bases, multicentre, multiethnic Response rate for cases 70%, for controls 58%

*p for trend when applicable

Table 87. Cohort studies of fruit and vegetable consumption and risk of prostate cancer

Author, year, country	Cases/ cohort size, (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Shibata *et al.*, 1992, USA	208/11 580 (including women) 9 y	FFQ (59, 23 fruits, 21 veg.), self-administered	≥ 7.9 vs < 5.5 servings/d (3)	1.10 (0.78–1.55)	NS	Age and smoking	Incidence Retirement community
Schuurman *et al.*, 1998, Netherlands	642/ 58 279 6.3 y	FFQ (150, 8 fruits, 17 veg.), self-administered	519 vs 177.7 g/d (median values) (5)	1.05 (0.76–1.45)	$p = 0.58$	Age, family history, socio-economic status	Incidence Netherlands cohort study

* p for trend when applicable

Table 88. Case–control study of fruit and vegetable consumption and risk of prostate cancer

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Deneo-Pellegrini *et al.*, 1999, Uruguay	175/233	FFQ (64, 9 fruits, 12 veg.), interviewed, not validated, but reproducible	> 1390 vs < 685 times/y (4)	0.5 (0.3–0.9)	$p = 0.04$	Age, residence, urban/rural, education, family history, BMI, energy	Hospital-based

* p for trend when applicable

Table 89. Case-control studies of fruit and/or vegetable consumption and risk of testicular cancer

Author, year, country	Cases/ controls	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Sigurdson *et al.*, 1999, USA	160 (82 non-seminomas, 46 seminomas, 32 mixed germ-cell)/136	FFQ (152), self-administered, validated	Fruit: > 147.2 vs < 29.7 g/1000 kcal (4)			Age, education, income, ethnicity, cryptorchidism, energy	Hospital-based, friend-matched controls Response rates for cases 38%, for controls 73%
			Non-seminoma	[0.9(0.3–2.5)]	$p = 0.99$		
			Seminoma	[0.4(0.1–1.4)]	$p = 0.29$		
			Mixed germ-cell	[0.3(0.1–1.3)]	$p = 0.09$		
			Veg.: > 58.9 vs < 18.6 g/1000 kcal (4)				
			Non-seminoma	[0.8(0.3–2.5)]	$p = 0.81$		
			Seminoma	[1.7(0.5–5.0)]	$p = 0.25$		
			Mixed germ-cell	[1.4(0.4–5.0)]	$p = 0.48$		
Swerdlow *et al.*, 1999, UK	60 twin pairs	FFQ, self-administered	OR for having consumed more during childhood	Fruit: 1.0 (0.3–3.1) Veg.: 0.3 (0.1–1.0)			Study in twins

*p for trend when applicable

Table 90. Cohort studies of fruit consumption and risk of bladder cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Chyou *et al.*, 1993, USA	96/6790, M 22 y	FFQ (17) + 24-h dietary recall	≥ 5 vs ≤ 1/wk (3)	0.63 (0.37–1.08)	$p = 0.038$	Age, smoking	Incidence Japanese resident in Hawaii
Michaud *et al.*, 1999, USA	252/47 909, M 10 y	FFQ (131), validated	> 3.5 vs ≤ 1 servings/d (5)	1.12 (0.70–1.78)	$p = 0.68$	Age, geographical region, smoking, fluid intake, energy	Incidence Health professionals study
Nagano *et al.*, 2000, Japan	106/38 540, M, F 14 y	FFQ (22) self-administered	≥ 5 vs 0–1 times/wk (3)	0.75 (0.46–1.22)	$p = 0.29$	Age, gender, education, calendar time, radiation dose, smoking, BMI, green veg.	Incidence Atomic bombing survivors
Zeegers *et al.*, 2001, Netherlands	569/120 852, M, F 6.3 y	FFQ (150, 9 fruits), self-administered	≥ 256 vs < 83 g/d (5)	0.74 (0.53–1.04)	$p = 0.02$	Sex, age, smoking, veg.	Incidence Netherlands cohort study
Michaud *et al.*, 2002, Finland	344/27 111, M, smokers 13 y	FFQ (276, 45 fruits or veg.)	245.4 vs 25 g/d (median values) (5)	1.10 (0.77–1.57)	$p = 0.98$	Age, duration of smoking, smoking dose, energy, trial intervention	Incidence Follow-up of ATBC trial

Table 91. Case–control studies of fruit consumption and risk of bladder cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Riboli *et al.*, 1991, Spain	432/789, M, F	Dietary history, interviewed	Highest vs lowest (4)	0.95 (0.67–1.35)	$p = 0.62$	Age, tobacco, gender, energy	Hospital-based and population-based Multicentre study
Bruemmer *et al.*, 1996, USA	240/395, M, F	FFQ (71), self-administered	> 2.7 vs ≤ 0.9 times/d (4)	0.53 (0.30–0.93)	$p = 0.01$	Age, gender, county, smoking, energy	Population-based
Wakai *et al.*, 2000, Japan	297/295, M, F	FFQ (97), interviewed	Highest vs lowest (4)	All: 0.65 (0.40–1.06) M: 0.52 (0.30–0.90)	$p = 0.09$ $p = 0.03$	Age, gender, hospital, smoking, occupation	Hospital-based
Balbi *et al.*, 2001, Uruguay	144/576, M, F	FFQ (64, 8 fruits)	Highest vs lowest (3)	0.65 (0.40–1.04)	$p = 0.06$	Age, gender, urban/rural status, residence, education, BMI, smoking, energy, mate drinking	Hospital-based

*p for trend when applicable

Table 92. Cohort studies of vegetable consumption and risk of bladder cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Michaud *et al.*, 1999, USA	252/47 909, M 10 y	FFQ (131), validated	≥ 5 vs < 2 servings/d (5)	0.72 (0.47–1.09)	$p = 0.09$	Age, geographical region, smoking, fluid intake, energy	Incidence Health professionals study Statistically significant association for cruciferous veg.
Nagano *et al.*, 2000, Japan	95/38 540, M, F 14 y	FFQ (22), self-administered	Green-yellow veg.: ≥ 5 vs 0–1 times/wk (3)	0.60 (0.33–1.07)	$p = 0.07$	Age, gender, education, calendar time, radiation dose, smoking, BMI, fruit	Incidence Atomic bombing survivors
Zeegers *et al.*, 2001, Netherlands	538/120 852, M, F 6.3 y	FFQ (150, 21 veg.), self-administered	≥ 242 vs < 126 g/d (5)	0.91 (0.65–1.27)	$p = 0.38$	Sex, age, smoking, fruit	Incidence Netherlands cohort study
Michaud *et al.*, 2002, Finland	344/27 111, M, smokers 13 y	FFQ (276, 45 fruits or veg.)	205.3 vs 39.5 g/day (median values) (5)	1.16 (0.82–1.63)	$p = 0.14$	Age, duration of smoking, smoking dose, energy, trial intervention	Incidence Follow-up of ATBC trial

*p for trend when applicable

Table 93. Case–control studies of vegetable consumption and risk of bladder cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Riboli *et al.*, 1991, Spain	432/789, M, F	Dietary history, interviewed	Highest vs lowest (4)	1.04 (0.73–1.48)	$p = 0.45$	Age, gender, tobacco, energy	Hospital-based and population-based Multicentre study
Bruemmer *et al.*, 1996, USA	240/395, M, F	FFQ (71), self-administered	> 3.6 times/d vs ≤ 1.3 times/d (4)	0.87 (0.52–1.45)	$p = 0.65$	Age, gender, county, smoking, energy	Population-based
Wakai *et al.*, 2000, Japan	297/295, M, F	FFQ (97), interviewed	Green-yellow veg.: Highest vs lowest (4)	0.73 (0.45–1.20)	$p = 0.20$	Age, gender, hospital, smoking, occupation	Hospital-based
			Other veg.: Highest vs lowest (4)	1.04 (0.62–1.73)	$p = 0.73$		
Balbi *et al.*, 2001, Uruguay	144/576, M, F	FFQ (64, 11 veg.)	Highest vs lowest (3)	0.66 (0.40–1.09)	$p = 0.12$	Age, gender, residence, urban/rural status, education, BMI, smoking, energy, mate drinking	Hospital-based

*p for trend when applicable

Table 94. Cohort studies of total fruit and vegetable consumption and risk of bladder cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Steineck *et al.*, 1988, Sweden	70/16 477 14 y	FFQ (8), self-administered	"Exposed to fruit and veg."	1.0 (0.6–1.6)		Age, sex, smoking	Incidence Twin study
Zeegers *et al.*, 2001, Netherlands	538/120 852, M, F 6.3 y	FFQ (150, 9 fruits, 21 veg.), self-administered	≥ 471 vs <241 g/d (5)	0.98 (0.60–1.61)	$p = 0.39$	Age, sex, smoking	Incidence Netherlands cohort study

* p for trend when applicable

Table 95. Case–control studies of total fruit and vegetable consumption and risk of bladder cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Claude *et al.*, 1986, Germany	531/531, M, F	FFQ, interviewed	Eaten regularly	M: 0.59 (0.37–0.95) F: 0.90 (0.37–2.21)		Age, smoking	Hospital-based
De Stefani *et al.*, 1991, Uruguay	111/222, M, F	FFQ, interviewed		"Moderately elevated OR for infrequent consumers of green and yellow veg. and raw fruits"		Age, gender, residence, social class	Hospital-based
Balbi *et al.*, 2001, Uruguay	144/576 M, F	FFQ (64, 8 fruits, 11 veg.)	Highest vs lowest (3)	0.67 (0.41–1.09)	$p = 0.11$	Age, gender, urban/rural status, residence, education, BMI, smoking, energy, mate drinking	Hospital-based

*p for trend when applicable

Table 96. Cohort studies of total fruit consumption and risk of renal-cell cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Fraser *et al.*, 1990, USA	14/34 198, M, F 6 y	FFQ (51)	> 3 vs < 3/wk (2)	0.21 (0.05–1.45)	$p = 0.097$	Age, sex	Incidence Seventh-Day Adventists (58% lactoovo vegetarians), 3.7% current smokers
Prineas *et al.*, 1997, USA	62/35 192, F 8 y	FFQ (127)	> 15 vs < 9 servings/wk (3)	1.00 (0.55–1.80)		Age	Incidence Postmenopausal women

*p for trend when applicable

Table 97. Case–control studies of fruit consumption and risk of renal-cell cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Talamini *et al.*, 1990, Italy	240/665, M, F	FFQ (14), interviewed	≥ 14 servings/wk vs lowest (3)	0.92 (0.63–1.35)		Age, sex, education, area of residence, BMI	Hospital-based Response rate for cases 97%, for controls 96%
Negri *et al.*, 1991, Italy	147/6147, M, F	FFQ (24–37, depending on cancer site)	Highest vs lowest (3)	0.6 (0.4–1.0)	$p < 0.05$	Age, area of residence, education, smoking, veg. consumption	Hospital-based, data from a network of case–control studies Response rate 97%
McLaughlin *et al.*, 1992, China	154 (90 M, 64 F)/157	Structured questionnaire, interviewed	Highest vs lowest (4)	M: 0.2 (0.0–0.5) F: 0.7 (0.2–2.0)	$p < 0.001$ $p = 0.07$	Age, education, smoking, BMI	Population-based Response rate for cases 87%, for controls 100%
Chow *et al.*, 1994, USA**	415/650, M, F	FFQ (65, 8 fruits), self-administered	Highest vs lowest (4)	1.2 (0.8–1.7)		Age, sex, smoking, BMI	Population-based Next-of-kin interviews for 117 cases Response rate 79%
Mellemgaard *et al.*, 1996, Denmark**	351 (216 M, 135 F)/340	FFQ (92), interviewed, validated	> 3 vs ≤ 1 times/wk (4)	M: 0.6 (0.3–1.4) F: 0.9 (0.4–2.3)	$p = 0.34$ $p = 0.73$	Age, smoking, BMI, socioeconomic status	Population-based Response rate for cases 73%, for controls 68%
Boeing *et al.*, 1997, Germany	155/212, M, F	FFQ (122), self-administered	Highest vs lowest (3)	0.40 (0.23–0.69)	$p = 0.001$	Age, sex, education, smoking, alcohol	Population-based Response rate for cases 47%, for controls 56%
Lindblad *et al.*, 1997, Sweden**	378/350, M, F	FFQ (63, 8 fruits), interviewed	≥ 1907 vs ≤ 576 g/wk (4)	0.65 (0.42–1.02) Non-smokers: 0.37 (0.19–0.72) Smokers: 1.08 (0.58–2.02)	$p = 0.05$ $p = 0.003$ $p = 0.94$	Age, sex, BMI, smoking, education	Population-based Response rate for cases 70%, for controls 72%
Wolk *et al.*, 1996, Australia, Denmark, USA, Sweden	1185/1526, M, F	FFQ (63–205, depending on study centre), interviewed or self-administered	Highest vs lowest (4)	0.85 (0.66–1.10) Non-smokers: 0.6 (0.4–0.9)		Age, sex, study centre, BMI, smoking, energy	Population-based. Multicentre analysis Response rate for cases 54–72%, for controls 53–78%

*p for trend when applicable
**Substudy in the multicentre analyses (Wolk *et al.*, 1996)

Table 98. Cohort study of vegetable consumption and risk of renal-cell cancer

Author, year, country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.	Adjustment for confounding	Comments
Prineas *et al.*, 1997, USA	62/35 192, F 8 y	FFQ (127)	> 27 vs < 17 servings/wk (3)	1.44 (0.80–2.59)		Age	Incidence Postmenopausal women

Table 99. Case–control studies of vegetable consumption and risk of renal-cell cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
McLaughlin *et al.*, 1992, China	154/157, M, F	Structured questionnaire, interviewed	Highest vs. lowest (4)	M 0.3 (0.1–0.7) F 1.6 (0.6–4.6)	$p = 0.01$ $p = 0.33$	Age, education, smoking, BMI	Population-based Response rate for cases 87%, for controls 100%
Chow *et al.*, 1994, USA**	415/650, M, F	FFQ (65, 9 veg.), self-administered	M: ≥ 12.4 vs ≤ 5.1 servings/wk (4) F: ≥ 14.1 vs. ≤7.3 servings/wk (4)	1.0 (0.7–1.5)		Age, sex, smoking, BMI	Population-based Response rate 79%
Boeing *et al.*, 1997, Germany	155/212	FFQ (122), self-administered	Highest vs. lowest (3)	0.75 (0.44–1.27)	$p = 0.285$	Age, sex, education, smoking, alcohol	Population-based Response rate for cases 47%, for controls 56%
Lindblad *et al.*,1997, Sweden**	378/350	FFQ (63, 13 veg.), interviewed	≥ 816 vs < 290 g/wk (4)	0.84 (0.53–1.31) Non-smokers: 0.60 (0.30–1.16) Smokers: 1.04 (0.56–1.94)	$p = 0.74$ $p = 0.35$ $p = 0.72$	Age, sex, BMI, smoking, education	Population-based Response rate for cases 70%, for controls 72%
Yuan *et al.*, 1998, USA	1204/1204 M, F	FFQ (40), interviewed	Dark-green veg.: ≥ 13.1 vs ≤ 2.0 times/mo (5) Yellow-orange veg.: ≥ 17.1 vs ≤ 4.3 times/mo (5)	0.51 (0.38–0.69) 0.64 (0.48–0.86)	$p < 0.001$ $p < 0.001$	Age, sex, education, BMI, hypertension, smoking, analgesics, amphetamines	Population-based, neighbourhood controls
Wolk *et al.*, 1996, Australia, Denmark, USA, Sweden	1185/1526, M, F	FFQ (63–205, depending on study centre), interviewed or self-administered	Highest vs lowest (4)	0.81 (0.61–1.08)		Age, sex, study centre, BMI, smoking, energy	Population-based Multicentre analysis Response rate for cases 54–72%, for controls 53–78%

* p for trend when applicable. **Substudy in the multicentre analyses (Wolk *et al.*, 1996)

Table 100. Cohort study of fruit and vegetable consumption and risk of renal-cell cancer

Author, year, country	Cases/ cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.	Adjustment for confounding	Comments
Prineas *et al.*, 1997, USA	62/35 102. F 8 y	FFQ (127)	> 42 vs < 28 servings/wk (3)	1.56 (0.83–2.92)		Age	Incidence Postmenopausal women

Table 101. Case-control studies of fruit and vegetable consumption and risk of renal cell cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
McLaughlin *et al.*, 1984, USA	M 313/428 F 182/269	FFQ (28), interviewed	Highest vs lowest (4)	M: 1.5 F: 0.7	NS NS	Age, cigarette smoking, relative weight	Population-based Response rate 98%
Yu *et al.*, 1986, USA	160/160 M, F	FFQ, interviewed		No difference in consumption of fresh fruit and veg. between cases and controls		Matched by age	Population-based, neighbourhood controls Response rate for cases 73%

* *p* for trend when applicable

Table 102. Case–control studies of fruit consumption and risk of adult brain cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hu *et al.*, 1998, China	218(glioma)/ 436, M, F	FFQ (15 fruit and veg.), interviewed	≥ 46 vs ≤ 19 kg/y (4)	0.28 (0.16–0.51)	$p = 0.0005$	Income, education, alcohol, selected occupational exposures, veg.	Hospital-based
Hu *et al.*, 1999, China	129 (73 glioma, 56 meningioma)/258, M, F	FFQ (57, 5 fruits), interviewed	Highest vs lowest (4)	0.15 (0.1–0.4)	$p < 0.01$	Income, education, cigarette smoking, alcohol, selected occupational exposures, energy	Hospital-based Continuation of study of Hu *et al.*, 1998 with more comprehensive questionnaire

* *p* for trend when applicable

Table 103. Case–control studies of vegetable consumption and risk of adult brain cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hu *et al.*, 1998, China	218 (glioma)/ 436, M, F	FFQ (15 fruit and veg.), interviewed	≥ 125 vs ≤ 84 kg/y (4)	0.51 (0.29–0.89)	$p = 0.009$	Income, education, alcohol, selected occupational exposures, fruit	Hospital-based
Hu *et al.*, 1999, China	129 (73 glioma, 56 meningioma)/ 258, M, F	FFQ (57, 17 veg.), interviewed	Fresh veg.: Highest vs lowest (4)	0.29 (0.1–0.7)	$p < 0.01$	Income, education, cigarette smoking, alcohol, selected occupational exposures, energy	Hospital-based Continuation of study of Hu *et al.* (1998) with more comprehensive questionnaire
Chen *et al.*, 2002b, USA	236 (glioma)/ 449, M, F	FFQ (48), interviewed by telephone	Highest vs lowest (4)	0.5 (0.3–1.0)	$p = 0.06$	Age, gender, energy, respondent type, education level, family history, farming experience	Population-based Response rate for cases 90%, for controls 71%, reinterviewed following a previous study

* *p* for trend when applicable

Table 104. Case–control studies of fruit consumption and risk of childhood brain cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Bunin *et al.*, 1993, USA	166/166	FFQ, interviews of mothers regarding their diet during pregnancy	Fruit and fruit juices: Highest vs lowest (4)	0.28 (0.14–0.59)	$p = 0.003$	Sex, birth order, birth weight, duration of breast feeding for child, age, history of miscarriage, month of first prenatal visit, educational level, income level for mother, use during pregnancy of cigarettes, bottled water, electric blanket, duration of nausea, child's diet in first year of life	Population-based Study of primitive neuroectodermal tumours (mostly medulloblastomas) 74% first eligible control contacted
Cordier *et al.*, 1994, France	75/113, M, F	Interview on maternal diet during pregnancy	Fresh fruit: Highest vs lowest (4)	0.6 (0.1–3.0)		Child's age and sex, maternal age, number of years of schooling of the mother	Population-based Response rate for identified cases 69%, for eligible controls contacted 71.5%
McCredie *et al.*, 1994a, Australia	82/164, M, F	FFQ based on maternal diet during pregnancy, interviewed	> 952.3 vs < 299.7 items/y (4)	1.5 (0.6–3.7)	$p = 0.39$	Age, sex, mother's education, mother's BMI before pregnancy, vegetables, cured meats	Population-based Response rate for eligible cases 85%, for controls 60%
McCredie *et al.*, 1994b, Australia	82/164, M, F	FFQ based on child's diet in the perinatal and early postnatal period, interviewed	Blended or solid fruit: > 240 vs < 154.8 times/first year (4)	0.4 (0.1–1.1)		Age, sex, mother's education, ever/never use of a dummy, other food groups	Population-based Response rate for eligible cases 85%, for controls 60%
Lubin *et al.*, 2000, Israel	300/574, under age 10 y, M, F	FFQ (100), interviewed	Highest vs lowest (3)	During gestation: 1.24 (0.7–1.8) As a child: 1.24 (0.8–2.1)	$p = 0.50$ $p = 0.39$	Energy	Population-based

*p for trend when applicable

Table 105. Case–control studies of vegetable consumption and risk of childhood brain cancer

Author, year, country	Cases/ controls gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Bunin *et al.*, 1993, USA	166/166	FFQ, interviews of mothers regarding their diet during pregnancy	Highest vs lowest (4)	0.37 (0.19–0.72)	$p = 0.005$	Sex, birth order, birth weight, duration of breast feeding for child, age, history of miscarriage, month of first prenatal visit, educational level, income level for mother, use during pregnancy of cigarettes, bottled water, electric blanket, duration of nausea, child's diet in first year of life	Population-based Study of primitive neuroectodermal tumours (mostly medulloblastomas) 74% first eligible control contacted
McCredie *et al.*, 1994a, Australia	82/164, M, F	FFQ based on maternal diet during pregnancy, interviewed	> 1109.9 vs < 597.6 items/y (4)	0.4 (0.1–1.0)	$p = 0.06$	Age, sex, mother's education, mother's BMI before pregnancy, fruit, cured meats	Population-based Response rate for eligible cases 85%, for controls 60%
Lubin *et al.*, 2000, Israel	300/574, under age 10, M, F	FFQ (100), interviewed	Highest vs lowest (3)	During gestation: 1.25 (0.8–1.9) As a child: 1.30 (0.8–2.3)	$p = 0.35$ $p = 0.24$	Energy	Population-based

* p for trend when applicable

Table 106. Case–control studies of fruit consumption and risk of thyroid cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Franceschi *et al.*, 1991b, Italy and Switzerland	385/798, M, F	FFQ (30–38)	Fresh fruit: Highest vs lowest (3)	0.9	NS	Centre, age, sex, education	Hospital-based Pool of three studies from northern Italy, and one from Swiss Canton Vaud Response rates in cases and controls > 95%
Galanti *et al.*, 1997, Sweden and Norway	246/440, M, F	FFQ (56), self-administered	> 42 vs < 19 pieces/mo (3)	1.0 (0.6–1.5)	NS	Univariate analysis	Population-based Response rates for cases/controls: Norway, 75%/56%; Sweden, 86%/69%

**p* for trend when applicable

Table 107. Case–control studies of vegetable consumption and risk of thyroid cancer

Author, year, country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Franceschi *et al.*, 1991b, Italy and Switzerland	385/798, M, F	FFQ (30–38)	Green veg.: Highest vs lowest (3)	0.9	NS	Centre, age, sex, education	Hospital-based Pool of three studies from northern Italy and one from Swiss Canton Vaud Response rates in cases and controls > 95%
Hallquist *et al.*, 1994, Sweden	171/325, M, F	FFQ, self-administered	Green veg.: Several vs some times/ week (3)	Age ≤ 20 y: 0.8 (0.5–1.4) Age > 20 y: 0.7 (0.3–1.6)		Age, gender	Population-based Response for cases 95%, for controls 90%
Galanti *et al.*, 1997, Norway and Sweden	246/440, M, F	FFQ (56), self-administered	> 60 vs ≤ 40 portions/mo (3)	0.9 (0.6–1.4)	NS	Univariate analysis	Population-based Response rates in cases/controls: Norway, 75%/56%; Sweden, 86%/69%
Bosetti *et al.*, 2002b	2241/3716, M, F	Different information in each study	Other than cruciferous veg.: Highest vs lowest (3)	0.82 (0.69–0.98)		Age, sex, prior radiotherapy, thyroid nodules, goitre	Collaborative re-analysis of 11 case–control studies from USA (3), Asia (1), and Europe (7) Weighted mean of OR from each study Test for heterogeneity between studies: $p < 0.02$ for both

* p for trend when applicable

Table 108. Cohort studies of fruit consumption and risk of non-Hodgkin lymphoma

Author, year, country	Cases/ cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Chiu *et al.*, 1996, USA	104/35 156, F 7 y	Semi-quantitative FFQ (126)	> 84 vs < 54 servings/mo (3)	0.67 (0.41–1.08)	$p = 0.09$	Age, energy	Incidence Iowa Women's Health Study
Zhang *et al.*, 2000, USA	199/88 410, F 14 y	Semi-quantitative FFQ (61)	≥ 3 vs < 1 servings/d (4)	0.79 (0.49–1.27)	$p = 0.39$	Age, energy, length of follow-up, geographical region, cigarette smoking, height, beef, pork or lamb as a main dish	Incidence Nurses' Health Study

* p for trend when applicable

Table 109. Case–control studies of fruit consumption and risk of non-Hodgkin lymphoma

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.	Adjustment for confounding	Comments
Tavani *et al.*, 1997, Italy	429/1157 M, F	FFQ (14)	Highest vs lowest (3)	0.9	NS	Centre, age, sex	Hospital-based Response rates ~97%

Table 110. Cohort studies of vegetable consumption and risk of non-Hodgkin lymphoma

Author, year, country	Cases/ cohort size, gender (years (follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hirayama, 1990, Japan	219 lympho-sarcoma, 29 other lympho-ma/265 118, M, F 17 y	FFQ (7)	Green-yellow veg.: Daily vs non-daily (2)	1.15 (90% CI, 0.95–1.40)		Not reported	Mortality Census-based cohort in seven prefectures
Chiu *et al.*, 1996, USA	104/35 156, F 7 y	Semi-quantitative FFQ (126)	> 98 vs < 62 servings/mo (3)	0.96 (0.58–1.60)	$p = 0.88$	Age, energy	Incidence Iowa Women's Health Study
Zhang *et al.*, 2000, USA	199/88 410, F 14 y	Semi-quantitative FFQ (61)	≥ 3 vs < 1 servings/d (4)	0.65 (0.37–1.13)	$p = 0.04$	Age, energy, length of follow-up, geographical region, cigarette smoking, height, beef, pork or lamb as a main dish	Incidence Nurses' Health Study

* *p* for trend when applicable

Table 111. Case–control study of vegetable consumption and risk of non-Hodgkin lymphoma

Author, year, country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Ward *et al.*, 1994, USA	315 (171 M, 144 F)/1075	FFQ (30), interviewed by telephone	> 27 vs < 16 times/wk (4)	M: 1.0 (0.6–1.6) F: 0.9 (0.5–1.7)	NS NS	Age	Population-based Response rate for cases 90%, for controls 84%

* *p* for trend when applicable

Table 112. Cohort study of vegetable consumption and risk of leukaemia

Author, year, country	Cases/ cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrasts (no. of categories)	Relative risk (95% CI)	Stat. sign.	Adjustment for confounding	Comments
Hirayama, 1990, Japan	206/265 118, M, F 17 y	FFQ (7)	Green-yellow veg.: Daily vs non-daily (2)	0.92 (90% CI, 0.71–1.18)		Not reported	Mortality Census-based cohort in seven prefectures

Preventable fraction

The proportion of any disease potentially preventable by modification of a risk factor in a population is determined by both the strength of the risk factor, as represented by the relative risk, and the prevalence of the risk factor. This proportion is commonly known as the "preventable fraction" (also sometimes called the "population attributable risk") (WHO, 2002). The certainty in any estimate of preventable fraction, including that for the fraction of cancers that is due to low intake of fruit and vegetables, is dependent on the precision of both the relative risk associated with low intake and the proportion of the population consuming low levels. The review presented earlier in this chapter makes it clear that many of the relative risk estimates are uncertain and that the prevalence of exposure to low intake varies widely across studies and cancer sites. Therefore, confidence in an estimate of any particular cancer's preventable fraction for low fruit and vegetable intake must be low.

Nevertheless, the Working Group calculated the preventable fractions for cancer sites for which it judged there was at least limited support for a causal association, in order to estimate the approximate extent of the potential prevention that could be linked to increasing fruit and vegetable intake. Although the relative risks and prevalences of low intake vary widely between studies, in many of the studies reviewed, the levels of fruit and vegetable intake being compared were the highest versus lowest quartiles or tertiles (i.e., range of prevalence of low intake 25% to 33%), and the relative risk estimates were generally in the range of 20% to 30% lower risk for subjects in the highest category of intake. Applying this range of risk difference to the range of prevalence of low intake, the preventable fraction for low fruit and vegetable intake would fall into the range of 5–12%. It is important to recognize that this is only a crude range of estimates and that the proportion of cancers that might be preventable by increasing fruit and vegetable intake may vary beyond this range for specific cancer sites and across different regions of the world.

There have been many estimates of the fraction of cancer preventable by increasing fruit and vegetable intake based on individual case–control studies, but only two based on meta-analyses. Van't Veer *et al.* (2000) reviewed published studies and estimated the population attributable risks for all cancer sites due to consumption of 250 grams of fruit and vegetables per day as compared to the recommended 400 grams per day. They made three estimates based on different assumptions of the size of the relative risks: a "best guess" estimate (19%), an "optimistic" estimate (28%), and a "conservative" estimate (6%). Norat and Riboli (2002) estimated the preventable fractions for oesophageal, stomach and colorectal cancers in various populations around the world using relative risks derived from a meta-analysis of published studies (largely from developed countries), coupled with regional prevalence estimates derived from sources including FAO data. This approach led to estimates of the proportion of cancers preventable by increasing fruit and vegetable intake from current levels to 350 grams per day in the range of 8–16% for colorectal cancer and 20–30% for oesophageal and gastric cancers; these estimates varied substantially in different regions of the world.

The preventable fraction estimates of 5–12% for the groups of cancers evaluated here as having limited evidence for an inverse association with fruit and vegetable consumption are similar to the estimates for all cancer sites made by van't Veer *et al.*, and to the estimates for colorectal cancer by Norat and Riboli, but they are lower than the Norat and Riboli estimates for oesophageal and stomach cancers. The range of estimates of the fraction of selected cancers preventable by increasing intake of fruit and vegetables is only an approximation. The true relative risk for low intake is quite uncertain given limitations in dietary assessment and in study designs. In addition, the mix of various cancers as well as the prevalence of low intake can vary substantially across different populations.

The present estimates for the fraction of selected cancers preventable by increasing fruit and vegetable intake could be either high or low. They would be too high if the relative risk estimates on which the measure is based are inflated by biases in study design and/or uncontrolled confounding by other factors. On the other hand, they would be too low if the relative risks were underestimated because of misclassification arising from random errors in estimating dietary intake. In addition, benefits of increasing fruit and vegetable intake may well extend beyond those at the lowest levels of intake. Shifting the diets of entire populations over long periods to lower levels of risk can have a greater impact on population health than reducing risk only for a subgroup at highest risk (Rose, 1985). Increasing fruit and vegetable intake in populations is likely also to be accompanied by other beneficial changes in diet composition and in other chronic diseases.

Ecological studies

Ecological studies are analyses of associations between characteristics of populations and disease rates in populations. The essential feature of an ecological study is that *populations,* rather than *individuals,* are the unit of analysis. Populations compared with

the ecological design can be populations in different countries, populations in different regions within a single country, or the same population across different times. Ecological studies can also compare populations defined by characteristics such as religion, racial/ethnic characteristics or special historical circumstances, such as the experience of famine. Thus, ecological studies, also referred to sometimes as *correlational* studies, can be cross-sectional or longitudinal.

The study of changing disease risk among people who migrate from one country to another combines the elements of geography and time in ecological analysis. Migrant studies build on geographical studies, as they are uncontrolled experiments in which presumed changes in lifestyle related to migration (notably diet) can be assessed as affecting cancer risk. The appeal of migrant studies is the internal control for the many characteristics of people that are unchanged after migration, notably the inherited genotype of individuals. Changes in cancer risk with migration have therefore been critical observations for estimating the proportion of differences in cancer risk between countries that may be due to genetic rather than non-genetic etiology (Doll & Peto, 1981).

The main weakness of ecological studies is suggested by their inherent design – that the characteristics being examined are population-level characteristics and cannot be directly linked to individual disease risk. Confounding at the population level between a suspected risk factor and disease cannot be accounted for properly in ecological studies (Morgenstern, 1995; Greenland, 2001). Thus, ecological studies may result in biased estimates of the true individual-level relationship between exposure and disease risk – a problem that is known as the "ecological fallacy" – and group-level associations may be reflective only of the spurious association between the factor of interest and other truly causal factors.

Ecological studies of differences diet and disease between regions within a single country and ecological studies comparing changes in diet with changes in disease across time within a single population are somewhat less susceptible to the ecological fallacy than are international ecological studies. This is because cultural differences apart from diet may be fewer across regions within a single country or across time in a single population. However, the very presence of variation between regions or over time in diet and disease suggests that there may also be other differences that could confound the association. Because of this important limitation, ecological studies have usually been regarded solely as hypothesis-generating.

Despite these weaknesses, ecological studies do offer substantial strengths for elucidating relationships between diet and cancer. If factors in the diet affect cancer risk only over long periods of time, perhaps even across generations, it becomes very difficult or impossible to estimate the relevant exposures to diet at the individual level. The ecological study design, in which long-term diet differences between populations can be examined, may offer a better means to observe hypothesized associations between long-term dietary exposures and cancer risk. When a hypothesized dietary exposure is very specific and discrete (e.g., soy), ecological studies can be more useful. When the exposure is less specific, such as total fruit and vegetable intake, ecological studies are less useful. The presence of a biologically plausible link between aspects of diet and particular cancers can help to strengthen the internal consistency of ecological studies. With fruit and vegetables and cancer, however, there is little specificity for cancer types that can be useful in this regard.

Ecological studies can be refined by correlating disease rates and dietary exposures within specific subgroups of the population for which both disease rates and diet can be stratified, such as age and gender. This type of detail is usually available for disease rates, but is often lacking in the dietary data used in ecological analyses. If ecological associations are to be interpreted as causal, the argument for the proper temporality of the relationship between diet and disease can be strengthened by lagging the analysis so that the dietary measures precede the disease rates. Information on diet lagged by 10 years or more may be more relevant than contemporaneous information to cancer rates in a population. This type of lagging of analyses is often not possible, however, due to insufficient historical information.

Cancer rates used in ecological analyses can be either mortality rates or incidence rates. In either case, attention to the quality of the cancer data is important, especially for comparisons between countries or across long time periods. Equally important is attention to the quality of the dietary data. Indicators as crude as the population-level estimates of food intake derived from crude agricultural data sources, or as refined as population-representative diet surveys, have been used. Even with the best possible measures of cancer risk and food intake, however, the fundamental problem of the ecological fallacy will render any association observed in an ecological study no more than suggestive of a causal relationship.

Table 113 summarizes findings from two types of study – cross-sectional ecological studies comparing countries and those comparing regions within countries. Table 114 summarizes studies that analysed the rela-

tionship between fruit and vegetable intake and changes in cancer risk within single populations over time.

Cross-sectional studies between countries

International cross-sectional studies look for relationships between levels of fruit and vegetable intake and cancer rates among populations defined by national boundaries. In such studies, the cancer rates are either mortality or incidence rates as collected by each country, and the dietary data are typically crude food disappearance estimates from agricultural sources such as the food balance sheets, which are country-level estimates of food consumption at the population level as estimated by the Food and Agricultural Organization (FAO) (see Chapter 3).

A classic analysis of the association between food consumption patterns and cancer rates between countries (Armstrong & Doll, 1975) showed rather strong associations of several factors, such as fat, in the diet with several common cancers. Associations with fruit and/or vegetable intake were reported for cancers of the liver, breast, ovary and kidney. Positive associations were seen between fruit intake and cancers of the breast and ovary, while inverse associations were seen between fruit intake and liver cancer, and between vegetable intake and kidney cancer. In a similar analysis by Rose *et al.* (1986), inverse associations were observed between fruit intake and ovarian cancer, and between vegetable intake and cancers of the colon (for women only), breast, ovary and prostate. Thouez *et al.* (1990) reported an inverse association between energy intake from vegetables and oesophageal and pancreatic cancer across 29 countries, and a study by Hebert *et al.* (1993) including 59 countries showed inverse associations of both fruit and vegetables with oesophageal and oral cancers. A positive association between calorie intake from vegetables and cancer of the stomach was reported by Thouez *et al.* (1990), but that association was diminished after adjustment for age differences between countries. The rates of lung cancer across 10 nations in the South Pacific were found to be inversely associated with the intake of yellow-orange vegetables in models that adjusted for demographic differences as well as tobacco use and other dietary factors (Le Marchand *et al.*, 1995). Hebert and collaborators reported little relationship between fruit and vegetable intake and cancer of the bladder across 50 countries (Hebert & Miller, 1994) and little relationship between breast cancer and fruit intake across 66 countries (Hebert & Rosen, 1996), but there was a modest inverse association between cabbage intake and breast cancer (Hebert & Rosen, 1996). Another ecological study across 28 countries showed an inverse association between tomato consumption and prostate cancer risk (Grant, 1999), though this was found only with multivariate models also containing non-fat milk intake (data not shown). This analysis was inspired by observations from case–control and cohort studies of a protective association between tomato intake and prostate cancer risk, and provides a good example of the use of ecological studies to support or refute hypotheses emerging from studies with other designs.

In sum, the international studies tend to report more inverse associations than positive associations between cancer rates and intake of fruit and vegetables. These associations are generally stronger for vegetables than for fruit. There are many reported associations that are null, however, and the various reports cannot be easily compared due to different methods of analysis, different time periods of collection of cancer and diet data, the high likelihood of selective reporting of findings by cancer site, by food type, and according to the strength and statistical significance of the observations. It is quite possible, therefore, that the number of null associations is greater than the selective literature suggests.

Cross-sectional studies between regions within countries

Regional cross-sectional studies look for relationships between levels of fruit and vegetable intake and cancer rates across populations defined by regional boundaries within countries. In such studies, the cancer mortality or incidence data are usually collected in a uniform way across regions, and the dietary data are usually much more detailed and reliable than the FAO data, often being derived from national surveys of food intake as reported by individuals.

Bingham *et al.* (1979) reported strong inverse associations between intake of vegetables (other than potatoes) and colon cancer, using data from diet surveys in nine different regions of the United Kingdom. Shimada (1986) used similar methods to show an inverse association between vegetable intake and stomach cancer in five regions of Japan. The most extensive within-country ecological study ever conducted is the analysis of cancer rates in relation to diet across 65 counties in China (Zhuo & Watanabe, 1999). In this ambitious project, two communes in each of 65 Chinese counties were selected for dietary assessments, which included not only dietary measurements from households but also collection of samples from individuals for nutritional biomarker measurements. The study was substantially weakened by the use of cancer rates for a time period preceding the dietary assessments. Modest correlations, either positive or inverse, with fruit and

Table 113. Cross-sectional ecological studies of fruit and vegetables as related to cancer risk both between several countries and within single countries

Cancer site	Reference	Populations compared	Findings: correlation coeffecient		Comments
			Fruit	Vegetables	
Oesophagus	Thouez *et al.*, 1990	29 countries		Energy from veg.: –0.21 (men) –0.46 (women)	Mortality Adjusted for age
	Hebert *et al.*, 1993	59 countries	–0.34 (men) –0.27 (women)	–0.33 (men) –0.09 (women)	Mortality
	Zhuo & Watanabe, 1999	65 counties in China	–0.13	0.04	Mortality
Stomach	Shimada, 1986	5 areas in Japan		Inversely associated with risk	Mortality
	Chen *et al.*, 1990	65 counties in China	0.17	Green veg.: 0.05	Mortality
	Thouez *et al.*, 1990	29 countries		Energy from veg.: 0.34 (men) 0.42 (women)	Mortality Adjusted for age
	Corella *et al.*, 1996	50 provinces in Spain	–0.57 (men) –0.58 (women)	–0.61 (men) –0.67 (women)	Mortality Analysis lagged 20 years
	Sichieri *et al.*, 1996	10 state capitals of Brazil	–0.62	–0.28	Mortality Adjusted for sex and tobacco
	Tsubono *et al.*, 1997	5 areas in Japan	0.35	Green veg.: –0.88 Yellow veg.: –0.57	Mortality Adjusted for sex and tobacco
	Azevedo *et al.*, 1999	18 districts in Portugal	–0.69 (men) –0.65 (women)	–0.81 –0.74	Mortality Intake of 100 g veg./person/day predicted 10 fewer deaths per 100 000 persons/year among men (95% CI 6–14) and 5 fewer death among women (95% CI 3–7)
	Takezaki *et al.*, 1999	China (low vs high risk area)	Consumption higher in lower-risk area	Consumption higher in lower-risk area	
	Zhuo & Watanabe, 1999	65 counties in China	0.18	–0.11	Mortality

Table 113 (contd)

Cancer site	Reference	Populations compared	Findings: correlation coeffecient		Comments
			Fruit	Vegetables	
Colon	Bingham *et al.*, 1979	9 regions in Great Britain		–0.94	Mortality
	Rose *et al.*, 1986	30 countries	0.03 (men) –0.03 (women)	0.06 (men) –0.17 (women)	Mortality Adjusted for age
	Chen *et al.*, 1990	65 counties in China	–0.08	Green veg.: –0.03	Mortality
	Sichieri *et al.*, 1996	10 state capitals of Brazil	–0.05	0.09	Mortality Adjusted for sex and tobacco
	Zhuo & Watanabe, 1999	65 counties in China	–0.08	–0.13	Mortality
Liver	Armstrong & Doll, 1975	23 countries	–0.38 (men) –0.46 (women)		Incidence
	Chen *et al.*, 1990	65 counties in China	–0.06	Green veg.: 0.11	Mortality
Pancreas	Thouez *et al.*, 1990	29 countries		Calories from veg.: –0.58 (men) –0.56 (women)	Adjusted for age
	Vioque *et al.*, 1990	Regions of Spain	Fruits, other than citrus: –2.01 (men)		
Lung	Le Marchand *et al.*, 1995	10 island nations of the South Pacific		Yellow-orange veg.: associated with decreased risk (p=0.06)	Incidence Multivariate models adjusting for age, sex, tobacco, and selected other dietary factors
	Chen *et al.*, 1990	65 counties in China	–0.22 (men) –0.20 (women)	Green veg.: 0.15 (men) 0.22 (women)	Mortality
Breast	Armstrong & Doll, 1975	32 countries	0.44		Mortality
	Rose *et al.*, 1986	30 countries	0.09	–0.11	Mortality Adjusted for age
	Chen *et al.*, 1990	65 counties in China	–0.09	Green veg.: –0.16–0.02	Mortality

Table 113 (contd)

Cancer site	Reference	Populations compared	Findings: correlation coeffecient		Comments
			Fruits	Vegetables	
Breast (contd)	Ishimoto *et al.*, 1994	12 districts in Japan	0.62	Green-yellow veg.: –0.02	Mortality Adjusted for age
	Hebert & Rosen, 1996	66 countries	–0.05	–0.23 (cabbage)	Mortality
Ovary	Armstrong & Doll, 1975	21 countries	0.31		Mortality
	Rose *et al.*, 1986	26 countries	–0.26	–0.54	Mortality Adjusted for age
Prostate	Rose *et al.*, 1986	29 countries	–0.09	–0.38	Mortality Adjusted for age
Bladder	Hebert & Miller, 1994	50 countries	–0.09 (men) –0.05 (women)	0.20 (men) –0.04 (women)	Mortality
Kidney	Armstrong & Doll, 1975	21 countries		–0.43 (men) –0.51 (women)	Mortality
All sites	Farchi *et al.*, 1996	Regions of Italy		1 g increase veg. proteins associated with reduction of 2.5 cases per 100	Mortality

vegetable intake were found for several cancer sites. Fruit intake was inversely associated with risk of stomach cancer across 50 provinces in Spain (Corella *et al.*, 1996), 10 states in Brazil (Sichieri *et al.*, 1996) and 18 districts in Portugal (Azevedo *et al.*, 1999), and between high- versus low-risk areas in China (Takezaki *et al.*, 1999); but the corresponding association was positive with stomach cancer across the 65 counties in China (Chen *et al.*, 1990) and across five areas in Japan (Tsubono *et al.*, 1997). Vegetable intake has been consistently observed to be inversely associated with risk for stomach and colon cancers in many countries (Bingham *et al.*, 1979; Shimada, 1986; Corella *et al.*, 1996; Sichieri *et al.*, 1996; Tsubono *et al.*, 1997; Azevedo *et al.*, 1999; Zhuo & Watanabe, 1999).

In sum, studies of correlations between cancer rates and diet within countries also tend to show inverse associations between fruit and vegetable intake and many cancers, especially cancers of the stomach and colon.

Time trend studies

Analyses of time trends are ecological studies correlating fruit and vegetable intake with cancer rates over time either within a single population or across several populations. These studies suffer from the same ecological fallacy as the cross-sectional studies among and within countries, but they have the advantage of following the same population over time. Since many characteristics of the population do not change over time, the number of potential confounding factors is reduced. Table 114 summarizes findings from the few such studies that have examined fruit and vegetables specifically. The analyses of temporal relationships between fruit and vegetables and cancer have had a variety of methods and mixed findings. The most consistently reported inverse associations have been for stomach cancer (Jedrychowski & Popiela, 1986; Swistak *et al.*, 1996; Tominaga & Kuroishi, 1997). The interpretation of these observations is particularly difficult, however, due to potential confounding by improving socioeconomic conditions that have led to both a more varied diet and a lower risk of infection with *Helicobacter pylori*.

Migrant studies

Migrant studies are ecological studies examining cancer rates in relation to migration of people from countries of differing cancer rates. Studies of migrants from Asia to America (Ubukata *et al.*, 1986; Story & Harris, 1989) showed that migrants themselves tended to retain Asian dietary patterns, whereas their children acquired the food preferences of America. Such changes, either within the generation of migrants or in subsequent generations of their offspring, feature increased intake of meats and fats and decreased intake of vegetables (Lee *et al.*, 1999). This shift to a more "western" diet is associated with substantial increases in the risk of cancers of the breast (Wu & Bernstein, 1998) and colon (Bernstein & Wu, 1998). Ziegler *et al.* (1993) conducted a large, population-based case–control study that in many ways serves as an example of how migration can be better studied. They assessed migration effects on breast cancer for childhood, adolescent and adult exposures among Asian-American women in California by interviewing both study participants and their mothers. They found a gradient in breast cancer risk related to migration history that was quite comparable with the international differences in breast cancer incidence rates.

Summary

Ecological analyses have been generally consistent with the hypothesis that increased fruit and vegetable intake is associated with lower risk of cancer at many sites. International correlational studies, studies across regions in single countries and studies of time trends and migrating populations are all congruent in this conclusion.

Ecological studies offer both limitations and advantages for assessing the relationship between fruit and vegetable intake and cancer risk. The large contrasts between countries in diet that reflect long-term dietary differences over decades or entire lifetimes are difficult to measure in studies based on assessments of dietary exposures in individuals. The strength of ecological studies is their ability to examine such long-term differences. Their weakness is that there are many confounding factors that limit the ability to conclude causality attributable to any particular dietary factor. As fruit and vegetable intake varies substantially along with many other factors, including both dietary and non-dietary factors, any association between fruit and vegetable intake and cancer risk emerging from ecological analyses cannot be interpreted as causal. Another limitation is the apparently selective reporting of findings by cancer site, food type, or non-null results.

Intermediate markers of cancer

Experimental dietary studies in humans serve as an important link between the nutritional epidemiological studies and experiments conducted in animal models. They rely on intermediate end-points related to disease risk, using biological markers that may also provide insight into the modes of action of fruit and vegetable constituents in humans. At the same time, they are limited by the sensitivity

Table 114. Studies of trends in fruit and vegetable consumption as related to cancer trends

Cancer site	Reference	Country or areas studied	Years of trend	Findings: correlation coeffecient		Comments
				Fruit	Vegetables	
Stomach	Jedrychowski & Popiela, 1986	Poland	1951–83	Fruit increased 87%, while mortality decreased about 50%	Veg. increased 14%, while mortality decreased about 50%	
	Swistak *et al.*, 1996	4 European countries	1970–92	Mortality decreased as fruit increased	Mortality decreased as veg. increased	
	Tominaga & Kuroishi, 1997	Japan	1955–93	–0.83 (men) –0.82 (women)	Green yellow veg.: –0.38 (men) –0.40 (women) Other veg.: –0.61 (men) –0.62 (women)	10-year time lag between diet and cancer Adjusted for age
Colon/rectum	McMichael *et al.*, 1979	4 countries	1921–74	Fruit tended to be relatively stable, while mortality varied depending on country, age, sex	Veg. tended to be relatively stable, while mortality varied depending on country, age, sex	
	Holmqvist, 1997	15 European countries	1961–90	No consistent pattern of association	No consistent pattern of association	
	Tominaga & Kuroishi, 1997	Japan	1955–93	0.81 (men) 0.83 (women)	Green-yellow veg.: 0.44 (men) 0.40 (women) Other veg.: 0.59 (men) 0.62 (women)	10-year time lag between diet and cancer Adjusted for age
Breast	Prieto-Ramos *et al.*, 1996	50 provinces in Spain	30 years	Correlation between breast cancer mortality rates in 1981–85 and fruit intake in 1964–65 Citrus fruit: –0.10 Other fresh fruit: –0.16	Provinces with highest increase in veg. consumption from 1964 to 1981 had lowest breast cancer mortality level in 1981–85	

and specificity of the biological markers, access to relevant biological specimens and the logistics of conducting experimental studies in humans. Most of the markers reflect very early processes in the pathways of carcinogenesis (e.g., carcinogen metabolism, adduct formation), since downstream signal-transduction markers relevant to cancer progression are lacking. These early markers may not associate directly with cancer risk.

Dietary intervention studies in humans using disease end-points would provide the strongest evidence for an effect of fruit and vegetables on disease risk. However, such dietary intervention studies need to have thousands of participants in order to have sufficient statistical power and are very expensive. Issues such as timing and dose of the intervention, choice of study populations and compliance also influence interpretation of the results. As a result, no fruit and vegetable interventions have yet been conducted with cancer as the outcome.

Intervention studies

This section reviews the human experimental studies that have examined the capacity of fruit and vegetables to modulate biological processes relevant to cancer (Table 115–119). Several of these studies were designed to test the effect of fruit and vegetables on biomarkers of cardiovascular or other diseases. Results of these studies are applicable to cancer in so far as the markers are shared. The interventions differ greatly in duration, sample size and study design. Study duration ranges from single doses to months or years of intervention and is typically determined by the biology of the marker and its responsiveness to change. Ideally, sample size is dictated by the variance associated with the biomarker and the statistical power needed to detect an effect of intervention, but in practice, logistic and cost considerations often limit the sample size, so that the studies may be statistically underpowered to test effectively the fruit and vegetable treatments. The majority of intervention studies in humans have been of short duration and sample sizes have been small. No long-term, randomized clinical trials have tested solely the effects of increasing fruit and vegetable intake on intermediate cancer markers. Those that have included other diet alterations as part of the treatment, e.g., reduced energy intake from fat and/or increased whole grain intake (Schatzkin *et al.,* 2000), have limited capacity to examine the effects of fruits and vegetables alone.

A variety of study designs have been used. Study designs described in the table as "crossover" or "x-arm trial" refer to randomized intervention studies in which participants are recruited, screened for eligibility and interest in participating, randomly assigned to one or more interventions and/or control groups and followed over time until the end of the study. Crossover studies may or may not include washout periods between different treatments. Crossover designs lacking washout periods of sufficient duration are prone to carryover effects that can jeopardize interpretation of the results. Numerous studies examining effects of fruit and vegetables have employed less stringent designs that do not use randomization or a control group. These designs include taking measurements before and after the intervention (e.g., "pre–post") or the sequential addition of treatments (tx) after an initial, dietary-restricted control period (e.g., "control–tx1–tx2"). Interventions such as these have the potential to produce biased results.

The degree of dietary control also varies. In the following tables, "controlled intervention" refers to a study in which the diet is provided to study participants. In this type of study, volunteers may be free-living, eating the food at a feeding centre or taking it home, or they may be housed in a metabolic ward. There are also different degrees of control within these types of study; the loosening of control (e.g., including free days on which participants can deviate from the study diet, drink alcohol, etc.) is more characteristic of studies of longer duration, where long-term participant retention is often most challenging. The term "supplementation of habitual diet" refers to addition of fruit or vegetables to a participant's usual diet. This common approach allows participants more control over their diets and minimizes metabolic effects of drastic changes in diet that are a potential problem with controlled interventions. In some cases, habitual diets may be modified to restrict particular foods (e.g., certain fruits and vegetables) that may influence the outcome of the study.

The following review is limited to plant foods, excluding grains, nuts, seeds, dried legumes, starchy tubers, spices and products used for infusions (e.g., teas).

Antioxidant effects (Table 115)

Oxidative damage, resulting from an imbalance between free-radical generation and antioxidant defence, has been hypothesized to play a role in cancer (Rock *et al.*, 1996). The antioxidant defence system has both enzymatic and non-enzymatic components that prevent radical formation and remove radicals before damage can occur.

Antioxidant enzymes

Several studies have reported altered activities of antioxidant enzymes in red blood cells (RBC) after fruit and vegetable interventions; however, the responses have varied widely according to the type and dose of fruit or vegetable and only a few very different

foods have been tested. In three studies, RBC glutathione reductase activities increased with spinach, parsley and grape-skin extract supplementation (Castenmiller *et al.*, 1999; Nielsen *et al.*, 1999; Young *et al.*, 2000). RBC glutathione peroxidase activity increased in interventions using grape-skin extract (Young *et al.*, 2000) and blackcurrant and apple juice (Young *et al.*, 1999) and was unchanged with onion and parsley (Lean *et al.*, 1999; Nielsen *et al.*, 1999). RBC superoxide dismutase activity increased with parsley (Nielsen *et al.*, 1999) and was unchanged with onion (Lean *et al.*, 1999) and with blackcurrant and apple juice (Young *et al.*, 1999). Catalase activity decreased with spinach (Castenmiller *et al.*, 1999) and was unchanged with parsley (Nielsen *et al.*, 1999), blackcurrant and apple juice (Young *et al.*, 1999) and grape-skin extract (Young *et al.*, 2000).

Total antioxidant capacity

The antioxidant capacity of fruits and vegetables has been measured in human intervention studies. Most interventions relied on effects detectable in blood samples. Several assays measure serum total antioxidant capacity *ex vivo*. These include oxygen radical absorbance capacity (ORAC), ferric-reducing ability (FRAP) and Trolox equivalent antioxidant capacity (TEAC). Typically, these markers are indicative of recent exposure to antioxidants (Mayne, 2003). Interventions with fruits and fruit juices led to an increase in total antioxidant capacity (Day *et al.*, 1997; Cao *et al.*, 1998a,b; Serafini *et al.*,1998; Aviram *et al.*, 2000; Marniemi *et al.*, 2000; Pedersen *et al.*, 2000; van den Berg *et al.*, 2001; Kay & Holub, 2002), whereas those with cruciferous and allium vegetables, spinach and tomatoes had no effect (Zhang *et al.*, 1997; Cao *et al.*, 1998b; Castenmiller *et al.*, 1999; Lean *et al.*, 1999; Bub *et al.*, 2000; Pellegrini *et al.*, 2000).

Oxidative damage

If not quenched by antioxidants, free radicals react with, and may alter, the structure and function of a number of cellular components, such as lipid-containing cell membranes, lipoproteins, proteins, carbohydrates, RNA and DNA.

Lipids

Effects of fruits and vegetables on the susceptibility to oxidation of serum lipoprotein *ex vivo* have been explored extensively in relation to cardiovascular disease; however, since lipid peroxidation products form adducts with DNA, they may also increase cancer risk (see section on mechanisms in this chapter). The majority of intervention studies found that low-density lipoprotein (LDL) oxidation was decreased and lag time to oxidation increased following supplementation of a wide range of fruits and vegetables, including tomato products and juice at various doses (Agarwal & Rao, 1998; Bub *et al.*, 2000), orange (Harats *et al.*, 1998), grape (Day *et al.*, 1997) and pomegranate juices (Aviram *et al.*, 2000), a mixture of vegetables (Hininger *et al.*, 1997) and garlic powder (Phelps & Harris, 1993). Tomato or orange juice was not consistently effective; two studies reported no change in LDL oxidation with these juices (Abbey *et al.*, 1995; Maruyama *et al.*, 2001). Other treatments that did not significantly alter these markers included sea buckthorn juice (Eccleston *et al.*, 2002) and aged garlic extract (Steiner & Lin, 1998). O'Reilly *et al.* (2001), testing the effects of onion and black tea supplementation, found no change in plasma F2-isoprostane or malondialdehyde–LDL autoantibody titre, suggesting no alteration in LDL oxidation *in vivo*. In addition, two studies have reported no change in urinary malondialdehyde with onion supplementation (Boyle *et al.*, 2000) and with increasing fruit and vegetable intake to twelve servings per day (Thompson *et al.*, 1999a).

Proteins

Five studies have tested the effects of fruit and vegetable interventions on plasma protein oxidation, specifically protein carbonyl formation. Three found no effect of intervention (Castenmiller *et al.*, 1999; Nielsen *et al.*, 1999; van den Berg *et al.*, 2001). One reported an increase in formation of plasma 2-aminoadipic semialdehyde (a specific carbonyl at lysine residues) with a blackcurrant–apple juice mixture (Young *et al.*, 1999)—a prooxidant effect significantly positively correlated with plasma vitamin C concentrations (Castenmiller *et al.*, 1999; Dragsted *et al.*, 2001). Another study reported a non-significant increase in oxidation with grape-skin extract (Young *et al.*, 2000).

DNA oxidation and adduct formation

Interaction of reactive oxygen or nitrogen species with DNA bases can result in the formation of adducts, which, during the course of attempted repair or replication, can lead to mutations that may contribute to the development of neoplastic cells (see section on mechanisms in this chapter). To test whether antioxidant scavenging of free radicals diminishes the production of DNA adducts, studies have measured oxidative DNA damage in humans in relation to various fruit and vegetable treatments. Urinary and/or peripheral blood leukocyte concentrations of 8-hydroxydeoxyguanosine (8-OHdG) were decreased after interventions with Brussels sprouts (Verhagen *et al.*, 1995, 1997), various tomato products (Rehman *et al.*, 1999; Chen *et al.*, 2001b), vegetable juice (Fan *et al.*, 2000) and a diet high in fruit and vegetables (Thompson *et al.*, 1999a). Results have been inconsistent for allium interventions (Hageman *et al.*, 1997; Beatty *et al.*, 2000; Boyle *et al.*,

Table 115. Studies of effects of fruit and vegetable interventions on antioxidant activity in humans

Author, year, country	Subjects, age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Antioxidant enzymes					
Castenmiller *et al.*, 1999, Netherlands	Healthy NS normolipidaemic, 30 M, 42 F; 18–58 y	Parallel arm; controlled intervention	Tx1: carotenoid supplement; tx2: whole-leaf spinach 20 g/MJ, tx3: minced spinach 20 g/MJ, tx4: liquefied spinach 20 g/MJ, tx5: liquefied spinach 20 g/MJ + beetroot fibre 10 g/kg	3 wk	Increased RBC glutathione reductase and decreased catalase activities with spinach. No effect on SOD.
Lean *et al.*, 1999, UK	Type II diabetics, 5 M, 5 F; 50–74 y	Crossover, two-arm trial; supplementation of restricted habitual diet	Onion 400 g + tea 250 mL or onion 400 g + ketchup 20 g + Italian seasoning herbs 1 g + tea 250 mL	14 d	No effect on plasma SOD or glutathione peroxidase activity
Nielsen *et al.*, 1999, Denmark	NS, 7 M, 7 F; 20–31 y	Crossover; controlled intervention	Parsley 20 g/10 MJ	1 wk each tx	Increased RBC glutathione reductase and SOD activities; no effect on RBC catalase and glutathione peroxidase
Young *et al.*, 1999, Denmark	Healthy NS 4 F, 1 M; 22–28 y	Crossover; supplementation of restricted habitual diet	Fruit juice (blackcurrant and apple juice, 1:1): 750, 1000 and 1500 mL	1 wk each tx	Increased RBC glutathione peroxidase activity with juice. No effect on glutathione reductase, catalase and SOD
Young *et al.*, 2000, Denmark	Healthy NS 9 F, 6 M; 21–33 y	Crossover; supplementation of restricted habitual diet	Grape-skin extract 600 mg	1 wk each tx	Increased RBC glutathione reductase and glutathione peroxidase activities. No effect on catalase and SOD
Aviram *et al.*, 2000, Israel	NS; Study 1: 13 Study 2: 3 20–35 y	Study 1: pre–post; supplementation of habitual diet Study 2: pre–post; supplementation of habitual diet	Study 1: 50 mL pomegranate juice Study 2: increasing doses of pomegranate juice 20–80 mL	Study 1: 2 wk Study 2: 10 wk	Increased serum paraoxonase
Total antioxidant capacity					
Day *et al.*, 1997, UK	Healthy adults, 6 M, 1 F	Pre–post; supplementation of habitual diet	Red grape juice concentrate 125 mL	1 wk	Increased serum TAC
Zhang *et al.*, 1997, UK	Healthy, 52 M, F	3-arm trial; supplementation of habitual diet	8 mg garlic oil or 1.0 g garlic powder	11 wk	Increased plasma TAC at 4 and 6 wk, but no difference at 11 wk
Cao *et al.*, 1998a, USA	Healthy NS, 8 F; mean age 66.9 y	5 treatments assigned to each subject in a random sequence	Coconut drink or coconut drink + strawberries 240 g; ascorbic acid 1250 mg; raw spinach 294 g; red wine 300 mL	Single dose, each 2 wk apart	Increased serum TAC (ORAC, TEAC and FRAP) with all tx and increased urinary TAC (ORAC) with strawberries, spinach and ascorbic acid

Table 115 (contd)

Author, year, country	Subjects, age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Cao *et al.*, 1998b, USA	Healthy, 17 M, 17 F; 20–40 y and 60–80 y	Crossover; controlled intervention	Tx1: fruit and vegetables 10 servings tx2: fruit and vegetables 10 servings + broccoli 2 servings (205 g) days 6–10	15 d per tx	Increased plasma TAC (ORAC) on both tx; no further effect of broccoli
Serafini *et al.*, 1998, Italy	Healthy non-smokers, 6 F, 4 M; 25–50 y	Tx1–tx2–tx3	Tx1: dealcoholized red wine 113 mL; tx2: dealcoholized white wine; tx3: tap water	Single doses per tx	Increased plasma TRAP with dealcoholized red wine
Castenmiller *et al.*, 1999, Netherlands	Healthy non-smokers, normolipidaemic, 42 F, 30 M; 18–58 y	Parallel arm; controlled intervention	Tx1: carotenoid supplement; tx2: whole-leaf spinach 20 g/MJ, tx3: minced spinach 20 g/MJ, tx4: liquefied spinach 20 g/MJ, tx5: liquefied spinach 20 g/MJ + beetroot fibre 10 g/kg	3 wk	No effect on plasma FRAP
Lean *et al.*, 1999, UK	Type II diabetics, 5 M, 5 F; 50–74 y	Crossover, two-arm trial; supplementation of restricted habitual diet	Onion 400 g + tea 250 mL or onion 400 g + ketchup 20 g + Italian seasoning herbs 1 g + 250 mL	14 d	No effect on plasma TEAC
Leighton *et al.*, 1999, Chile	Healthy omnivorous 42 M; 20–27y	2-arm trial; controlled intervention	Mediterranean diet or high fat diet; red wine 240 mL/d added	3 months; during the second month wine added	Increased plasma TAC with Mediterranean diet and with wine in both diets
Young *et al.*, 1999, Denmark	Healthy non-smokers, 4 F, 1 M; 22–28 y	Crossover; supplementation of restricted habitual diet	Fruit juice (blackcurrant and apple juice 1:1): 750, 1000 and 1500 mL	1 wk each tx	No effect on plasma TEAC and FRAP
Aviram *et al.*, 2000, Israel	Non-smokers M; Study 1: 13 Study 2: 3 20–35 y	Study 1: pre–post; supplementation of habitual diet Study 2: pre–post; supplementation of habitual diet	Study 1: 50 mL pomegranate juice Study 2: increasing doses of pomegranate juice 20–80 mL	Study 1: 2 wk Study 2: 10 wk	Increased serum TAC
Bub *et al.*, 2000, Germany	Healthy non-smoking 23 M; 27–40 y		Tx1: tomato juice 330 mL; tx2: carrot juice 330 mL; tx3: dried spinach powder 10 g	2 wk each tx	No effect on plasma FRAP
Lee *et al.*, 2000, UK	Healthy, 5 F, 1 M; 20–24 y		Tx1: tomato soup 200 g + canned tomatoes 230 g + olive oil 20 mL Tx2: tomato soup 200 g + canned tomatoes 230 g + sunflower oil 20 mL	7 d each tx	Increased plasma FRAP with tomatoes + olive oil

Table 115 (contd)

Author, year, country	Subjects, age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Marniemi *et al.*, 2000, Finland	Study 1: healthy, 60 M; 60 y Study 2: healthy, 6 M; mean age 48.7 y	Study 1: 3-arm trial; supplementation of habitual diet Study 2: pre–post; fasting	Study1: berries (bilberries or lingonberries or blackcurrants) 100 g ; tocopherol 100 mg + ascorbic acid 500 mg ; calcium gluconate 500 mg Study 2: berries 240 g	Study 1: 8 wk Study 2: single dose	Study 1: Increased serum TRAP with berries and LDL TRAP with supplement. Study 2: Increased LDL TRAP
Pedersen *et al.*, 2000, UK	Healthy, 9 F; 23–41 y	Crossover; fasting	Blueberry juice 500 mL; vitamin-C fortified cranberry juice 500 mL	Single dose	Increased plasma TAC (ESR spectroscopy and FRAP) with cranberry
Pellegrini *et al.*, 2000, Italy	Healthy, non-smokers, 11 F; mean age 25.4 y	Pre–post; supplementation of restricted habitual diet	Tomato puree 25 g	14 d	No change in plasma TAC (TRAP)
Record *et al.*, 2001, Australia	Healthy, non-smokers, 25 M; 25–60 y	Crossover; modification/supplementation of habitual diet	Fruit and vegetables 5–7 servings ; spray-dried fruit and vegetable supplement 30 g	2 wk each tx	No effect on plasma TAC
van den Berg *et al.*, 2001, Netherlands	Healthy, smokers, 22 M; 18–50 y	Crossover; supplementation of habitual diet	Veg. burger (lyophilized tomatoes, carrots, onions, broccoli, sweet red pepper; equivalent of 500 g mixed fresh veg.) and mixed fruit drink (orange, apple, blueberry, lemon, lime) 330 mL	3 wk each tx	Increase of plasma TAC (TEAC)
Kay & Holub 2002, Canada	Healthy, non-smokers, 8 M; 38–54 y	Crossover; fasting	Freeze-dried wild blueberry powder 100 g	Single dose with high-fat meal	Increased serum TAC (ORAC)
Oxidative damage - lipids					
Phelps & Harris 1993, USA	Healthy, 5 M, 5 F; mean age 32 y	Crossover; supplementation of habitual diet	Garlic powder 600 mg	2 wk	Decreased susceptibility of apolipoprotein B-containing lipoproteins to oxidation
Abbey *et al.*, 1995, Australia	Normocholesterolaemic smokers, 15 M; mean age 41.3 y	Pre–post; supplementation of habitual diet	Orange juice 250 mL + carrot juice 300 mL	3 wk of control; 3 wk of tx	Decreased MDA in copper-oxidized LDL; no effect on rate of LDL oxidation or lag time
Day *et al.*, 1997, UK	Healthy adults, 6 M, 1 F	Pre-post: supplementation of habitual diet	Red grape juice concentrate 125 mL	1 wk	Decreased LDL oxidation
Hininger *et al.*, 1997, France	Health smokers and non-smokers, 11 M, 11 F, 25–45 y	Pre-post; modification of habitual diet	Carrots 150 g + tomatoes 200 g + French beans, cabbage and/or spinach 300 g	2 wk	Lengthened lag time before the onset of LDL oxidation

Table 115 (contd)

Author, year, country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Agarwal & Rao, 1998, Canada	Healthy non-smokers, 10 M, 9 F; 25–40 y	Crossover; standardized breakfast with habitual diet	Tomato sauce 126 g; tomato juice 540 mL; lycopene 1.243 g	1 wk each tx	Decreased LDL oxidation (TBARS and conjugated dienes) with all tx
Harats *et al.*, 1998, Israel	Healthy 36 M; 18–23 y	2-arm trial; controlled intervention	Orange juice providing ~500 mg vitamin C	2 mo	Increased lag time of LDL oxidation
Rao & Agarwal, 1998, Canada	Healthy non-smokers, 10 M, 10 F; 25–40 y	Crossover; standardized breakfast with habitual diet	5 tx: tomato sauce 126 g; high-lycopene tomato sauce 126 g; tomato juice 540 mL; lycopene 1.232 g; lycopene 2.486 g	1 wk per tx	Decreased serum TBARS
Steiner & Lin, 1998, USA	Hypercholesterolaemic, 15 M; 30–65 y	Crossover; supplementation of habitual diet	Aged garlic extract 800 mg	6 mo one tx, 4 mo other	Decreased (not significant) susceptibility of LDL to oxidation
Young *et al.*, 1999, Denmark	Healthy non-smokers, 1 M, 4 F; 22–28 y	Crossover; supplementation of restricted habitual diet	Fruit juice (blackcurrant and apple juice 1:1): 750, 1000 and 1500 mL	1 wk each tx	Decreased plasma MDA with 1500 mL
Thompson *et al.*, 1999a, USA	Healthy, 28 F; 27–80 y	Pre–post; recipe-defined modification of habitual diet	12 servings of fruit and veg.	14 days	No change in urinary MDA; increase of urinary EPG
Aviram *et al.*, 2000, Israel	Non-smokers; M Study 1: 13 Study 2: 3 20–35 y	Study 1: pre–post; supplementation of habitual diet Study 2: pre–post; supplementation of habitual diet	Study 1: 50 mL pomegranate juice Study 2: increasing doses of pomegranate juice 20–80 mL	Study 1: 2 wk Study 2: 10 wk	Decreased lipid peroxidation; prolonged lag time of LDL oxidation
Boyle *et al.*, 2000, UK	Healthy non-smokers, 6 F; 20–44 y	Crossover; supplementation of restricted habitual diet	Onion 200 g ; onions 200 g + uncooked tomatoes 100 g	Single dose	No effect on urinary MDA
Bub *et al.*, 2000, Germany	Healthy non-smokers, 23 M; 27–40 y	Control–tx1–tx2–tx3; supplementation of restricted habitual diet	Tx1: tomato juice 330 mL; tx2: carrot juice 330 mL; tx3: dried spinach powder 10 g	2 wk each tx	Tomato juice reduced plasma TBARS and LDL oxidation; no effect of other tx
Caccetta *et al.*, 2000, Australia	Healthy non-smokers, 12 M; 40–63 y	Crossover; supplementation of restricted habitual diet	Tx1: red wine; tx2: dealcoholi-zed red wine; tx3: phenol-stripped red wine; tx4: water. Dose: 5 mL red wine equivalents/kg bw	Single dose after 12-h fast	No effect of any tx on serum or LDL oxidation

Table 115 (contd)

Author, year, country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Chopra *et al.*, 2000, UK	18 non-smokers and 14 smokers, F; 24–52 y	Crossover; supplementation of habitual diet	Creamed spinach 200 g and mango puree 100 g; tomato puree 200 g and watermelon 100 g/d	1 wk each tx	Increased lag-phase of LDL oxidation only in non-smokers on tomato and watermelon tx
Fuhrman *et al.*, 2000, Israel	Healthy non-smokers, 4; 30–45 y	Pre–post	Tomato oleoresin (lycopene 30 mg)	Single dose with high-fat meal	Reduced susceptibility of LDL to oxidation
Young *et al.*, 2000, Denmark	Healthy non-smokers, 6 M, 9 F; 21–33 y	Crossover; supplementation of restricted habitual diet	Grape-skin extract 600 mg	1 wk each tx	No effect on plasma- or LDL-MDA
Böhm *et al.*, 2001, Germany	Not reported	Pre–post	Tomato juice 500 mL	2 wk	Decreased *ex vivo* lymphocyte membrane damage by reactive oxygen species
Lau, 2001, USA	4 M, 4 F; mean age 68 y	Placebo-controlled crossover; supplementation of habitual diet	Aged garlic extract 3.6 g	2 wk	Increased resistance to LDL oxidation
Maruyama *et al.*, 2001, Japan	Healthy, 31 F; mean age 21.3 y	3-arm trial; supplementation of habitual diet	Tomato juice 160 g; tomato juice 480 g	1 menstrual cycle	No change in lag time of LDL oxidation
O'Reilly *et al.*, 2001, UK	Healthy non-smokers, 20 M, 22 F; 20–60 y	Crossover; supplementation of restricted habitual diet	Onion 150 g + black tea 300 mL	2 wk	No effect on plasma F2-isoprostane or MDA-LDL autoantibody titre
van den Berg *et al.*, 2001, Netherlands	Healthy smokers, 22 M; 18–50 y	Crossover; supplementation of habitual diet	Veg. burger (lyophilized tomatoes, carrots, onions, broccoli, sweet red pepper; equivalent of 500 g mixed fresh veg.) and mixed fruit drink (orange, apple, blueberry, lemon, lime) 330 mL	3 wk each tx	No effect on MDA or F2-isoprostane
Eccleston *et al.*, 2002, UK	Healthy non-smokers, 20 M; 18–55 y	2-arm trial; supplementation of habitual diet	Sea buckthorn juice 300 mL	8 wk	Increased (not significant) lag time of LDL oxidation
Oxidative damage – proteins					
Castenmiller *et al.*, 1999, Netherlands	Healthy non-smokers, normolipidaemic, 30 M, 42 F; 18–58 y	Parallel arm; controlled intervention	Tx1: carotenoid supplement; tx2: whole leaf spinach 20 g/MJ, tx3: minced spinach 20 g/MJ, tx4: liquefied spinach 20 g/MJ, tx5: liquefied spinach 20 g/MJ + beetroot fibre 10 g/kg	3 wk	No effect on plasma 2-amino-adipic semialdehyde formation

Table 115 (contd)

Author, year, country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Nielsen *et al.*, 1999, Denmark	Non-smokers, 7 M, 7 F; 20–31 y	Crossover; controlled intervention	Parsley 20 g/10 MJ	1 wk each tx	No effect plasma 2-aminoadipic semialdehyde formation
Young *et al.*, 1999, Denmark	Healthy non-smokers, 1 M, 4 F; 22–28 y	Crossover; supplementation of restricted habitual diet	Fruit juice (blackcurrant and apple juice 1:1): 750, 1000 and 1500 mL	1 wk each tx	Increased plasma 2-aminoadipic semialdehyde formation with juice dose; no effect on RBC 2-aminoadipic semialdehyde and γ-glutamyl semialdehyde formation.
Young *et al.*, 2000, Denmark	Healthy non-smokers, 6 M, 9 F; 21–33 y	Crossover; supplementation of restricted habitual diet	Grape-skin extract 600 mg	1 wk each tx	Non-significant increase in plasma 2-aminoadipic semialdehyde formation
van den Berg *et al.*, 2001, Netherlands	Healthy smokers, 22 M; 18–50 y	Crossover; supplementation of habitual diet	Veg. burger (lyophilized tomatoes, carrots, onions, broccoli, sweet red pepper; equivalent of 500 g mixed fresh veg.) and mixed fruit drink (orange, apple, blueberry, lemon,lime) 330 mL	3 wk each tx	No effect on protein carbonyl formation
Oxidative damage and adduct formation – DNA					
Verhagen *et al.*, 1995, Netherlands	Healthy non-smokers, 10 M; 20–28 y	2-arm trial; controlled intervention	Brussels sprouts 300 g	3 wk	Decreased urinary 8-OHdG
Hageman *et al.*, 1997, Netherlands	Healthy non-smokers, 9 M	Crossover; supplementation of habitual diet	Cucumber salad 100 g; cucumber salad 100 g + raw garlic 3 g	8 d each tx	Decreased *ex vivo* PBL benzo[*a*]pyrene–DNA adduct formation and PBL 8-OHdG with both tx. Additional decrease of benzo[*a*]pyrene–DNA adduct with garlic
Pool-Zobel *et al.*, 1997, Germany	Healthy non-smokers, 23 M; 27–40 y	Control–tx1–tx2–tx3; supplementation of restricted habitual diet	Tx1: tomato juice 330 mL; tx2: carrot juice 330 mL; tx3: dried spinach powder 10 g	2 wk each tx	Decreased lymphocyte DNA strand breaks (comet assay) with all tx and decreased oxidative DNA base damage (endonuclease III assay) with carrot juice only
Verhagen *et al.*, 1997, Netherlands	Healthy non-smokers, 5 M, 5 F	Crossover; supplementation of restricted habitual diet	Brussels sprouts 300 g	1 wk per tx	Decreased urinary 8-OHdG in 4/5 men; no effect in women
Rao & Agarwal 1998, Canada	Healthy non-smokers, 10 M, 10 F; 25–40 y	Crossover; standardized breakfast with habitual diet	Tomato sauce 126 g; high-lycopene tomato sauce 126 g; tomato juice 540 mL; lycopene 1.232 g; lycopene 2.486 g	1 wk per tx	No significant change in lymphocyte 8-OHdG

Table 115 (contd)

Author, year country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Lein *et al.*, 1999, UK	Type II diabetics, 5 M, 5 F; 50–74 y	Crossover, 2-arm trial; supplementation of restricted habitual diet	Onion 400 g + tea 250 mL; onion 400 g + ketchup 20 g + Italian seasoning herbs 1 g + tea 250 ml	14 d	Increased *ex vivo* antioxidant resistance (comet assay with H_2O_2 with tx; no effect on oxidative DNA base damage (endonuclease III assay)
Leighton *et al.*, 1999, Chile	Healthy omnivorous, 42 M; 20–27y	2-arm trial; controlled intervention	Mediterranean diet; high fat diet; red wine 240 mL/d added	3 mo; wine added during month 2	No change in PBL 8-OHdG with Mediterranean diet; increased with high-fat diet; decreased with wine with both diets
Rehman *et al.*, 1999, UK	Healthy volunteers, 1 M, 4 F; mean age 27.2 y	Pre–post; restricted habitual diet	Tomatoes 360–728 g (8 g/kg bw)	Single dose	Decreased 8-hydroxyguanine in individuals with high baseline values; increase of 8-hydroxyadenine; no effect on damage of other bases or on total damage
Riso *et al.*, 1999, Italy	Healthy, 10 F; mean age 23.1 y	Crossover; supplementation of restricted habitual diet	Tomato puree 60 g	21 d each tx	Increased *ex vivo* antioxidant resistance (comet assay with H_2O_2)
Thompson *et al.*, 1999a, USA	Healthy 28 F; 27–80 y	Pre–post; recipe-defined modification of habitual diet	12 servings of fruit and veg.	14 d	Decreased lymphocyte and urinary 8-OHdG
Beatty *et al.*, 2000, UK	Healthy non-smokers, 16 M, 20 F; 21–57 y	Crossover; supplementation of restricted habitual diet	Onion 150 g + black tea 300 mL	14 d	No effect on leukocyte DNA damage (individual bases and total damage)
Boyle *et al.*, 2000, UK	Healthy non-smokers, 6 F; 20–44 y	Crossover; supplementation of restricted habitual diet	Onion 200 g ; onions 200 g + uncooked tomatoes 100 g	Single dose	No effect on lymphocyte DNA damage (comet assay); increased *ex vivo* antioxidant resistance (comet assay with H_2O_2) on onion tx; decreased oxidative DNA base damage (endonuclease III assay) with both tx; decreased urinary 8-OHdG after onion, but not onion + tomato, meal
Fan *et al.*, 2000, Japan	Healthy athletes, 11 M; mean age 21.0 y	2-arm trial; controlled intervention	Veg. juice 480 mL	4 d	Decreased urinary 8-OHdG
Porrini & Riso, 2000, Italy	Healthy, 9 F; mean age 25.4 y	Pre–post; supplementation of restricted habitual diet	Tomato puree 25 g	14 d	Increased *ex vivo* antioxidant resistance (comet assay with H_2O_2)

Table 115 (contd)

Author, year, country	Subject; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Chen *et al.*, 2001b, USA	32 M, localized prostate adenocarcinoma; mean age, 65.7	Pre-post; substitution in habitual diet	Tomato sauce 200 g incorporated into pasta dishes	3 wk	Decreased leukocyte and prostate tissue 8-OHdG
Collins *et al.*, 2001, UK	Healthy, non-smokers, 6 M, F; 24–55 y	Crossover; supplementation of habitual diet	Homogenized kiwi fruit 500 mL	Single dose	No effect on endogenous lymphocyte DNA damage (comet assay) or oxidative DNA base damage (endonuclease III assay), but increased *ex vivo* antioxidant resistance (to H_2O_2)
Dragsted *et al.*, 2001, Denmark	Healthy non-smokers, 4 F, 1 M; 22–28 y	Crossover; supplementation of restricted habitual diet	Fruit juice (blackcurrant and apple juice 1:1): 750, 1000 and 1500 mL	1 wk each tx	No effect on urinary 8-OHdG
van den Berg *et al.*, 2001, Netherlands	Healthy smokers, 22 M; 18–50 y	Crossover; supplementation of habitual diet	Veg. burger (lyophilized tomatoes, carrots, onions, broccoli, sweet red pepper; equivalent of 500 g mixed fresh veg.) and mixed fruit drink (orange, apple, blueberry, lemon, lime) 330 mL	3 wk each tx	No effect on PBMC DNA damage (comet with and without H_2O_2; endonuclease III)
Porrini *et al.*, 2002, Italy	Healthy non-smokers, 9 F; mean age 25.2 y	Control–tx1–washout–tx2; supplementation of restricted habitual diet	tx1: spinach 150 g per day tx2: spinach 150 g + tomato puree 25 g	3 wk each tx	Increased *ex vivo* antioxidant resistance (comet assay with H_2O_2) with both tx; no additional effect of tomato
Vogel *et al.*, 2002, Denmark	Healthy non-smokers, 22 M, 21 F; 21–56 y	Controlled intervention; parallel arm	Flavonoid-food free basal diet + tx1: fruits and vegetables 600 g; tx2: vitamin-mineral tablets; tx3: placebo tablets	25 d	No effect of fruit and vegetables on PBL DNA-repair enzyme expression (OGG1 and ERCC1)

bw, body weight; EPG, 8-isoprostane; ESR, electron spin resonance spectroscopy; FRAP, ferric-reducing ability of plasma; LDL, low-density lipoprotein; MDA, malondialdehyde; ORAC, oxygen radical absorbance capacity; 8-OHdG, 8-hydroxydeoxyguanosine; PBL, peripheral blood lymphocyte; RBC, red blood cell; SOD, superoxide dismutase; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TEAC, trolox equivalent antioxidant capacity; TRAP, antioxidant potential; tx or Tx, treatment

2000), which ranged in length from a single dose to 14 days. In addition, Chen *et al.* (2001b) reported concomitantly decreased levels of 8-OHdG in both peripheral leukocytes and in prostate tissue of prostate adenocarcinoma patients whose diets were supplemented with tomato sauce (200 g/d) for three weeks.

The other main approach to study DNA damage in response to interventions has been to measure lymphocyte damage *ex vivo*, using a single-cell gel electrophoresis or "comet" assay. Two modifications of this assay, hydrogen-peroxide-induced DNA damage and endonuclease III cleavage to determine the presence of oxidized pyrimidines, indicate the susceptibility of lymphocyte DNA to oxidative damage. Using the comet assay, several studies (Pool-Zobel *et al.*, 1997; Lean *et al.*, 1999; Riso *et al.*, 1999; Boyle *et al.*, 2000; Collins *et al.*, 2001; Porrini *et al.*, 2002), but not all (van den Berg *et al.*, 2001), have shown that various fruits and vegetables (e.g., tomato products, onions, carrot juice and kiwi fruit) reduce endogenous and/or hydrogen-peroxide-induced DNA strand breaks; however, these treatments do not always concurrently inhibit base oxidation. Another study showed that addition of raw garlic to a cucumber salad intervention for eight days further inhibited *ex vivo* lymphocyte benzo[*a*]-pyrene–DNA adduct formation (Hageman *et al.*, 1997).

Nitrosation (Table 116)

Some of the same factors that contribute to oxidative damage and the production of reactive oxygen species can also lead to production of reactive nitrogen species. A wide range of nitrogen-containing compounds and nitrosating agents to which humans are exposed react *in vivo* to form potentially carcinogenic *N*-nitroso, *C*-nitroso and reactive diazo compounds (Bartsch & Frank, 1996). Nitrosating agents can also be synthesized endogenously by bacteria in the gut and activated macrophages.

Nitrosation in humans can be estimated quantitatively by monitoring urinary excretion of *N*-nitrosoproline (NPRO) after an oral dose of L-proline (Ohshima & Bartsch, 1981). Various studies have shown reduced urinary excretion of nitrosation products after single doses or one-week interventions of vitamin-C-rich fruits, vegetables and juices (Knight & Forman, 1987; Helser *et al.*, 1992; Xu *et al.*, 1993; Chung *et al.*, 2002). In contrast, a longer-term (15-day) intervention of broccoli, green peas (*Pisum sativum*) and Brussels sprouts had no effect on *N*-nitrosation, particularly in the large intestine (Hughes *et al.*, 2002). Some vegetables that are significant sources of nitrate and certain vegetable-canning methods increase body nitrite load (Lowenfels *et al.*, 1978; Xu *et al.*, 1993).

Modulation of biotransformation enzymes (Table 117)

Drug-metabolizing enzymes metabolize many endogenous compounds and detoxify numerous xenobiotics (Yang *et al.*, 1994). Phase I enzymes such as cytochrome P450-dependent monooxygenases (CYP) catalyse oxidation, hydroxylation and reduction reactions, converting hydrophobic compounds to reactive electrophiles in preparation for reaction with water-soluble moieties (conjugation) to enhance their excretion. Phase II enzymes, such as UDP-glucuronosyltransferases (UGT), sulfotransferases and glutathione *S*-transferases (GST), catalyse these conjugation reactions.

Research efforts on effects of constituents of fruit and vegetables on biotransformation enzymes have focused particularly on the phase II conjugating enzymes. These enzyme systems are rapidly induced; enzymatic activities rose and reached a plateau within five days of continued daily ingestion of a food with inducing capacity (coffee or broccoli) and dropped rapidly when the food was removed from the diet (Sreerama *et al.*, 1995). This suggests that most of the interventions to date, which have been short (one to two weeks), are of sufficient duration to evaluate the initial effect of diet on these enzyme systems. Several controlled dietary interventions have shown that cruciferous vegetables at doses of at least 300 g per day increase plasma (Bogaards *et al.*, 1994; Nijhoff *et al.*, 1995a; Lampe *et al.*, 2000a) and rectal (Nijhoff *et al.*, 1995b) GST-α concentrations. A lower dose of broccoli (~85 g) as part of a lyophilized mixed-vegetable treatment had no effect on plasma GST-α (van den Berg *et al.*, 2001). GST-π in plasma and peripheral white blood cells did not respond to a cruciferous vegetable intervention, although rectal GST-π increased after feeding with Brussels sprouts (Nijhoff *et al.*, 1995a, b). In two other studies, GST-π mRNA and/or protein in white blood cells decreased when participants were fed mixtures of vegetables of which Cruciferae were a minor component (Persson *et al.*, 2000; van den Berg *et al.*, 2001). However, another study reported a trend towards higher lymphocyte GSTP1 with high-carotenoid vegetable juices (Pool-Zobel *et al.*, 1998), suggesting that responses vary extensively depending on the treatment.

Biotransformation of xenobiotics and that of therapeutic drugs share many of the same enzyme systems; therefore, drug metabolites can be monitored in intervention studies designed to test the effects of exposures on these systems. This is useful because in human studies it is often difficult to obtain particular tissue samples to measure enzyme activities directly. Five studies have used caffeine metabolite ratios to test broccoli, Brussels sprouts or mixed cruciferous

vegetables and found increased CYP1A2 activity (McDanell *et al.*, 1992; Vistisen *et al.*, 1992; Kall *et al.*, 1996; Lampe *et al.*, 2000b; Murray *et al.*, 2001), slightly increased CYP2E1 activity (Kall *et al.*, 1996) and no change in *N*-acetyltransferase (NAT) 2 or xanthine oxidase (XO). In contrast, single doses of watercress modestly reduced activities of CYP2E1 (Leclercq *et al.*, 1998) and CYP2A6 (Murphy *et al.*, 2001) and oxidation of acetaminophen (paracetamol) (Chen *et al.*, 1996), but had no effect on CYP2D6 (Caporaso *et al.*, 1994). Few studies have examined effects of non-cruciferous vegetables on phase I metabolism; however, one reported inhibition of CYP1A2 with a six-day apiaceous vegetable intervention (Lampe *et al.*, 2000b) and another reported that garlic increased NAT activity without changes in CYP1A2, CYP2A6 or XO (Hageman *et al.*, 1997). Numerous studies have reported inconsistent effects of acute grapefruit juice dosing on phase I metabolism of a wide variety of drugs (Bailey *et al.*, 1994). Phase II conjugation also is affected by cruciferous vegetables (including watercress); increased glucuronidation of several drugs has been reported (Pantuck *et al.*, 1979, 1984), although there are no studies on induction of specific UGT families. Garlic did not appear to alter glucuronidation of acetaminophen, but slightly increased its sulfation (Gwilt *et al.*, 1994).

Human intervention studies have also examined direct effects of supplementation with cruciferous vegetables on metabolism of carcinogens. Addition of watercress to diets of smokers significantly increased glucuronidation of nicotine and tobacco-carcinogen metabolites, while having modest effects on oxidative metabolism of these compounds (Hecht *et al.*, 1999). Similarly, broccoli and Brussels sprouts increased the metabolism of cooked meat-derived heterocyclic aromatic amines (i.e., reduced urinary excretion of MeIQx and PhIP), implicating the induction of both CYP1A2 and phase II enzymes that are involved in heterocyclic amine metabolism (Murray *et al.*, 2001; Knize *et al.*, 2002).

Urinary mutagenicity (Table 118)

Bacterial assays (Ames *et al.*, 1975) can be used to detect mutagenicity of human urine as a biomarker of exposure to carcinogens in cooked meats, cigarette smoke and certain occupational agents (see Ohyama *et al.*, 1987a). This biomarker has been used to evaluate the effects of vegetables and grape juice on clearance of mutagens after interventions varying in length from a single dose to six weeks. Cabbage consumed as a single dose concurrently with fried salmon had no effect on urinary mutagenicity (Ohyama *et al.*, 1987a). However, longer-term cruciferous vegetable supplementation increased mutagenicity in two separate studies (DeMarini *et al.*, 1997; Murray *et al.*, 2001), supporting the hypothesis that induction of biotransformation enzymes by cruciferous vegetables leads to increased excretion of mutagens. The decreased mutagenic activity of urine after a single dose of parsley (Ohyama *et al.*, 1987b) suggests that constituents of parsley directly inhibit activity of enzymes involved in mutagen metabolism.

Other biomarkers (Table 119)

Steroid hormone metabolism

Cytochrome P450 enzymes that metabolize, and/or are modulated by, constituents of vegetables and fruit have the capacity to alter the potency of testosterone, estrogens and their derivatives via oxidation and hydroxylation reactions (Aoyama *et al.*, 1990). This has been evaluated in relation to formation of specific 2-hydroxy- and 16α-hydroxy-estrogen metabolites, which have been hypothesized to affect breast cancer risk (Bradlow, 1986). Cruciferous vegetables fed at levels of at least 200 g/d increased the urinary ratio of 2-hydroxy- to 16α-hydroxyestrone in men and women (Kall *et al.*, 1996; Fowke *et al.*, 2000).

Tissue markers and clinical markers of cancer risk

Very few studies have examined the effects of fruit and vegetables on tissue markers or established clinical markers of cancer risk. In one pre–post study in the USA, serum concentrations of prostate-specific antigen (PSA) decreased with tomato-sauce supplementation in patients with prostate adenocarcinoma (Chen *et al.*, 2001b). To date, the largest and longest intervention involving fruit and vegetables and using a clinical marker of cancer risk is the Polyp Prevention Trial (Schatzkin *et al.*, 2000), described under Colon and rectum in the section of this chapter on cancer-preventive effects in humans. Four years of this dietary intervention had no protective effect; polyp recurrence did not differ between the treatment and control groups.

Immune function

Immune status has not been clearly linked to cancer etiology; however, it is biologically plausible that immune function is important in cancer development and growth (see section on mechanisms in this chapter). Three interventions, ranging in duration from two to eight weeks, have demonstrated modest changes in markers of cell-mediated immunity. Tomato-juice supplementation in young men consuming a low-carotenoid diet significantly increased interleukin (IL)-2 and IL-4 secretion but had no effect on lymphocyte proliferation (Watzl *et al.*, 1999). In contrast, in older individuals consuming their habitual diet, addition of tomato juice for eight weeks had no effect on a panel of immune function

Table 116. Studies of effects of fruit and vegetable interventions on nitrosation in humans

Author, year, country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Lowenfels *et al.*, 1978, France	Oesophageal cancer patients, 20 M (cases) 39–78 y and hospital employees, 15 M (control) 20–50 y	Pre–post; controlled meal	Beet juice 100 mL	Single dose	Increased salivary nitrite
Knight & Forman 1987, UK	19 F; 20–28 y	Control–tx1 3-arm trial (tx2, tx3 or tx4); supplementation of restricted habitual diet	Control : test meal (high nitrate salad) Tx1: test meal + foods rich in vitamin C (green pepper, strawberries and blackcurrant drink) Tx2: tx1 + high-fat cheese and salad dressing Tx3: tx1 + white wine 225 mL Tx4: tx1 + coffee 2 cups	1 wk per tx	Decreased urinary NPRO with tx1; no effect of tx2, tx3 and tx4
Helser *et al.*, 1992, USA	Healthy non-smokers, 16 M; 22–38 y	Crossover; controlled intervention	Juices (carrot, strawberry, pineapple, tomato, green pepper, or celery) 100 mL	Single dose each day	Decreased urinary NPRO with green pepper, tomato, pineapple, strawberry and carrot juices
Xu *et al.*, 1993, China	Subjects from a high-risk area for gastric cancer, 44 M, 42 F; mean age 53 y	Pre–post; parallel arm; controlled intervention	Tx1: *Phylanthus emblica* juice 16.5 mL Tx2: kiwi juice 30 mL on day 6, processed vegetable juice 300 mL on day 8, and Cili juice 30 mL on day 10 Tx3: green tea extract 4.65 g on day 6, orange peel powder 6 g on day 8 and *Rosa laevigata* juice 57 mL on day 10	1 d tx separated by 1 d	Decreased urinary NPRO with fruit juices and orange-peel powder; increased NPRO with heat-processed juice
Chung *et al.*, 2002, Republic of Korea	Healthy non-smokers; 27 M, 13 F, 17–30 y	Pre–post; restricted habitual diet and controlled intervention	Whole strawberries 300 g or garlic juice 75 g or kale juice 200 g	Single doses	Decreased urinary NDMA; no change in salivary nitrite
Hughes *et al.*, 2002, UK	Healthy, 11 M; 30–59 y	Crossover; 7 subjects completed Tx4; controlled intervention	Tx1: vegetable (broccoli, green peas and Brussels sprouts) 400 g Tx 2: tea (500 mg tea extract per cup) 6 cups Tx3: vegetables + tea Tx4: soy beans 100 g	15 d each tx	No effect of vegetables alone on faecal or urinary markers

NDMA, *N*-nitrosodimethylamine; NPRO, *N*-nitrosoproline

Table 117. Studies of effects of fruit and vegetable interventions on biotransformation enzymes

Author, year, country	Subjects: age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Pantuck *et al.*, 1979, USA	Healthy non-smokers, 7 M, 3 F; 21–32 y	Control–tx–control; controlled intervention	Brussels sprouts 300 g + cabbage 200 g	7 d	Increased metabolism of antipyrine and conjugation of phenacetin metabolite
Pantuck *et al.*, 1984, USA	Healthy non-smokers, 10 M; 23–35 y	Control–tx–control; controlled intervention	Brussels sprouts 300 g + cabbage 200 g	7 d	Increased acetaminophen glucuronidation, but not sulfation. No effect on oxazepam conjugation
McDanell *et al.*, 1992, UK	Healthy non-smokers, Study 1: 4 M Study 2: 3 M, 3 F; 20–57 y	Study 1: pre–post; Study 2: pre–post; controlled intervention	Study 1: cabbage 200 g each meal Study 2: Brussels sprouts 200 g each meal	Study 1: 2 days (3 meals on day 1 and breakfast on d 2); Study 2: 1 day (2 meals)	Reduced mean plasma half-life of caffeine
Vistisen *et al.*, 1992, Denmark	Healthy, 4 M, 5 F; mean age 33 y	Pre–post; supplementation of habitual diet	Broccoli 500 g or non-cruciferous veg. 500 g	10 d	Increased CYP1A2 with broccoli compared to non-cruciferous veg.; no effect on XO or NAT2 (caffeine)
Bogaards *et al.*, 1994, Netherlands	Healthy non-smokers, 10 M; 20–28 y	2-arm trial; controlled intervention	Brussels sprouts 300 g	3 wk	Increased plasma GST-α
Caporaso *et al.*, 1994, USA and UK	15 M, 16 F; 21–42 y	Pre–post; controlled meal	Watercress 50 g	Single dose	No effect on CYP2D6 (debrisoquine)
Gwilt *et al.*, 1994, USA	Non-smokers, 16 M; mean age 25.7 y	Pre–post; supplementation of restricted habitual diet	10 mL aged garlic extract with 120 mL orange juice	12 wk	No effect on oxidative metabolism of acetaminophen and glutathione conjugation of reactive metabolites; slight increase in sulfate conjugation
Hecht *et al.*, 1995, USA	Healthy smokers, 5 M, 6 F; 24–48 y	Control–tx–control; supplementation of *Brassica*-restricted habitual diet	Watercress 170.4 g	3 d	Increased urinary NNAL and NNAL-glucuronide
Nijhoff *et al.*, 1995a, Netherlands	Healthy non-smokers, 5 M, 5 F; 21–29 y	Crossover; supplementation of *Brassica*-restricted habitual diet	Brussels sprouts 300 g	1 wk each tx	Increased plasma GST-α in men; no change in plasma GST-π

Table 117 (contd)

Author, year country	Subjects: age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Nijhoff *et al.*, 1995b, Netherlands	Healthy non-smokers, 5 M, 5 F; mean age 24 y	Crossover; supplementation of *Brassica*-restricted habitual diet	Brussels sprouts 300 g	1 week each tx	Increased rectal GST-α and GST-π; no effect on duodenal or lymphocyte GST
Sreerama *et al.*, 1995, USA	Healthy, 1 F; 28 y	Control–tx–control; supplementation of restricted habitual diet	Broccoli 300 g	12 d	Increased activities of GST, class 3 aldehyde dehydrogenase and DT-diaphorase (NAD(P)H:quinone oxidoreductase) in saliva
Chen *et al.*, 1996, USA	Healthy non-smokers, 7 M, 3 F, 23–48 y	Crossover; fasting	Watercress 50 g	Single dose	Decreased oxidative metabolites of acetaminophen
Kall *et al.*, 1996, Denmark	Healthy non-smokers, 2 M, 14 F; 21–35 y	Control–tx1–tx2; supplementation of modified habitual diet	Tx1: standard diet avoiding GST inducers Tx2: standard diet + broccoli 500 g	Tx 1: 6 d; Tx 2: 12 d	Increased CYP1A2 (caffeine); non-significant increase in CYP2E1 (chlorzoxazone)
Hageman *et al.*, 1997, Netherlands	Healthy non-smokers, 9 M	Pre–post; supplementation of habitual diet	Raw garlic 3 g	8 d	Increased NAT activity; no change in CYP1A2, XO, or CYP2A6 (caffeine)
Pool-Zobel *et al.*, 1998, Germany	Healthy non-smokers, 23 M; 27–40 y	Control–tx1–tx2–tx3; supplementation of restricted habitual diet	Tx1: tomato juice 330 mL; tx2: carrot juice 330 mL; tx3: dried spinach powder 10 g	2 wk each tx	Increased lymphocyte cytosolic protein and GSTP1 with tomato and carrot juice, but not spinach
Leclercq *et al.*, 1998, Belgium	Healthy, 6 M, 4 F; 26–55 y	Pre–post; fasting	Watercress 50 g	Single dose	Decreased CYP2E1 (chlorzoxazone)
Hecht *et al.*, 1999, USA	Healthy smokers, 5 M, 6 F; 24–48 y	Control–tx–control; supplementation of *Brassica*-restricted habitual diet	Watercress 170.4 g	3 d	Increased urinary glucuronides of cotinine and trans-3'-hydroxycotinine; no effect on oxidative metabolism of nicotine and cotinine
Lampe *et al.*, 2000b, USA	Healthy non-smokers, 19 M, 17 F; 20–40 y	Randomized crossover; controlled intervention	*Brassica* vegetables 436 g; allium veg. 190 g; apiaceous veg. 265 g	6 d each tx	*Brassica* increased and apiaceous decreased CYP1A2 compared with basal and allium diets; no effect on NAT2 and XO activities (caffeine)
Lampe *et al.*, 2000a, USA	Healthy non-smokers, 21 M, 22 F; 20–40 y	Crossover; controlled intervention	*Brassica* vegetables 436 g; allium veg. 190 g; apiaceous veg. 265 g	6 d each tx	Increased GST-α and GST activity with *Brassica* in GSTM1-null individuals; decreased GST-α with apiaceous in GSTM1+ men; increased GST-μ activity with *Brassica* and *Allium* in GSTM1+ women

Table 117 (contd)

Author, year, country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Persson *et al.*, 2000, China	Healthy non-smokers, 6 M; 20–30 y	Pre–post; supplementation of habitual diet	Mixed veg. (peppers, onions, white cabbage, carrots, peas, corn, and tomatoes) 250 g	3 wk	Decreased lymphocyte GSTP1 mRNA and protein
Murphy *et al.*, 2001, USA	Healthy non-smokers, 8 M, 7 F; 19–30 y	Pre–post; supplementation of restricted habitual diet	Watercress 170.4 g	2 d and breakfast on the third day	Marginal inhibition of CYP2A6 (coumarin)
Murray *et al.*, 2001, UK	Healthy non-smokers, 20 M; 22–46 y	Control–tx–control; supplementation of restricted habitual diet	Brussels sprouts 250 g and broccoli 250 g	12 d	Increased CYP1A2 (caffeine) and reduced urinary excretion of MeIQx and PhIP
van den Berg *et al.*, 2001, Netherlands	Healthy smokers, 22 M; 18–50 y	Crossover; supplementation of habitual diet	Vegetable burger (lyophilized tomatoes, carrots, onions, broccoli, sweet red pepper; equivalent of 500 g mixed fresh veg.) and mixed fruit drink (orange, apple, blueberry, lemon, lime) 330 mL	3 wk each tx	Decreased PBMC GSTπ; no effect on plasma GSTα or erythrocyte GSH or GSSG
Knize *et al.*, 2002, USA	Healthy non-smokers; 6; age NA	Control–tx–control; supplementation of restricted habitual diet	Broccoli 1 cup	3 d	Increased urinary excretion of PhIP metabolites in 5 of 6 subjects

CYP, cytochrome P450; GSH, reduced glutathione; GST, glutathione *S*-transferase; GSSG, oxidized glutathione; MeIQx, 2-amino-3,8-dimethylimidazo(4,5-*f*)quinoxaline; NAT, *N*-acetyltransferase; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; PhIP, 2-amino-1-methyl-6-phenyl-imidazo(4,5-*b*)pyridine; XO, xanthine oxidase

Table 118. Studies of effects of fruit and vegetable interventions on urinary mutagenicity in humans

Author, year, country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Sousa *et al.*, 1985, USA	Non-smokers, 3 M, 2 F; age N/A	Pre–post; restricted diet and fasting	Grape juice 1180 mL	Single dose	No effect on mutagenic activity of urine concentrates (in *S. typhimurium* TA98 and TA100)
Ohyama *et al.*, 1987a, Japan	Non-smokers, 3 M, 1 F; 25–42y	Control–tx1–control–tx2; controlled intervention	Tx1: fried salted sal-mon 120 g Tx2: fried salted salmon 120 g + cabbage 240 g	2 d per tx	No change in mutagenic activity of urine concentrate with cabbage (in *S. typhimurium* TA98, 100, 1535, 1538)
Ohyama *et al.*, 1987b, Japan	Healthy non-smokers, 3 M; 27–42 y	Tx1–tx2–controlled intervention	Tx 1: fried salmon 150 g. Tx 2: fried salmon 150 g + parsley 70 g	Single dose: tx 1 on d 1 and tx 2 on d 2	Decreased mutagenic activity of urine concentrate with parsley (*S. typhimurium* TA98)
DeMarini *et al.*, 1997, USA	Healthy non-smokers, 3 M, 5 F; 40–65 y	2-arm trial; controlled intervention	Tx1: fried meat + cruciferous veg. or Tx2: fried meat + non-cruciferous veg.	6 wk	Increased (non-signficant) conjugated urinary mutagenicity with cruciferous veg. (in *S. typhimurium* YG1024)
Murray *et al.*, 2001, UK	Healthy non-smokers, 20 M; 22–46 y	Control–tx–control; sup. of restricted habitual diet	Brussels sprouts 250 g and broccoli 250 g	12 d	Increased urinary mutagenicity with cruciferous veg. (in *S. typhimurium* YG1024)

Table 119. Studies of effects of fruit and vegetable interventions on other intermediate end-points in humans

Author, year, country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Steroid hormone metabolism					
Kall *et al.*, 1996, Denmark	Healthy, non-smokers, 2 M, 14F; 21–35 y	Control–tx1–tx2; supplementation of restricted habitual diet	Tx1: standard diet avoiding GST inducers Tx2: standard diet + broccoli 550 g	Tx 1: 6 d; Tx 2: 12 d	Increased urinary 2-OH-E1: 16α-OH-E1 ratio with broccoli
Fowke *et al.*, 2000, USA	Healthy post-menopausal, 34 F; 49–77 y	Pre–post; supplementation of habitual diet through counselling	*Brassica* vegetable up to 193 g	4 wk	Increased urinary 2-OH-E1: 16α-OH-E1 ratio
Tissue markers and clinical markers of cancer risk					
Schatzkin *et al.*, 2000, USA	1228 M, 677 F; one or more histologically-confirmed colorectal adenoma; >35 y	2-arm trial; modification of diet through counselling	20% energy from fat + dietary fibre 18 g/1000 kcal, + fruit and veg. 3.5 servings/1000 kcal	4 y	No difference in rate of recurrence of colorectal adenomas
Chen *et al.*, 2001b, USA	32 M; localized prostate adenocarcinoma; mean age 65.7 y	Pre–post; substitution in habitual diet	Tomato sauce 200 g incorporated into pasta dishes	3 wk	Decreased serum PSA levels
Immune function					
Kandil *et al.*, 1988	HIV+ men	2-arm trial; supplementation of habitual diet	0.5 g raw garlic/kg bw; 1800 mg garlic powder	3 wk	Enhanced NK cell activity
Watzl *et al.*, 1999, Germany	Healthy non-smokers, 23 M; 27–40 y	Non-randomized trial; supplementation to diet restricted in high carotenoid veg. and fruit	Tomato juice 330 mL; carrot juice 330 mL; spinach powder 10 g	8 wk: 2 wk per tx	Tomato juice consumption significantly enhanced IL-2 and IL-4 secretion compared to restricted diet. No change in lymphocyte proliferation
Watzl *et al.*, 2000, Germany	Healthy, 18 M, 32 F; 63–86 y	2-arm trial; supplementation to	Tomato juice 330 mL	8 wk	No change in: number or lytic activity of NK cells; IL-2 or –4 or TNF-α secretion by activated PBMC; lymphocyte proliferation; or delayed hypersensitivity skin response

Table 119 (contd)

Author, year country	Subjects; age (mean or range)	Study design	Daily dose of food/agent	Duration of intervention	Treatment outcomes
Antibacterial activity					
Aydin *et al.*, 1997, Turkey	*H. pylori*-positive dyspeptic patients, 5 M, 15 F; 21–61 y	2-arm trial; supplementation of habitual diet	Garlic oil 275 mg capsules (800 μg allicin) 3 times or garlic-oil capsules 3 times + omeprazole 20 mg 2 times	2 wk	No change in grade of gastritis or *H. pylori*-positivity (gastric mucosal urease test)
Graham *et al.*, 1999, USA	Healthy, 7 M, 5 F, proven *H. pylori* infection; 18–75 y	Crossover; controlled test meals	Tx1: fresh garlic (10 sliced cloves);Tx2: capsaicin (6 sliced fresh jalapenos peppers); Tx3 (+ control): bismuth subsalicylate 2 tablets	1 meal per tx	No effect of garlic or capsaicin on *H. pylori* (urea breath test)
McNulty *et al.*, 2001, UK	Dyspeptic patients with positive serology for *H. pylori*, 5; 18–75 y	Pre–post; supplementation of habitual diet	Garlic oil (4 mg) capsule 4 times	14 d	No eradication or suppression of *H. pylori* (urea breath test) or symptom improvement
Other biomarkers					
Ross *et al.*, 1995, USA	Healthy, 19 M, F, ages N/A	Crossover; controlled intervention	Carrot coins 165 g + carrot puree 125 g + chopped spinach 250 g; broccoli 390 g + cauliflower 300 g; tofu and textured vegetable protein product 45 g	9 d each tx	No effect of vegetable tx on PDGF and mitogenic activity
Jenkins *et al.*, 2001, Canada	Healthy, 8 M, 2 F; 24–60 y	Crossover; controlled intervention	Tx1: high-fruit and veg. diet (63 servings/2500 kcal diet); Tx2: starch-based diet (11 servings of fruit and veg.) Tx3: low-saturated fat diet (5 servings of fruit and veg.)	2 wk each tx	High-fruit and veg. diet resulted in: greatest faecal bile acid output, faecal bulk, and faecal short-chain fatty acid outputs; lowest concentrations of faecal bile acids; and increased urinary mevalonic acid excretion

bw, body weight; E1, estrone; IL, interleukin; NK, natural killer; PBMC, peripheral blood mononuclear cells; PDGF, platelet-derived growth factor; PSA, prostate-specific antigen; TNF, tumour necrosis factor

markers: number or lytic activity of natural killer (NK) cells, IL-2, IL-4 and tumour necrosis factor (TNF)-α secretion by activated mononuclear cells, lymphocyte proliferation or delayed hypersensitivity skin response (Watzl *et al.*, 2000). One small study using garlic suggested that natural killer (NK) cell activity can be increased in immunocompromised individuals (e.g., human immunodeficiency virus (HIV)-positive patients) (Kandil *et al.*, 1988).

Antibacterial activity

Garlic has received attention as a potential antibacterial agent, particularly in the treatment of *Helicobacter pylori* infection. This Allium vegetable has long been used as an antibiotic, antiviral and antifungal agent and in countries where modern medicines are scarce, it remains a treatment for various infections (Reuter *et al.*, 1996); however, few clinical interventions have been conducted to test its efficacy. Three studies using garlic or garlic oil have been unsuccessful in eradicating existing *H. pylori* infection or associated gastrointestinal symptoms (Aydin *et al.*, 1997; Graham *et al.*, 1999; McNulty *et al.*, 2001). These studies were small and of short duration – from a single meal up to two weeks – possibly not long enough to assess therapeutic efficacy (Mahady & Pendland, 2000).

Observational studies

Some biomarkers have been determined as part of case–control studies in order to evaluate possible carcinogenic mechanisms in relation to the observed cases.

Hemminki *et al.* (2002) investigated whether high consumption of fruit and vegetables can reduce mutations in the *von Hippel-Lindau* (*VHL*) gene, a gatekeeper gene for renal-cell cancer. Somatic *VHL* mutations appear to be associated with some 50% of sporadic renal-cell cancer (Gnarra *et al.*, 1994; Prowse *et al.*, 1997; Yang *et al.*, 1999; Brauch *et al.*, 2000). In a molecular epidemiological sub-study of 102 Swedish patients with renal-cell cancer, within a previously reported case–control study (Lindblad *et al.*, 1997), consumption of total fruits was not associated with mutation, but consumption of citrus fruit (≥ 421 versus < 421 g/mo) was protective against mutation in both smokers and all subjects. Among smokers, vegetable intake (> 1039 versus < 1039 g/mo) also was significantly protective (Hemminki *et al.*, 2002).

In a study on total aromatic DNA adducts in human white blood cells (Peluso *et al.*, 2000), among 162 bladder cancer cases and 104 hospital controls, high consumption of fruit and vegetables during the previous 24 h decreased the strength of the association between adducts and the risk for bladder cancer: for vegetables, OR for 0–1 servings: 7.80, 95% CI 3.00–20.30; OR for two servings: 4.98; 95% CI 1.56–15.92; OR for 3 servings: 1.97 95% CI 0.48–8.02). In a study on 4-aminobiphenyl–DNA adducts in bladder biopsies, high consumption of fruit and vegetables was non-significantly associated with lower levels of adducts (Airoldi *et al.*, 2002).

In approximately 100 volunteers in Italy, a strong inverse association between lymphocyte bulky DNA adducts and frequency of consumption of fresh fruit (p for trend = 0.04) and vegetables (p for trend = 0.01) was reported (Palli *et al.*, 2000). Also in Italy, oxidative DNA damage, measured by comet assay with formamidopyrimidine DNA glycosylase in lymphocytes from 71 healthy adults, was inversely associated with tomato consumption (p for trend = 0.05) (Giovannelli *et al.*, 2002). Regarding DNA adducts derived from lipid peroxidation products, levels of 1,N^6-ethenodeoxyadenosine in white blood cells were inversely correlated with vegetable consumption (p = 0.02) among 42 healthy female volunteers (Hagenlocher *et al.*, 2001) and levels of malondialdehyde-deoxyguanosine were inversely, although non-significantly, associated with fruit and salad consumption in colorectal biopsies from normal mucosa in men (Leuratti *et al.*, 2002).

Experimental studies

Animal studies

The review in this section covers studies on the effects of fruit and vegetables administered individually or in combination during the initiation stage of carcinogenesis (just before and during the carcinogen treatment), during the post-initiation and progression stages (after carcinogen treatment until the end of the study) and during the initiation, post-initiation and progression stages (Table 120). Also, the effects of mixtures of fruit and vegetables on intestinal tumours in transgenic mouse models are reviewed. As elsewhere in this volume, fruit and vegetables are taken to include edible plant foods, excluding cereal grains, nuts, seeds, dried beans, starchy roots, spices and products used mainly as infusions.

Both cereal-based and semi-purified diets have been used in studies of the effects of diet on carcinogenesis. Cereal-based diets include the dietary ingredients from whole-grain cereals and protein-rich foods. Semi-purified diets include defined ingredients such as casein, soybean protein, starch, sucrose and vitamins. Semi-purified diets have the advantage that each component can be modulated independently of the others in a controlled manner.

Effects on spontaneous tumours

The influence of dietary factors such as total composition, thermal pro-

Table 120. Effect of vegetables, fruits, berries or their extracts on carcinogenesis in experimental animals

Organ, species, strain (sex)	Age at beginning of study	No. of animals per group	Carcinogen (dose, route, duration)	Vegetables, fruit, berries, or their extract (dose)	Treatment (route, and duration duration of study*)	Preventive effect	Reference
Numerous[a]							
Rat							
Wistar (M + F)	4	50	None (spontaneous tumours)	19.5% fruit and veg. mixture added to animal diet or to a human diet composed of meat, bread and eggs (raw or cooked)	Fed *ad libitum* for 142 wks	No effect on tumour incidence	Alink *et al.* (1989)
Oral cavity							
Hamster							
Syrian golden (sex not specified)	Not reported	5–8	0.5% DMBA painted on buccal pouches, 3/wk, 10 wk	Ground garlic, 10% in diet	Fed for 8 wk beginning 1 wk before DMBA treatment; control diet for 18 wk (initiation)	Reduced multiplicity and volume of tumours per pouch (S)	Shyu & Meng (1987)
Syrian golden (sex not specified)	Not reported	5–8	0.5% DMBA painted on buccal pouches, 3/wk, 10 wk	Garlic extract, 0.5, 25 or 50% in mineral oil	Applied topically to buccal pouches 3/wk for 3 wk starting 14 wk before DMBA treatment; experiment terminated at wk 30	Increased latency of tumour appearance in all treated groups; reduced tumour multiplicity and volume in animals treated with 25 and 50% garlic extract (all S)	Meng & Shyu (1990)
Syrian golden (M)	4–5	15	0.2% DMBA painted on buccal pouches 3/wk, 8 wk	Lyophilized black raspberries, 5 or 10% in diet	Fed for 12–13 wk starting 2 wk before DMBA treatment	No effect on size or incidence; reduced tumour multiplicity (S) in animals fed 5% berries	Casto *et al.*, (2002)
Oesophagus							
Rat							
Fischer 344 (M)	5–6	15	NMBA, 0.25 mg/kg s.c., 1/wk, 15 wk	Freeze-dried strawberries, 5 or 10% in diet	Fed for 32 wk starting 2 wk before NMBA treatment	No effect on tumour incidence; reduced tumour multiplicity (papillomas) (S)	Stoner *et al.*, (1999)
			NMBA, 0.5 mg/kg s.c., 3/wk, 5 wk	Freeze-dried strawberries, 5 or 10% in diet	Fed for 25 wk starting 24 h after last NMBA dose	Reduced tumour multiplicity (S)	Carlton *et al.* (2001)

Table 120 (contd)

Organ, species, strain (sex)	Age at beginning of study	No. of animals per group	Carcinogen (dose, route, duration)	Vegetables, fruit, berries, or their extract (dose)	Treatment (route, and duration; duration of study*)	Preventive effect	Reference
Fischer 344 (M)	7–8	15	NMBA, 0.25 mg/kg s.c., 1/wk, 15 wk	Lyophilized black raspberries, 5 or 10% in diet	Fed for 30 wk starting 2 wk before NMBA treatment	Reduced tumour multiplicity (S)	Kresty *et al.*, (2001)
	5–8	8–15	NMBA, 0.25 mg/kg s.c., 3/wk, 5 wk	Lyophilized black raspberries, 5 or 10% in diet	Fed for 15, 25, 35 wk starting 3 d after last NMBA dose	Decreased tumour incidence and multiplicity and high-grade dysplasia after 25 wk with both treatments (all S)	
Fischer 344 (M)	6–7	10–25	NMBA, 0.25 mg/kg s.c., 1/wk, 15 wk	Freeze-dried blueberries, 5 or 10% in diet	Fed for 25 wk starting 2 wk before NMBA treatment	No effect on incidence, size or multiplicity	Aziz *et al.*, (2002)
Colon							
Mouse							
Swiss ICR (M+F)	5–7	14–17	DMH, 23–56 mg/kg s.c., 1/wk, 7 wk, (total dose 320 mg/kg)	Fresh cabbage, 13% in diet	Fed for 21.5 wk starting 31 d before DMH treatment	Slight increase in tumour incidence in females (NS)	Temple & El-Khatib (1987)
Swiss ICR (F)	5–7	20–40	DMH 17–65 mg/kg s.c., 1/wk 8 wk (total dose, 291 mg/kg)	Fresh cabbage, 13% in diet	(*a*) Fed beginning 5 wk before DMH treatment until 3 d after last DMH dose (initiation); control diet for 19.5 wk (*b*) Fed for 19.5 wk beginning 3 d after last DMH dose (promotion)	(*a*) Slight increase in tumour incidence (NS) (*b*) Reduction in tumour multiplicity (S)	Temple & Basu (1987)
Apc^{Min} mice (M + F)	Weanlings	14–17	None (spontaneous tumours)	Low- or high-fat diet with 19.5 or 22.3% freeze-dried fruit-veg. mixture, respectively	Exposure *in utero* until around day 90 of life	Inhibited multiplicity of intestinal polys in M fed low-fat (S). Increased multiplicity of intestinal polyps in M and F fed high-fat diet (S)	Van Kranen *et al.*, (1998)

Table 120 (contd)

Organ, species, strain (sex)	Age at beginning of study	No. of animals per group	Carcinogen (dose, route, duration)	Vegetables, fruit, berries, or their extract (dose)	Treatment (route, and duration; duration of study*)	Preventive effect	Reference
Rat							
Wistar (M)	4	36–43	DMH, 50 mg/kg s.c., 1 wk, 10 wk	19.5% fruit and veg. mixture added to animal diet or to a human diet composed of meat, bread and eggs (raw or cooked)	Fed for 8 months starting 4 wk before DMH treatment	Reduction in polypoid adenomas in animals fed animal diet (S); increase in adenocarcinomas in animals fed human diet(s)	Alink *et al.* (1993)
Wistar (M)	5	30	DMH, 50 mg/kg, s.c., 1/wk, 10 wk	Low- or high-fat diet containing 19.5% fruit-veg. mixture	Fed for up to 35 wk beginning 4 wk before DMH treatment	Slight decrease in incidence of colorectal adenomas with low- or high-fat diet (NS)	Rjinkels *et al.*, (1997a,b)
Wistar (M)	5	30	MNNG, 6 mg/kg, intrarectally, 1wk, 5 wks	Low- or high-fat diet containing 19.5% fruit-veg. mixture	Fed for 35 wk starting 4 wk before MNNG treatment	Reduced incicidence of colon adenocarcinomas in animals fed high-fat diet	Rijnkels *et al.* (1997c)
Fischer 344 (M)	5	30	AOM, 15 mg/kg bw, s.c., 1/wk, 3 wk	Low- or high-fat diet containing 19.5% fruit-veg. mixture	(*a*) Fed for 8 wk beginnning 4 wk before AOM treatment, control diet for 28 wk (initiation) (*b*) Fed for 2 wk starting 2 wk after last AOM dose (promotion)	No effect on colon carcinogenesis	Rjinkels *et al.*, (1998)
Fischer 344/NSIc (F)	7	24–25	MNU, 0.5 mL of 0.4% or 0.8%, intrarectally, 3/wk, 3 wk	Tomato juice diluted 1:2 or 1:14 (17 or 3.4 ppm lycopene) in drinking water	Given for 35 wk starting together with MNU treatment	Reduced colon incidence and multiplicity in animals given tomato juice diluted 1:2 (S)	Narisawa (1998)
Fischer 344 (M)	3	30	AOM, 15mg/kg, s.c., 1/wk, 2 wk	Orange juice in place of drinking water	Given for 28 wk beginning 1 wk after last AOM (post-initiation)	Reduced colon tumour incidence (S)	Miyagi *et al.* (2000)

Table 120 (contd)

Organ, species, strain (sex)	Age at beginning of study	No. of animals per group	Carcinogen (dose, route, duration)	Vegetables, fruit, berries, or their extract (dose)	Treatment (route, and duration; duration of study*)	Preventive effect	Reference
Fischer 344 (M)	7	20–29	AOM, 20 mg/kg, s.c., 1/wk, 2 wk	Mandarin juice in drinking-water at night	Given for 36 wk beginning 1 wk after last AOM dose (post-initiation)	Reduced incidence and multiplicity of colon adenocarcinoma (S)	Tanaka *et al.*, (2000)
Sprague-Dawley (sex not specified)	5	30–42	DMH, 20 mg/kg 1/wk, 6 wk (route not specified)	Orange pulp, 15% in diet	Fed for 8 months starting together with DMH treatment	Colon adenocarcinoma incidence not affected; decreased incidence of endophytic adenocarcinomas (S); increased incidence of exophytic adenocarcinomas (S)	Kossoy *et al.*, (2001)
Fischer 344 (M)	8–9	18	AOM 15 mg/kg i.p. 1/wk, 2 wk	Lyophilized black raspberries, 2.5, 5 or 10% in diet	Starting 24 h after last AOM dose; 9 wk for aberrant crypt foci and for 33 wk for tumours	Decreased total tumour multiplicity (all S); decreased multiplicity of adenocarcinoma (S for 10% raspberry group) and of aberrant cryptfoci (all S)	Harris *et al.*, (2001)
Liver							
Rat							
Fischer 344 (M)	Weanling	8–11	1 ppm AFB_1 in the diet for 26 wk	Freeze-dried ground beets or cabbage, 25% in diet	Fed together with carcinogen for 26 wk; control diet for 16 wk	Decreased tumour incidence with cabbage (S); increased incidence and size with beet (S)	Boyd *et al.*, (1982)
Sprague-Dawley (M)	8	25	NDEA in drinking water for 10 wk (total dose, 500 mg/kg bw)	120 or 160 g carrots 4 or 5 d/wk, respectively, without any other diet	Fed together with carcinogen for at least 14 wk	Delayed tumour occurrence and prolonged survival (S)	Rieder *et al.* (1983)
	16	30	NDEA, i.p., 1/wk, 8 wk (total dose, 400 mg/kg bw)	160 g carrots/wk, 5 d/wk without any other diet	Fed for 14 wk Starting 2 wk before NDEA treatment	Delayed appearance of tumours and prolonged survival (S)	

Table 120 (contd)

Organ, species, strain (sex)	Age at beginning of study	No. of animals per group	Carcinogen (dose, route, duration)	Vegetables, fruit, berries, or their extract (dose)	Treatment (route, and duration; duration of study*)	Preventive effect	Reference
Toad							
Bufo viridis (M + F)	Sexually mature	50 M, 50 F	DMBA, 0.5 mg/ toad, into dorsal lymph sac, 3/wk, 12 wk	Ground cabbage solution, 1 or 2 mL/day	Fed for 12 wk starting 3 h before or 3 h after DMBA treatment for 3 months	Reduced tumour incidence in animals treated before DMBA administration (S); no effect after DMBA administration	Sadek *et al.* (1995)
Lung							
Mouse							
A/J sex not specified)	5–6	20	NNK, 0.414 mg x 5 i.p or B[a]P 0.2 mg x 5 by gavage, over 2 wk	Freeze-dried strawberries, 10% in diet	Fed for 20 wk or 24 wk starting 1 wk before NNK or B[a]P treatment, respectively	No effect on incidence or multiplicity of lung tumours	Carlton *et al.* (2000)
A/J (M)	7	20–23	NNK, 10 μmol per mouse, i.p. single dose	Mandarin juice in place of drinking water at night	Given for 21 wk starting 1 wk after NNK injection (post-initiation)	No effect on lung tumour incidence or multiplicity or on alveolar cell hyperplasia	Kohno *et al.* (2001)
Skin							
Mouse							
Swiss albino (F)	4–5	25	1% DMBA (topical) (3x), followed by croton oil 2/wk, 2 months	Bitter gourd extract, 5% in water	50 μL/mouse/day, 12 wk, orally, starting together with DMBA-croton oil treatment	Skin papilloma incidence decreased (S); no effect on multiplicity	Ganguly *et al.* (2000)
Mammary gland							
Rat							
Sprague-Dawley (F)	5	15	DMBA, 60 mg/ kg, orally, single dose	Freeze-dried Brussels sprouts, 20% in diet	For 4 wk beginning 2 wk before DMBA treatment; control diet for 48 wk (initiation)	Reduced incidence of mammary tumours 15 wk after dosing and of adenocarcinomas 50 wk after dosing (S)	Stoewsand *et al.*, (1988)

Table 120 (contd)

Organ, species, strain (sex)	Age at beginning of study	No. of animals per group	Carcinogen (dose, route, duration)	Vegetables, fruit, berries, or their extract (dose)	Treatment (route, and duration; duration of study*)	Preventive effect	Reference
Sprague-Dawley (F)	4	16–20	DMBA, 50 mg/kg, orally, single dose	Freeze-dried Brussels sprouts, 20% in diet	For 4 wk beginning 2 wk before DMBA treatment; control diet for 25 wk (initiation)	Slightly reduced incidence and multiplicity of papillary carcinomas and adeno-carcinomas (NS)	Stoewsand *et al.* (1989)
Sprague-Dawley (F)	7	25–35	MNU, 50 mg/kg, i.v., single dose	5% or 10% dried cabbage, or 3.2% extracted residue, or 5% dried collards in low-fat diet; 5% cabbage or 5% collards in high-fat diet	Fed for up to 24 wk directly following MNU treatment	Low-fat diet containing 5% cabbage or cabbage residue inhibited mammary carcinogenesis (S); no effect with high-fat diet	Bresnick *et al.* (1990)
Sprague-Dawley (F)	6	20	DMBA, 25 mg/kg, orally, single dose	Garlic powder, 1, 2 or 4% in diet	(*a*) For 4 wk starting 2 wk before DMBA treatment; control diet for 20 wk (initiation) (*b*) Fed 2% garlic diet continuously for 24 wk* (initiation and post-initiation)	(*a*) inhibited tumour incidence and multiplicity in animals treated with 4% garlic (S) (*b*) Suppressed tumour incidence and multiplicity (S)	Liu *et al.*, (1992)
Sprague-Dawley (F)	6	25	DMBA, 10 mg, intragastric, single dose	Garlic powder, 2% in diet	(*a*) Fed for 3 wk starting 2 wk before DMBA treatment (initiation) (b) Fed continuously for 26 wk (initiation and post-intiation)	(*a*) Slight reduction in tumour incidence and multiplicity (NS) (*b*) Inhibited tumour incidence and multiplicity (S)	Ip *et al.* (1992)
Sprague-Dawley (F)	6	21	MNU, 15 mg/kg i.p., single dose	Garlic powder, 2% in diet	For 27 wk beginning 14 d before MNU treatment	Reduced incidence and multiplicity of mammary tumours (S)	Schaffer *et al.* (1996)

Table 120 (contd)

Organ, species, strain (sex)	Age at beginning of study	No. of animals per group	Carcinogen (dose, route, duration)	Vegetables, fruit, berries, or their extract (dose)	Treatment (route, and duration; duration of study*)	Preventive effect	Reference
Sprague-Dawley (F)	6	26	DMBA, 50 mg/kg, orally, single dose	Freeze-dried bitter gourds, 6.25 or 12.5% in diet	Fed for 3 wk beginning 2 wk before DMBA treatment; control diet for 24 wk initiation	Both diets reduced multiplicity of mammary tumours (S); no effect on incidence	Kusamran *et al.* (1999a)
Uterine cervix							
Mouse							
Swiss albino (F)	8–10	25–30	3-MC, 600 µg into uterine cervix canal by laparotomy	Ground garlic in water, 400 mg/kg/d, orally	For 6 wk beginning 2 wk before 3-MC thread insertion; experiment ended after 14 wk	Reduced incidence of squamous cell carcinoma (S); no effect on hyperplasia or dysplasia	Hussain *et al.* (1990)
Bladder							
Mouse							
C3H/HeN (F)	Age not reported	20	10^3 MBT2 bladder cancer cells in 0.1 mL culture medium s.c., into right thigh	Garlic extract, 5, 50 and 500 mg garlic/100mL in drinking water	Given for 53 or 65 d beginning 1 month before MDT2 tumour transplantation	Dose-dependent decrease in tumour volume with 50 and 500 mg mg garlic extract (S)	Riggs *et al.* (1997)
Rat							
Fischer 344 (M)	6	24	BBN, 0.05% in drinking water for 8 wk	Tomato juice diluted 1:4 in drinking water (25 ppm lycopene)	For 12 wk starting directly after BBN treatment	Decreased multiplicity of transitional-cell carcinomas (S); no effect on incidence	Okajima *et al.* (1998)

AFB_1, aflatoxin B_1; AOM, azoxymethane; B[a]P, benzo[a]pyrene; BBN, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMH, 1,2-dimethylhydrazine; i.p., intraperitoneal; 3-MC, 3-methylcholanthrene; MNNG, *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine; MNU, *N*-methyl-*N*-nitrosourea; NDEA: *N*-nitrosodiethylamine; NMBA: *N*-nitrosomethylbenzylamine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NS, not significant; p.c., percutaneous; S, significant, s.c., subcutaneous

[a] Abdominal cavity, adrenal glands, bone, brain, haemotopoietic system, liver, mammary glands, ovaries, pancreas, pituitary gland, skin, soft tissues, thymus, thyroid, uterus, other sites

*When study continued beyond last carcinogen or fruit/vegetable treatment. The number of weeks is counted from the beginning of the study (and not from beginning of carcinogen treatment).

cessing and the presence of fruit and vegetables on tumour incidence was studied in a long-term experiment in rats (Alink *et al.*, 1989). Groups of 50 male and 50 female Wistar rats were fed one of the following diets: a semi-purified animal diet (A, control); diet A in which fruit and vegetables replaced macro- and micronutrients (B); an uncooked human diet (meat, bread and eggs) supplemented with semi-purified micronutrients (C); diet C with fried or baked products (D); or a complete human diet consisting of cooked products, fruit and vegetables (E). Diets B, C, D and E were prepared according to mean dietary composition figures for the Netherlands. The animal diets contained 21.6% energy fat and the human diets contained 40.6% energy fat. Rats were fed *ad libitum* for 142 weeks. Male but not female rats fed the human diets (C, D or E) had a significantly higher incidence of epithelial tumours ($p < 0.02$) than those fed the animal diets (A or B), mainly accounted for by tumours of the pituitary and thyroid glands. Compared with the uncooked human diet (diet C), frying and baking of food products (diet D) and the addition of fruit and vegetables (diet E) induced minor, non-significant differences in the tumour incidence in over 20 tissues examined.

Effects on carcinogen-induced tumours

Oral cavity

Hamster

Shyu & Meng (1987) studied the inhibitory effect of garlic (*Allium sativum*) administered during the initiation stage of carcinogenesis induced by 7,12-dimethylbenz[*a*]anthracene (referred to as 9,10-dimethyl-1,2-benzanthracene; DMBA) in the buccal pouch of hamsters. Groups of 5–8 Syrian golden hamsters [age and sex not reported] received a diet containing 10% (w/w) peeled and ground garlic for eight weeks. Painting of 0.5% DMBA on the buccal pouches began in the second week, three times per week for 10 weeks. Animals were killed after 26 weeks. Garlic administration significantly reduced the number and total volume of DMBA-induced tumours per buccal pouch three- and four-fold, respectively [values read from diagrams].

In another study (Meng & Shyu, 1990), groups of 5–8 golden Syrian hamsters [age and sex not specified] were painted with 0.5, 25 or 50% garlic extract in mineral oil three times per week for three weeks and, after a lag period of 11 weeks, with 0.5% DMBA on the right pouch three times per week for 10 weeks. The animals were killed at week 30. Garlic extract treatment increased the latency period of tumour appearance in DMBA-treated animals (8–10 weeks after DMBA painting versus six weeks in controls). The numbers of tumours per pouch in animals treated with DMBA alone and with 25% and 50% garlic extract were 4.6, 1.1 and 1.4, respectively ($p = 0.01$ and 0.003, respectively). The average tumour volume per pouch was also significantly reduced in animals treated with 25% and 50% garlic extract (26.5 and 7.8 mm^3, respectively, versus 72.6 mm^3; $p < 0.01$). [The Working Group noted that the effect could be either local or systemic.]

The ability of black raspberries (*Rubus occidentalis*) of the Jewel variety to inhibit DMBA-induced tumorigenesis in the hamster cheek pouch was evaluated (Casto *et al.*, 2002). Male Syrian golden hamsters, 4–5 weeks of age, were fed 0, 5 or 10% freeze-dried black raspberries in AIN-76A diet for 12 weeks. The concentration of corn starch was adjusted to maintain an isocaloric diet among all groups. Beginning after two weeks, hamster cheek pouches were painted with 0.2% DMBA in dimethylsulfoxide (DMSO) three times per week for eight weeks. The animals were killed after 12–13 weeks and the number and volume of tumours determined. There was no difference in tumour size or incidence between groups. Treatment with 5% but not 10% raspberries resulted in a significant reduction in the multiplicity of tumours relative to DMBA controls (1.9 versus 3.2 tumours per animal; $p = 0.02$). [The Working Group noted inconsistencies between the text and table for the duration of treatment].

Oesophagus

Rat

The effect of strawberries (*Fragaria ananassa*) of the Commander variety on *N*-nitrosomethylbenzylamine (NMBA)-induced tumorigenesis in the oesophagus of male Fischer 344 rats was examined. In a first experiment (Stoner *et al.*, 1999), 5–6-week-old rats (15 animals per group) were placed on AIN-76A diet or a diet containing 5 or 10% freeze-dried strawberries and were maintained on these diets for the duration of the study. The energy content of the berry diets was maintained by appropriately reducing the corn starch content. From two weeks after diet initiation, rats were given a subcutaneous injection of NMBA (0.25 mg/kg bw) once per week for 15 weeks. Controls received either the vehicle (20% DMSO in water) or a diet containing 10% freeze-dried strawberries. Thirty weeks after initiation of NMBA treatment, the rats were killed and oesophageal tumours (papillomas) counted. The 5 and 10% strawberry diets had no effect on tumour incidence but reduced oesophageal tumour multiplicity by 24% ($p < 0.05$) and 56% ($p < 0.01$), respectively, relative to NMBA controls. In addition, both strawberry diets significantly reduced the incidence of lesions classified as dysplastic leukoplakia ($p < 0.05$), while significantly increasing that of lesions classified as simple leukoplakia ($p < 0.05$). In a post-initiation experiment (Carlton *et*

al., 2001), rats were fed AIN-76A diet and given subcutaneous injections of NMBA (0.5 mg/kg bw) three times per week for five weeks. Immediately after NMBA treatment, animals were placed on control diet or a diet containing 5 or 10% strawberries. The 5 and 10% strawberry diets reduced oesophageal tumour multiplicity at 25 weeks by 38 and 31%, respectively. Both reductions were statistically significant ($p < 0.05$), although there was not a significant dose–response relationship. [The Working Group noted discrepancies between the text and figure for the treatment regimen.]

Their ability of black raspberries of the Driscol and Bristol varieties to inhibit NMBA-induced tumorigenesis in the rat oesophagus was evaluated in both initiation and post-initiation bioassays (Kresty *et al.*, 2001). Groups of 15 male Fischer 344 rats, 7–8 weeks old, were given AIN-76A diet or AIN-76A diet containing 5 or 10% freeze-dried black raspberries. The energy content of the berry diets was maintained by appropriately reducing the corn starch content. Animals were maintained on their respective diets throughout the 30-week study. Starting two weeks after initiation of the experimental diets, rats were given subcutaneous injections of NMBA (0.25 mg/kg bw) once per week for 15 weeks. Controls received either the vehicle (20% DMSO in water) or a diet containing 10% black raspberries. At 30 weeks, the animals were killed and oesophageal papillomas counted. Control animals had no tumours. Feeding 5 and 10% black raspberries significantly reduced the multiplicity of NMBA-induced oesophageal tumours by 39 and 49%, respectively ($p < 0.05$). In a post-initiation bioassay, black raspberries were administered in the diet at 5 and 10% after completion of NMBA treatment. Animals were given subcutaneous injections of NMBA (0.25 mg/kg bw) three times per week for five weeks and maintained on their respective diets until killed at 15, 25 or 35 weeks of the study. Both 5 and 10% black raspberry diets reduced tumour incidence at 25 weeks by 54 and 46%, respectively, tumour multiplicity by 62 and 43%, respectively, and high-grade dysplastic lesions by 43 and 32%, respectively. After 35 weeks, similar significant reductions were seen only with the diet containing 5% black raspberries.

The effect of blueberries (*Vaccinium corymbosum*) of the Rubel variety on NMBA-induced tumorigenesis in the rat oesophagus was investigated (Aziz *et al.*, 2002). Male Fischer 344 rats, 6–7 weeks old, were placed on AIN-76A diet or AIN-76A diets containing 5 or 10% freeze-dried blueberries. The energy content of the berry diets was maintained by appropriately reducing the corn starch content. Animals were maintained on the respective diets throughout the study. Two weeks after initiation of the experimental diets, three groups of rats (25 animals per group) were given subcutaneous injections of NMBA (0.25 mg/kg bw) once per week for 15 weeks. Control groups received either the vehicle (20% DMSO in water) or a diet containing 10% blueberries only. At 25 weeks, the rats were killed and oesophageal tumours were counted and sized. There were no significant differences in tumour incidence, multiplicity or size in berry-fed animals versus animals treated with NMBA only. The authors concluded that the lack of tumour-inhibitory effect of blueberries, in contrast to that of strawberries and black raspberries under similar conditions, might be explained, at least in part, by their relatively low content of ellagic acid.

Colon

Mouse

Mice were treated with 1,2-dimethylhydrazine (DMH) to induce colon tumours and fed cabbage during the initiation and/or post-initiation periods (Temple & El-Khatib, 1987; Temple & Basu, 1987). In the first study, groups of 14–17 male and female Swiss ICR mice, aged 5–7 weeks, were fed control diet or a diet containing 13% cabbage throughout the study. After 31 days, the mice received weekly subcutaneous injections of DMH at gradually increased doses of 23–56 mg/kg bw for seven weeks. All animals were killed 17 weeks after the first dose of DMH. Feeding of the cabbage diet had no significant effect on colon tumour incidence or multiplicity (Temple & El-Khatib, 1987). In the second experiment, cabbage was fed (*a*) starting five weeks before the first injection of DMH until three days after the last (initiation period) or (*b*) starting three days after the first DMH injection for 19.5 weeks (promotion period). DMH was injected once weekly for eight weeks at doses increasing from 17 to 65 mg/kg bw. Feeding of cabbage during the initiation period led to a modest increase in incidence of adenocarcinomas. In contrast, the incidence of adenomas was reduced by 30% and multiplicity by 50% ($p < 0.05$) when cabbage was given during the promotion period (Temple & Basu, 1987).

Van Kranen *et al.* (1998) evaluated the effect on intestinal neoplasia of the amount of dietary fat and a fruit–vegetable mixture. Groups of 14–17 male and female weanling Apc^{Min} mice, a model for multiple intestinal neoplasia, were fed a low-fat (20% fat energy) or a high-fat (40% fat energy) diet with or without a freeze-dried fruit–vegetable mixture (19.5 and 22.3% w/w, respectively). The choice of fruits and vegetables was based on the mean fruit and vegetable consumption in The Netherlands. The composition of the high-fat diets was adjusted to allow for decreased food consumption in these groups. Because of the early onset of tumours in these mice, exposure to the

diets was started *in utero* and continued until around day 90 after birth. The fruit–vegetable mixture added to the low-fat diet significantly lowered the multiplicity of polyps in the small intestine (from 16.2 to 10.2 per mouse) but not in the colon, in male mice only. Surprisingly, the multiplicity of intestinal polyps was significantly increased in both male and female mice on the high-fat diet containing fruit–vegetable mixture (from 16.5 to 26.8 polyps per mouse on average).

Rat

Alink *et al.* (1993) studied the modulating effect of heat processing and of addition of fruit and vegetables to human diets on DMH-induced colon tumours in male Wistar rats. The same diets as in the chronic study were used, which included 19.5% of fruit and vegetable mixture (Alink *et al.*, 1989; see Effects on spontaneous tumours above). These diets were fed throughout the study. After four weeks, each rat was given one weekly subcutaneous injection of DMH (50 mg/kg bw) for 10 weeks. Animals were killed after eight months. A lower multiplicity of polypoid adenomas was found in rats consuming the animal diet with fruit and vegetables compared with the control animal diet (1.4 versus 2.6; $p < 0.01$). In contrast, adding fruit and vegetables to the fried or baked human diet increased the multiplicity of adenocarcinomas (2.9 versus 2.1; $p < 0.05$). The authors hypothesized that this might be due to an interaction between fat and non-nutrient components of the fruit and vegetables.

In a further experiment, the effect of low- and high-fat diets in combination with a fruit–vegetable mixture on DMH-induced colon carcinogenesis was studied (Rijnkels *et al.*, 1997a, b). Groups of 30 five-week-old male Wistar rats were maintained on low-fat (20% fat energy) or high-fat (40% fat energy) diets with or without 19.5% of fruit–vegetable mixture. After four weeks, each rat was given one weekly subcutaneous injection of DMH (50 mg/kg bw) for 10 weeks. The experiment was terminated 35 weeks after initiation of the diet regimen. The fruit–vegetable mixture added to either the low-fat or the high-fat diet induced a non-significant decrease in the number of adenomas.

The effect of a fruit–vegetable mixture on *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)-induced colon carcinogenesis was studied in male Wistar rats (Rijnkels *et al.*, 1997c). Groups of 30 five-week-old rats were fed low-fat or high-fat semi-purified diets with or without 19.5% of a fruit–vegetable mixture. After four weeks, all animals were given weekly intrarectal instillations of MNNG (6 mg/kg bw) for five weeks. After 35 weeks, all animals were killed and colon tumours were evaluated histopathologically. The fruit–vegetable mixture significantly reduced the development of colon adenocarcinomas ($p < 0.01$) when added to the high-fat diet, but not when added to the low-fat diet.

The effects of a fruit–vegetable mixture administered during the initiation and promotion stages of azoxymethane (AOM)-induced colon carcinogenesis were studied in rats (Rijnkels *et al.*, 1998). Groups of 30 five-week-old male Fischer 344 rats were fed semi-purified low-fat (20% fat energy) or high-fat (40% fat energy) diets with or without 19.5% of fruit–vegetable mixture. Four weeks after initiation of the experiment, all animals were given three weekly subcutaneous injections of AOM (15 mg/kg bw). Eight weeks after the start of the study, animals on control diets were switched to the corresponding diet supplemented with a fruit–vegetable mixture and those on the fruit–vegetable diets were switched to the corresponding control diet, in both cases until 36 weeks from the beginning of the experiment. The fruit–vegetable mixture administered during either the initiation or the post-initiation stage had no effect on AOM-induced colon carcinogenesis, irrespective of the fat content of the diet.

The effect of tomato juice on *N*-methylnitrosourea (MNU)-induced colon carcinogenesis was studied in female Fischer 344 rats (Narisawa *et al.*, 1998). Groups of 24 or 25 seven-week-old rats received intrarectal instillations of MNU at 2 mg or 4 mg three times per week for three weeks. Animals had free access to water (control group), a 17 ppm aqueous lycopene solution, or tomato juice diluted 1:2 or 1:14 and containing 17 ppm or 3.4 ppm [*sic*] lycopene, respectively. The colon tumour incidence was evaluated at week 35. After administration of 2 or 4 mg MNU, consumption of tomato juice containing 17 ppm lycopene significantly reduced colon tumour incidence compared with the other groups, and tumour multiplicity compared with controls only. The more dilute tomato juice had no effect on colon carcinogenesis.

Miyagi *et al.* (2000) studied the effect of orange juice administered during the post-initiation period of AOM-induced colon carcinogenesis in rats. Groups of 30 male Fischer 344 rats, 21 days old, were fed control diet until 36 days of age. At 22 and 29 days of age, all animals were given a subcutaneous injection of AOM (15 mg/kg bw). One week after the second dose of AOM, one group was switched from drinking water to orange juice and a modified diet, while the other group remained on the control diet. [The Working Group noted that the source of carbohydrate in the control diet was primarily corn flour, whereas the diet of the orange juice group was more sucrose-based]. The study was terminated at 33 weeks of age. There was a 22% lower colon tumour incidence

($p < 0.05$) in the animals given orange juice. [The Working Group noted that the total energy intake was not calculated, but final body weights were similar between the groups].

The effect of mandarin juice on AOM-induced colon carcinogenesis was studied in seven-week-old male Fischer 344 rats (20–29 per group) (Tanaka *et al.*, 2000). All animals were fed control diet and were given a subcutaneous dose of AOM (20 mg/kg bw) once per week for two weeks. Beginning one week after the second dose of AOM, one group was switched from drinking water to commercial mandarin juice at night-time, while maintained on a control diet. The experiment was terminated at week 38. The incidence and multiplicity of colon adenocarcinomas were significantly decreased in animals given mandarin juice (35% versus 69% in controls, $p < 0.02$; 0.40 ± 0.58 versus 0.76 ± 0.57 tumours per rat; $p < 0.05$, respectively).

The effect of orange pulp on DMH-induced colon tumorigenesis was studied in Sprague-Dawley rats (Kossoy *et al.*, 2001). Five week-old rats [sex unspecified] were fed control diet ($n = 30$) or experimental diet containing 15% orange pulp ($n = 42$). DMH was injected at 20 mg/kg bw once weekly for six weeks starting together with administration of experimental diet. The experiment was continued for eight months. Administration of orange pulp in the diet had no effect on the incidence of total colon adenocarcinomas, but significantly reduced the incidence of the more advanced endophytic adenocarcinomas in the colon ($p < 0.05$), while significantly increasing that of the less advanced exophytic adenocarcinomas ($p < 0.05$).

Inhibition of AOM-induced colon carcinogenesis by black raspberries (*Rubus occidentalis*) of the Jewel variety was studied in rats (Harris *et al.*, 2001). Groups of 18 male Fischer 344 rats, 8–9 weeks old, were given intraperitoneal injections of AOM (15 mg/kg bw) once per week for two weeks. Control animals received an equal volume of saline only or a diet containing 5% freeze-dried black raspberries. Animals were switched to a diet containing 0, 2.5, 5 or 10% black raspberries 24 hours after the last AOM injection and were maintained on these diets throughout the experiment. The sucrose content of the berry diets was reduced to maintain the energy content of the diets. The number of aberrant crypt foci nine weeks after the last dose of AOM decreased by 34%, 25% and 21% in the groups fed 2.5, 5 and 10% black raspberry, respectively, relative to the AOM-only group. The reductions were significant compared with controls in all groups ($p < 0.01$), although there was not a significant dose–response relationship. At 33 weeks after the last dose of AOM, the remaining animals were killed and the tumours analysed. Control animals had no tumours. Total tumour multiplicity (adenomas + adenocarcinomas) was reduced by 42, 45 and 71% in the groups fed 2.5, 5 and 10% black raspberry, respectively, relative to AOM controls ($p < 0.05$ for all groups). Adenocarcinoma multiplicity decreased by 28, 35 and 80% in the same groups; only the reduction in rats fed 10% black raspberry was significant ($p < 0.01$).

Liver

Rat

Groups of male weanling Fischer 344 rats were fed a semi-purified diet containing 25% (w/w) freeze-dried ground cabbage (*Brassica oleracea L.*) or table beet (*Beta vulgaris L.*), with or without 1 ppm aflatoxin B_1 (Boyd *et al.*, 1982). After 26 weeks of treatment, all animals were maintained on basal diet without aflatoxin for a further 16 weeks. Control animals had no tumours. The mean, median and maximum size, and the number of tumours exceeding 10 mm in diameter were all significantly lower ($p < 0.05$) in animals fed the cabbage diet. [The Working Group noted that the cabbage diet resulted in decreased food intake and thus decreased intake of aflatoxin B_1.]

Groups of 25 male Sprague-Dawley rats, two months old, were given N-nitrosodiethlamine (NDEA) in drinking water for 10 weeks (total dose 500 mg/kg bw) (Rieder *et al.*, 1983). Animals were fed a control diet or 120 or 160 g of carrots per week without any other supplementary food. [The Working Group considered that the amount of carrots given was very high (unbalanced diet), as was the dose of carcinogen administered.] In the first study (120 or 160 g carrots per week), feeding of carrots started together with carcinogen administration; in the second study (160 g of 'biological' or 'market' carrots per week), feeding started two weeks before carcinogen administration. Carrots were given for 14 weeks. Feeding 120 g or 160 g carrots per week together with or before carcinogen treatment significantly delayed tumour occurrence and prolonged survival compared with animals on the control diet. The effects with 160 g carrots per week were significantly greater than those with 120 g carrots per week. No difference was observed between the 'biological' and 'market' carrots.

Toad

Sadek et al. (1995) assessed the effect of cabbage on DMBA-induced hepatocarcinogenesis in toads (*Bufo viridis*). DMBA (0.5 mg in 0.1 mL olive oil) was administered into dorsal lymph sacos of sexually mature male and female toads weighting 40 g, three times per week for 12 weeks. Controls received olive oil only. A solution of ground cabbage leaves was fed at 1 or 2 mL per animal per day for 12 weeks starting 3 h before carcinogen treatment or 3 h

after carcinogen treatment. Toads treated with 1 or 2 mL cabbage 3 h before DMBA treatment (initiation period) showed a significantly lower incidence of hepatocellular carcinomas compared with those treated with DMBA alone. However, feeding of cabbage after carcinogen treatment (post-initiation period) had no effect on liver tumour incidence compared with animals treated with DMBA alone.

Lung

Mouse

The ability of strawberries (*Fragaria ananassa*) of the Allstar variety to inhibit lung tumorigenesis after induction with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) or benzo[*a*]pyrene (B[a]P) was examined in A/J mice (Carlton *et al.*, 2000). Groups of 20 mice were fed AIN-76A diet or a diet containing 10% freeze-dried strawberries for the entire duration of the study. The diet was modified to maintain total energy intake. One week after diet initiation, mice were treated with NNK or B[a]P over a two-week period. NNK was administered in saline by intraperitoneal injection in five doses of 0.414 mg each. B[a]P was administered in cottonseed oil by gavage in five doses of 0.2 mg each. Animals were killed 20 or 24 weeks after the first dose of NNK or B[a]P, respectively. There was no significant difference in lung tumour incidence or tumour multiplicity between the 10% strawberry groups and their respective control groups.

The effect of mandarin juice on NNK-induced pulmonary carcinogenesis was studied in male A/J mice (Kohno *et al.*, 2001). Seven-week-old mice (20–23 per group) were given a single intraperitoneal injection of NNK (10 μmol per mouse). One week later, one group received mandarin juice in drinking water at night for 21 weeks. Administration of mandarin juice had no effect on lung tumour incidence or multiplicity or on incidence of alveolar cell hyperplasia.

Skin

Mouse

The effect of bitter gourd extract in water (*Momordica charantia*) was studied in 4–5-week-old female Swiss albino mice (Ganguly *et al.*, 2000). One group of 25 mice received three topical applications of 1% DMBA on alternate days followed by 1% croton oil applied twice weekly for two months. The other group of 25 mice received the same treatment simultaneously with oral administration of 5% bitter gourd extract (50 μL per mouse) daily for three months. Treatment with bitter gourd extract delayed the appearance of skin papillomas and significantly reduced the incidence of papillomas at 12 weeks (control diet, 78%; bitter gourd diet, 19.5% [values read from diagram]; $p < 0.05$), but did not affect the multiplicity.

Mammary gland

Rat

The effect of Brussels sprouts (*Brassica oleracea* L.) administered during the initiation and progression stages of DMBA-induced mammary carcinogenesis was studied in Sprague-Dawley rats (Stoewsand *et al.*, 1988). Female rats, five weeks old, were divided into groups of 15 animals. One group (I) was fed 20% freeze-dried Brussels sprouts for the first four weeks, followed by 48 weeks on basal diet. The other group (II) was fed basal diet for 17 weeks and then switched to the Brussels sprouts diet for 35 weeks, until termination of the study. All animals received a single oral dose of DMBA (60 mg/kg bw) two weeks after the beginning of the study. Administration of Brussels sprouts during the initiation period (group I) significantly reduced the incidence of DMBA-induced palpable mammary tumours 15 weeks after dosing (13% versus 77%; $p < 0.01$) and of adenocarcinomas 50 weeks after dosing ($p < 0.05$). [The Working Group noted that the study did not include appropriate controls for the progression period and that animals in group II had significantly lower body weight.] In another study with the same initiation protocol (Stoewsand *et al.*, 1989), administration of Brussels sprouts 27 weeks after DMBA injection reduced the incidence and multiplicity of DMBA-induced papillary carcinomas and adenocarcinomas, and significantly reduced proliferation, anaplasia and invasiveness in these tumours.

Groups of 50-day old female Sprague-Dawley rats were given a single injection of MNU (50 mg/kg bw) into the tail vein. Rats were then assigned to groups (25–35 in each group) and fed a control-fat (5%) diet containing 5 or 10% dried cabbage, 3.2% cabbage residue or 5% collards, or a high-fat (24.6%) diet containing 5% cabbage or 5% collards. The study was terminated when palpable mammary tumours reached a diameter of 0.5 cm or at 24 weeks. The rats on the control-fat diet containing 5% cabbage or 3.2% cabbage residue had significantly lower incidence [25 to 38% decrease] of mammary adenocarcinomas than rats fed the control diet without cabbage. This effect was not observed in rats on the high-fat diet containing cabbage (Bresnick *et al.*, 1990).

Liu *et al.* (1992) determined the efficacy of garlic powder administered during the initiation and post-initiation periods of DMBA-induced mammary carcinogenesis in rats. In an initiation study, groups of 41-day old female Sprague-Dawley rats were fed a diet containing 0, 1, 2 or 4% garlic powder for two weeks before and two weeks after a single DMBA treatment by intubation (25 mg/kg bw). In an initiation and post-initiation study, groups of female Sprague-Dawley rats were fed

2% garlic powder from two weeks before DMBA treatment until termination of the study at 24 weeks. Garlic administered during initiation (at the 4% level) and during initiation and post-initiation significantly ($p < 0.05$) reduced DMBA-induced mammary tumour incidence (35% and 40%, respectively, versus 85% in controls) and multiplicity (1.57 and 1.50 tumours per tumour-bearing rat, respectively, versus 2.41 in controls).

Three groups of 25 female Sprague-Dawley rats, 41 days of age, were fed control diet or a 2% freeze-dried milled garlic powder diet two weeks before and one week after intragastric administration of 10 mg DMBA (initiation period), or the same diet from two weeks before until 24 weeks after DMBA administration (initiation and post-initiation period), when the experiment was terminated (Ip *et al.*, 1992). Administration of garlic powder during the initiation stage had a slight but not significant effect on mammary tumour incidence and multiplicity, whereas continuous administration of garlic powder significantly ($p < 0.05$) reduced both mammary tumour incidence (84 versus 56%) and multiplicity [2.84 versus 1.52 tumours per rat].

The effect of garlic powder on MNU-induced mammary carcinogenesis was studied in female Sprague-Dawley rats (Schaffer *et al.*, 1996). Groups of rats, 41 days of age, were fed the control diet or experimental diet containing 2% garlic powder for 14 days (21 rats per group). All rats then received MNU intraperitoneally (15 mg/kg bw) and continued on their dietary regimen for 25 weeks. Administration of garlic powder in the diet significantly ($p < 0.05$) reduced mammary tumour incidence (by 76%) and tumour multiplicity (by 81%).

The effect of dietary Thai bitter gourd administered during the initiation stage of DMBA-induced mammary carcinogenesis was studied in female Sprague-Dawley rats (Kusamran *et al.*, 1998a). Groups of 41-day-old animals were pair-fed on control diet or experimental diet containing 6.25 or 12.5% freeze-dried Thai bitter gourd for two weeks before and one week after a single oral dose of DMBA (50 mg/kg bw) and killed 25 weeks after dosing. Administration of Thai bitter gourd at 6.25 and 12.5% during the initiation stage significantly suppressed the multiplicity of mammary tumours [by 50%, read from diagram], but had no effect on the incidence.

Uterine cervix

Mouse

The effect of garlic on 3-methylcholanthrene (3-MC)-induced cervical carcinogenesis was evaluated in groups of random-bred 8–10-week-old virgin Swiss albino mice (Hussain *et al.*, 1990). A sterile cotton thread impregnated with beeswax containing about 600 µg 3-MC was inserted into the canal of the uterine cervix by means of a laparotomy. Ground garlic prepared in distilled water at a level of 1% was administered orally at a dose of 400 mg/kg bw per day for two weeks before and four weeks after 3-MC thread insertion. Twelve weeks after the insertion of threads, all animals were killed and tissues were processed for histopathological examination. Administration of garlic significantly decreased the incidence of 3-MC-induced squamous-cell carcinoma of the uterine cervix (23% versus 73% in controls). However, garlic had no effect on the incidences of hyperplasia and dysplasia in the uterine cervix.

Bladder

Mouse

The effect of aged garlic extract on bladder carcinogenesis was evaluated in female C3H/HeN mice given implants of MBT2 bladder tumour cells (Riggs *et al.*, 1997). MBT2 bladder tumours were originally induced in C3H/HeN mice by oral administration of *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT). Tumour cells for transplantation were prepared by mincing tumours and mechanically dispersing the tissue into a single-cell suspension. Garlic extract was administered orally at doses of 5, 50 and 500 mg/100 mL drinking water. One month after initiation of garlic treatment, 1000 MBT2 cells in 0.1 mL cell culture medium were subcutaneously injected into the right thigh. The experiment was terminated 23 days after tumour cell implantation for determination of tumour incidence and after 35 days for tumour volume. Treatment with garlic led to a dose-dependent reduction in tumour incidence, which was statistically significant at the highest dose (500 mg/100 mL). In addition, animals that received 50 and 500 mg garlic extract in drinking water had significant reductions in tumour volume (2563 and 1644 mm^3, respectively, versus 4047 mm^3 in controls).

Rat

The inhibitory properties of tomato juice against urinary bladder carcinogenesis were evaluated in rats (Okajima *et al.*, 1998). Bladder cancer was induced in six-week-old male Fischer 344 rats by 0.05% *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) given in the drinking water for eight weeks. This was followed by tap water (control) or tomato juice diluted 1:4 for 12 weeks. BBN induced simple hyperplasia, nodulopapillary hyperplasia and transitional-cell carcinomas in the urinary bladder. Tomato juice reduced the multiplicity (1.17 ± 0.9 versus 2.20 ± 1.4; $p < 0.05$) but not the incidence of transitional-cell carcinomas, and had no effect on simple or nodulopapillary hyperplasia in the bladder.

Biomarkers

Intermediary biomarkers that are potentially related to cancer risk include markers for uptake, chemical activation, deactivation and DNA-binding of carcinogens, DNA repair, cytogenetic markers and markers for oxidative damage to DNA. Other intermediary cancer biomarkers relate to cell turnover and apoptosis, to intercellular communication and to altered expression of genes involved in the cell cycle and its regulation. The following review covers studies of the effect of diets enriched with fruits and vegetables on such biomarkers in experimental animals, which have mostly used extracts prepared from single fruits and vegetables. Much research has concentrated on the effects of compounds contained in *Brassica* vegetables, *Allium* vegetables and polyphenol-rich plants or their extracts.

Effects on phase I and II enzymes

Total fruit and vegetables

Several studies have considered the effects of fruit and vegetable mixtures on enzyme induction. In a three-month feeding study on the effects of human-type diets on hepatic drug-metabolizing enzymes (Alink *et al.*, 1988), groups of five male and five female Wistar SPF rats were fed a semi-synthetic control diet or a complete northern European (Dutch) diet without vegetables and fruit, or a complete northern European diet including 19.9% local summer vegetables and fruit (40.1% potato, 3.4% banana, 10.3% orange, 21.8% apple, 4.3% each of lettuce, tomato, cucumber and cauliflower, 2.9% each of leek and spinach, and 1.4% pepper) or lyophilized semi-synthetic diets containing 20.1% local summer vegetables plus fruit or 20.0% local winter vegetables (44.6% potato, 3.8% banana, 11.5% orange, 24.2% apple, 3.2% each of red cabbage, white cabbage, sauerkraut and beet, and 1.6% each of carrot and Brussels sprout) plus fruit. Vitamins and minerals were added to all diets to the same final content and diets were isocaloric and with similar distribution of energy from fat (40%), protein (13%) and carbohydrate (47%) by addition of semi-purified components identical to those used in the control feed. The diets were irradiated at 500 krad and analysed to ensure equal contents of vitamins and minerals in each diet and stored at –40 °C until use. All three diets containing fruits or vegetables significantly increased hepatic ethoxycoumarin-*O*-deethylase activity (ECOD) in the male rats by 33–42%, whereas only hepatic ethoxyresorufin-*O*-deethylase (EROD) activity was increased (by 96–122%) in the female group fed summer vegetables and fruit compared to the control group. The increase in the females dosed with summer vegetables based on the northern European diet also was not significant compared with the group given the corresponding diet without vegetables and fruit (12%). Aminopyrine-*N*-demethylase was not affected by any of the treatments in either sex. Total CYP enzyme activity was increased only in male rats given the northern European diet without vegetables and in the winter vegetables group (by 20%). Hepatic glutathione-*S*-transferase (GST) was only increased in the males by summer vegetables and fruits (by 81%), while UDP-glucuronosyltransferase (UGT) activity was unaffected. Microsomes from the rat livers were subsequently screened in *Salmonella typhimurium* TA98 for their ability to activate benzo[a]pyrene (B[a]P) to mutagenic products. All fruit- and vegetable-containing diets decreased the ability of subsequently prepared hepatic microsomes to activate B[a]P by 20–40% (estimated from diagram). A similar assay in *S. typhimurium* TA100 showed that all human diets, except the complete northern European diet including summer vegetables and fruit, caused a 25–50% decrease (estimated from diagram) in the activation of *N*-nitrosodimethylamine (NDMA) by subsequently prepared hepatic microsomes.

Hepatic and colonic enzyme activities induced by six weeks' feeding of a vegetable–fruit mixture (19.5% w/w) (35.1% potato, 3.0% banana, 9.0% orange, 19.1% apple, 3.75% lettuce, 1.25% green pepper, 3.75% tomato, cucumber and cauliflower, 2.5% each of spinach, leek, red cabbage, white cabbage, sauerkraut and beetroot, and 1.25% each of carrot and Brussels sprout) was investigated in groups of five male Wistar rats fed low- or high-fat diets (20 or 40% of energy) (Rijnkels & Alink, 1998). Half of the animals in each group were treated with DMH (four subcutaneous injections of 50 mg/kg bw from week 2 to 5). In the liver of control rats on the low-fat diet, the vegetable mixture increased GST, decreased NDMA-demethylase and left EROD and pentoxyresorufin-*O*-deethylase (PROD) unaffected. In low-fat DMH-treated rats, the effect was reversed and PROD was increased by the vegetable and fruit treatment. The reported changes in enzyme activities were from 1.2- to 2.1-fold. In rats fed the high-fat diet, fruit and vegetable treatments had no effect.

Studies with several individual vegetables

A few studies have been performed to compare the effects of individual vegetables on enzyme induction. Bradfield *et al.* (1985) fed a range of powdered vegetables (cauliflower, carrot, kale, beet, Brussels sprout, egg plant or onion), mixed individually at a 20% level into isocaloric feeds, for 10 days to groups of four or five male C57BL/6 mice. Kale, cauliflower and carrots significantly increased hepatic ECOD activity 1.3, 2.2 and 1.2-fold,

respectively, whereas Brussels sprouts, cauliflower and onions similarly increased hepatic epoxide hydrolase (1.6-, 1.6-, and 2.3-fold) and GST activities (2.0-, 1.2-, and 1.8-fold), respectively.

Dried powdered preparations of cabbage (20% w/w) or Brussels sprouts (20% w/w) fed individually to groups of 5–10 female ICR/Ha mice for two weeks also significantly increased GST activity in the small intestine (2.1- and 3.1-fold, respectively) (Sparnins *et al.*, 1982). In the liver, only Brussels sprouts increased the activity (1.8-fold). [The Working Group noted that no compensation for the vegetables was made to the control diets.]

Lyophilized vegetables were individually added (12 g per rat per day) to human-type diets (23 g per rat per day) offered for three weeks to groups of three male Fischer 344 rats and induction of phase I and II enzymes in the liver and colon was measured (O'Neill *et al.*, 1997). [The Working Group noted that actual intakes were not recorded.] Broccoli and Brussels sprouts significantly increased hepatic GST by 24–64%, whereas broccoli decreased colonic GST by 35%. Spinach, tomato paste, peas and peppers significantly decreased GST, mainly in the liver, and changes were all below 20%. [The Working Group noted that the changes seemed too small to be truly statistically significant taking into account the small numbers in each group]. GST activity determined with either chloro-dinitrobenzene (CDNB) or dichloro-nitrobenzene (DCNB) as substrate gave highly correlated results. No effect on quinone reductase (QR) in liver or colon was reported. CYP 1A1 was increased in liver only after treatment with Brussels sprouts, whereas no effects on this enzyme or on CYP 1A2, 2B1, 2B2, 3A or 2E11 were observed in liver or colon with any other treatment.

Kusamran *et al.* (1998b) fed two freeze-dried preparations of vegetables commonly consumed in Thailand (Thai and Chinese bitter gourd, both at 12.5% in the diet, substituting proportional amounts of carbohydrate, fibre and protein) to groups of 10 pair-fed male Wistar rats for two weeks. Thai bitter gourd decreased hepatic aniline hydroxylase and aminopyrine-*N*-demethylase by 37% and 28%, respectively, increased GST by 59% and counteracted *ex vivo* activation by hepatic S9 preparations of aflatoxin B_1 and B[a]P by 30–64%.

Single fruits and vegetables

Various studies have examined the ability of a single fruit or vegetable to modify activities of phase I or II enzymes in experimental animals. Experiments with *Brassica* (broccoli, cabbage, Brussels sprout), *Allium* (garlic and onion), *Momordica* (bitter gourd) and citrus (grapefruit) species have been reported.

Groups of female ICR/Ha mice [number of animals per group not given] were given suspensions of broccoli tablets in 1% carboxymethylcellulose, 25% glycerol (1 g/kg bw) by gavage (Clapper *et al.*, 1997). [The Working Group noted that the dose was unclear; the concentration of broccoli in the suspension was not stated.] The broccoli tablets contained 5 g of lyophilized pesticide-free broccoli. GST activity in colon tissues was higher one day after broccoli administration, but decreased by day two. GSTμ and π were significantly induced one day after the treatment and decreased almost to baseline by day 2 [the Working Group noted that the exact increase was not stated].

Groups of five female Wistar rats were fed a 10% broccoli diet for seven days or a control diet containing the same amount of carbohydrates, fibres, proteins and vitamins (Vang *et al.*, 1991). In the liver, levels of CYP1A1, 1A2, 2B and 2E1 proteins and of total CYP1A mRNA increased, whereas mRNAs corresponding to the other proteins were unaffected. In the colon, CYP1A1, 2B and 2E1 proteins as well as CYP1A1 mRNA increased, whereas CYP2B mRNA decreased. CYP1A2 protein and mRNA were either unaffected or undetectable.

A subsequent study with a similar design examined the effects of feeding broccoli samples, varying in their contents of glucosinolates, on testicular phase I and II enzymes and antioxidant enzymes (Vang *et al.*, 1999). The broccoli, grown with varying amounts of N and S fertilizer or organically, was fed at a level of 10% in the diet to groups of 8–10 male Wistar rats for one week. Broccoli, most prominently that grown with high levels of N fertilizer, affected GST (1.6-fold induction) and UGT (1.8-fold induction), but did not statistically significantly change the activities of epoxide hydrolase, QR, p-sulfotransferase or the anti-oxidative enzymes catalase (CAT) and glutathione peroxidase (GPX) in rat testes. CYP enzyme activities were also measured in this study (Vang *et al.*, 2001). Dietary broccoli induced the CYP1A activities, EROD and 7 methoxyresorufin-*O*-demethylase (MROD), in rat liver and weakly in colon, but not in kidney. Consistent with this finding, the hepatic metabolism of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) to the proximate carcinogen *N*-hydroxy-PhIP, a CYP1A-related activity, was enhanced by broccoli. PROD activity, an assay for CYP2B1/2, was weakly induced in colon and kidney but not in liver. The 2β-hydroxy- and 6β-hydroxy-testosterone hydroxylase activities were induced in liver microsomes, showing that broccoli increased CYP3A activity. The observed modulations of CYP activities depended clearly on the broccoli sample used, the Shogun cultivar giving a higher response than Emperor. Significantly

different levels of enzyme induction were observed with broccoli samples grown under different conditions.

Groups of four male Wistar rats (McDanell *et al.*, 1989) were fed *ad libitum* during six days a semi-synthetic diet with or without 25% freeze-dried Brussels sprouts, or an equivalent amount of aqueous methanolic Brussels sprouts extract, or the residue remaining after this extraction. Feeding Brussels sprouts increased EROD 2.5-, 4.9- and 4.1-fold in the liver, small and large intestine, respectively; feeding the extract also increased, although slightly, the enzymatic activity, whereas the residue was without effect. In a time-course study, groups of four male Wistar rats were fed 20 g of a single semi-synthetic meal containing 25% (dry weight) cabbage [the Working Group noted that no modification was made to the control feed] (McDanell *et al.*, 1989). EROD activity was significantly decreased in the liver 1–2 hours after dosing and in the small intestine was significantly increased 4–6 h after dosing. No effect was observed in the large intestine.

In two dose–response studies (Bogaards *et al.*, 1990), groups of 5–8 newly weaned male Fischer 344 rats were fed a semi-synthetic diet with 0, 2.5, 5, 10, 15, 20 or 30% Brussels sprouts added (substituting for protein and fibre) during a 28-day period, after which the liver and small intestines were analysed for GST activity (using CDNB as substrate) and content of GST subunits 1, 2, 3, 4 and 7. Casein and cellulose were given to controls, for protein and fibre compensation. A significant dose–response relationship was observed, with increases of 17% in GST activity and 15% in GST protein content in the liver after the lowest dose. The corresponding figures were 182% and 121% after the highest dose. Subunits 1, 2 and 3 appeared to be the most responsive. In the small intestine, GST activity was induced only after feeding 15% or more of Brussels sprouts. GST protein subunits 1, 2 and 4 were significantly induced after feeding 15% or 30% Brussels sprouts. Total GST protein, determined only in the second experiment, was not significantly induced after feeding 20% Brussels sprouts.

Groups of six male Wistar rats were fed 0–20% cooked Brussels sprouts in the diet for periods of 2–28 days and liver and small intestines were assayed for various phase I and phase II activities (Wortelboer *et al.*, 1992). Hepatic microsomal EROD and PROD were increased from day 2 onwards in rats given 20% Brussels sprouts in the diet and from day 14 onwards in rats given 5%. No effect was observed at the 2.5% dietary level. In the small intestine, EROD and PROD activities were increased only at the highest dose, after 2 and 7 days, respectively. Hepatic microsomal testosterone 2β- and 6β-hydroxylase activities were increased from 7 and 14 days onwards in the highest dose group only and no effects were observed in microsomes from the small intestine. Western blots indicated dose-related increased levels of CYP1A2 in the liver and of CYP2B1/2 in the small intestine. Hepatic GST, UGT type 1 and DT-diaphorase tended to increase from day 2 at the two higher dose levels and glucuronyl transferase 1 also increased after 28 days of feeding with 2.5% Brussels sprouts. In contrast, glucuronyl transferase 2 decreased initially at the 2.5 and 5% levels, but after 28 days there was no effect at these lower dose levels, while an increase was observed in the rats fed 20% Brussels sprouts. In the small intestine, GST increased from day 2 at the 20% dose level whereas DT-diaphorase increased, on day 2 only, at both the 5% and 20% dose levels.

Groups of eight male Wistar rats were treated by gavage with Brussels sprouts extract equivalent to 7 g per day of fresh vegetable for four days and livers and kidneys were removed 6 h after the last dose to assay expression or activities of phase I and II enzymes (Sorensen *et al.*, 2001). No change was observed in the expression of hepatic CYP1A2, CYP2B or CYP2E1. The QR activity increased by 155% in liver but not in kidney, and hepatic expression of GSTπ increased by 30%.

Liu *et al.* (1992) examined the influence on liver and mammary GST activity of dietary supplements of garlic powder (2 or 4%) fed to groups of five female Sprague-Dawley rats. After two weeks of treatment, garlic at 2 or 4% increased GST activity by 91 and 100%, respectively, in liver and by 42% and 47% in the mammary tissue.

In groups of 6–8 male Sprague-Dawley rats, oral treatment with 200–1000 mg/kg bw garlic oil daily for 1–3 days led to increases in GST expression (50–150%) and activity (~40%) in rat liver and decreases in CYP activities, notably inducible CYP2E1 (Kwak *et al.*, 1995).

Groups of male Wistar rats [number of rats per group not given] were fed 0.1, 0.5 or 1% powdered garlic for four weeks before a single dose of B[a]P or 3-MC and urine was collected for 24 h (Polasa & Krishnaswamy, 1997). The animals were then killed and the liver and lungs assayed for QR and the liver for GST (CDNB substrate). Garlic dose-dependently decreased urinary mutagenicity in *S. typhimurium* TA98 after B[a]P dosing, whereas mutagenicity in TA100 or mutagenicity in both strains after 3-MC dosing was decreased to an equal extent by all three garlic dose levels. All three doses increased hepatic GST (30–43%) and QR (80–100%, read from diagram) and lung QR (40–50%, read from diagram) to similar extents.

The interaction with respect to hepatic phase I and II enzymes

between dietary fat and garlic oil (200 mg/kg bw) given as three weekly intubations during seven weeks was investigated in groups of 4–5 male Sprague-Dawley rats (Sheen *et al.*, 1999). Garlic oil increased GST activity by 38–40%, but did not significantly affect NDMA-demethylase, PROD, total CYP or total NADPH-cytochrome c reductase. Immunoblot analyses revealed increased hepatic levels of CYP2B1 and GST (placental form) and decreased CYP2E1 after intubation with garlic oil. The content of fat (5 or 20%) in the feed did not interact with garlic oil. In a subsequent study, groups of five male Sprague-Dawley rats, fed either a low- or high-fat diet, were treated with 0, 30, 80 or 200 mg/kg bw garlic oil by gavage three times per week for six weeks (Chen *et al.*, 2001a). Garlic oil dose-dependently increased liver GST and PROD activities and CYP2B1 mRNA and protein levels. Again, the effects of garlic oil were independent of dietary fat content.

Oral administration of bitter gourd extract (5% in water) daily for three months to groups of eight Swiss albino female mice significantly increased hepatic GST in normal mice and in mice skin-painted with DMBA (Ganguly *et al.*, 2000).

Grapefruit juice is known to have some capacity to modify the biotransformation of certain drugs (Bailey *et al.*, 1994). The effect was investigated in groups of 6–9 male Sprague-Dawley rats given a daily oral dose of 4 or 8 mL/kg of grapefruit juice for two days, followed on the second day by a dose of pentobarbitone sodium (50 mg/kg). The juice significantly increased sleeping time in a dose-dependent manner (46% and 79%, respectively) (Sharif & Ali, 1994). Administration of 4 mL grapefruit juice per day for two days (four rats per time point) inhibited theophylline metabolism up to 90 min after administration of theophylline (10 mg/kg bw). Pure commercial grapefruit juice offered instead of drinking water to groups of three male Fischer 344 rats did not affect the plasma clearance of a subsequent dose of PhIP (60 mg/kg bw) (Miyata *et al.*, 2002).

In summary, fruit and vegetable mixtures at levels relevant to human dietary intakes can increase both phase I and II xenobiotic-metabolizing enzyme activities. Evidence from studies with high doses of single vegetables indicates a stronger ability to induce phase II enzymes. Induction has been observed both in the liver and extrahepatically in lung, intestines and mammary tissue. In studies looking at dose–response effects, phase II enzymes were induced in a dose-related manner.

Inhibition of damage to macromolecules

Mixtures of fruit and vegetables

Groups of 4–5 female Sprague-Dawley rats were fed a standard diet, or a specially composed diet with cereals and cereal by-products, or vegetable by-products, milk and sugar, or vegetable by-products together with meat and fish by-products and vegetable oil. Blood samples were collected after four weeks to determine background levels of 4-aminobiphenyl adducts in haemoglobin (Richter *et al.*, 2000). [The Working Group noted that no information was given on the nature of the vegetables included in the diets and that only the vegetable and milk diet was similar to the control diet in macronutrient composition]. Adduct levels were significantly decreased by 50% in animals on both diets containing vegetable by-products, whereas the cereal-based (high-fibre) diet had no effect.

Individual fruit and vegetables

The protective effect of garden cress (*Lepidium sativum*) towards genotoxic effects induced by 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) was investigated by single-cell gel electrophoresis (SCGE) assays (Kassie *et al.*, 2002). Pretreatment of groups of three male Fischer 344 rats with fresh garden cress juice (0.8 mL) for three consecutive days led to significant reductions ($p < 0.05$) in DNA damage induced by IQ (90 mg/kg, 0.2 mL corn oil/animal) in colon and liver cells in the range of 75–92%.

The influence of dietary supplements of garlic powder (2 or 4%), offered two weeks before and two weeks after DMBA treatment (25 mg/kg bw), significantly and dose-dependently reduced mammary DNA adduct levels (approximately 30–70%, respectively), as determined by ^{32}P-postlabelling in groups of five female Sprague-Dawley rats (Liu *et al.*, 1992). In a subsequent study on the interaction between garlic and selenite on DMBA-induced liver and mammary DNA adducts, marked enhancement of the selenium-induced protection was observed with concomitant garlic treatment (Schaffer *et al.*, 1997). Groups of five female Sprague-Dawley rats were fed sodium selenite (0.1, 0.5 or 1 mg/kg diet) in combination with garlic powder (0, 20 or 40 mg/ kg diet) in a 3 × 3 factorial design. After two weeks of feeding, all rats were given 25 mg/kg bw DMBA in corn oil by intubation. After 24 h, total DNA adducts in mammary tissue were determined. Garlic dose-dependently decreased the adduct level in the low-selenium group (40–80%) and the effect was potentiated by dietary selenium, increasing to 50% and almost 100% in the high-selenium group (values read from diagram). A decrease in the specific *anti*-3,4-dihydrodiol-1,2-epoxide deoxyguanosine adduct accounted for almost the entire effect.

Various garlic preparations were fed to groups of six female Sprague-Dawley rats for two weeks before a

single intubation of DMBA (25–50 mg/kg bw) and 24 h later, DNA adducts in breast tissue were analysed by ^{32}P-postlabelling (Amagase & Milner, 1993). Feeding fresh garlic, which was frozen before grinding, at 2% in the diet decreased DMBA–DNA binding by 33%, and subsequently extracting the ground garlic with water for 1 h at 25°C yielded an active extract, which decreased binding by 46%. Two commercial preparations based on sliced garlic decreased binding by 51% when fed at the 2% level and by 78% at the 4% level. The postlabelling spots representing different DMBA–DNA adducts all decreased to similar extents. In a second experiment with groups of five pair-fed rats, fresh garlic powder fed at 1% in the diet did not significantly decrease DMBA–DNA binding (16% decrease), but the water extract decreased binding by 44%. An overnight ethanolic extract was less active, decreasing binding by 24%. The two commercial preparations based on sliced garlic were active after pair-feeding at the 1% level and decreased DMBA-binding by 65–71%.

The interaction of garlic with other dietary factors, including casein, corn oil, retinyl acetate, selenium and methionine, in mammary DMBA–DNA binding was subsequently investigated in experiments using groups of 5–6 female Sprague-Dawley rats fed diets varying in these components for two weeks before a single dose of DMBA (Amagase *et al.*, 1996). Garlic powder (20 g/kg diet), prepared by ethanol extraction of sliced garlic, decreased DMBA adduct levels to the same extent (32–35%) when fed with 36% or 12% casein (at the expense of corn starch and sucrose). Casein as such also decreased DMBA–DNA binding. In contrast, garlic depressed adduct formation to a greater extent in rats given 0.3 g methionine per 100 g diet than in those given 0.9 g (54% versus 26%) and also more in animals fed a 20% corn-oil diet than a 10% corn-oil diet [~60% versus ~30%, read from diagram]. Methionine itself decreased DNA binding, while lipid increased it. In animals fed only 5% corn oil, garlic did not significantly affect mammary adduct formation (corn oil was decreased while corn starch and sucrose were increased). A second experiment with adjustment for energy density while feeding corn oil at the same three dietary levels gave a similar result except that garlic decreased adduct formation only at the 20% corn-oil level. In a third experiment, DMBA–DNA binding was decreased by 35% with dietary selenite (0.5 mg/kg diet) and by 63% when the garlic extract was also fed. The corresponding decreases were 29% and 75% with dietary retinyl acetate (328 mg/kg diet) with or without garlic extract, and a combination of retinyl acetate, selenite and garlic extract gave a decrease in binding of 82%.

In groups of five female Sprague-Dawley rats, the ability of garlic to decrease (by 64%) DMBA-induced mammary gland DNA adducts was eliminated by heating the garlic with microwaves for 60 s; heating for 30 s had no effect (Song & Milner, 1999). There was no effect of heating after garlic was crushed and left to stand for 10 min, allowing the heat-sensitive alliinase to convert alliin present in garlic to active sulfur compounds.

The ability of garlic to inhibit DNA methylation adducts was investigated (Lin *et al.*, 1994). Feeding groups of six female Sprague-Dawley rats with garlic powder at 2 or 4% for three weeks in a diet containing aminopyrine and sodium nitrite (each at 600 mg/kg diet) decreased the formation of N^7-methyl-deoxyguanosine (N^7-Me-dG) in DNA by 60 and 82%, respectively, and of O^6-methyldeoxyguanosine (O^6-Me-dG) by 54 and 82%, respectively. Pretreatment with NDMA (150 mg/kg bw) also induced liver DNA methylation, which was counteracted by 2 and 4% garlic powder treatments for two weeks (N^7-Me-dG: 45% and 57%, respectively, and O^6-Me-dG: 40 and 66%, respectively). Mammary DNA methylation after pretreatment with MNU (50 mg/kg bw) was also counteracted by feeding 2 and 4% garlic powder for two weeks (N^7-Me-dG: 57 and 69%, respectively, and O^6-Me-dG: 51 and 71%, respectively).

In a subsequent study, groups of 21 female Sprague-Dawley rats were fed 2% garlic powder in the diet for two weeks before a single dose of MNU (15 mg/kg bw) (Schaffer *et al.*, 1996). In mammary tissue obtained 3 h later, N^7-Me-dG and O^6-Me-dG were decreased by 48 and 27%, respectively, in the garlic-fed animals compared with controls.

Groups of 24–26 male Fischer 344 rats were fed a control semi-synthetic diet or a similar diet containing 5 or 10% freeze-dried strawberries (at the expense of corn-starch) for two weeks, after which they received a single dose of NMBA (0.25–0.5 mg/kg bw) and were killed 24 h later for determination of gastric mucosal O^6-Me-dG (Stoner *et al.*, 1999). The animals fed 5 and 10% strawberries had levels of adducts lower by 68 and 57%, respectively, indicating no dose–response relationship. A subsequent study with a similar protocol showed significant decreases (59 and 64%, respectively) also in oesophageal O^6-Me-dG in NMBA-treated rats fed 5 and 10% strawberries (Carlton *et al.*, 2001).

In summary, four different fruit or vegetable preparations have been found to decrease carcinogen–DNA binding. The majority of studies evaluating dose–response effects found a relationship.

Oxidative damage and defence

No studies on modulation of oxidative damage or defence by treatment of experimental animals with combined

fruits, vegetables or their extracts were available. Several studies with individual fruits and vegetables have been reported.

The individual effects of chloroform-extracted tomato paste, orange juice concentrate and canned carrots on erythrocyte stability, blood glutathione and erythrocyte CAT and superoxide dismutase (SOD) activities were investigated in groups of 12 male Fischer 344 rats treated with aflatoxin B_1 (250 μg/kg bw, daily for two periods of five days with a two-day interval). The extracts were administered by gastric intubation either daily for a 12-day period from weeks 2 to 4 after aflatoxin dosing (initiation) or every second day for a 12-week period from four weeks onwards after aflatoxin dosing (promotion) (He *et al.*, 1997). Blood samples were collected at termination after 16 weeks in all groups. All extracts significantly increased erythrocyte stability by 33–98%, as determined as the amount of haemolysis 6 h after an ascorbate challenge. The effect was most pronounced after the 12-week treatment (49–98%) and carrot treatment had the greatest effect. An aflatoxin-induced increase in plasma glutathione was counteracted significantly by the extracts (17–45%), again most strongly with the longer treatment (33–45%) and with the carrot extract. The 12-week extract treatments also decreased erythrocyte CAT (25–29%) and SOD (34–41%).

Lyophilized apple (20% in the diet) fed for three weeks to groups of eight obese or lean Zucker rats significantly decreased urinary malondialdehyde excretion, measured as thiobarbituric acid-reactive substances (TBARS), by 45% in both strains (Aprikian *et al.*, 2002). Levels of malondialdehyde in the heart were also significantly decreased in the obese strain (11%). Ferric-reducing capacity of plasma, a measure of one-electron reduction capacity, did not change in either strain.

The effects of raw or cooked Brussels sprouts and of a mixture of cooked green beans and endives (1:1) on spontaneous and induced oxidative DNA damage, in terms of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) in tissue DNA or its urinary excretion, were determined in groups of 6–8 male Wistar rats (Deng *et al.*, 1998). Excess oxidative DNA damage was induced by 2-nitropropane (100 mg/kg bw). Four days' oral administration of 3 g of cooked Brussels sprouts homogenate reduced spontaneous urinary 8-oxodG excretion by 31% ($p < 0.05$), whereas raw sprouts or green beans and endive (1:1) had no significant effect. An aqueous extract of cooked Brussels sprouts (corresponding to 6.7 g vegetable per day for four days) decreased the spontaneous 8-oxodG excretion by 43%. Pretreatment with sprout extract reduced nitropropane-induced 8-oxodG excretion by 28%. The background level of 8-oxodG in nuclear DNA from liver and bone marrow was not significantly affected by the sprout extract, whereas the level in the kidney decreased by 27%. In the liver, the sprouts extract reduced the nitropropane-induced increase in nuclear 8-oxodG by 57% at 6 h, whereas there was no significant effect at 24 h. Pretreatment with the sprout extract altogether abolished the nitropropane-induced increase in the kidneys. Similarly, in the bone marrow, the extract protected completely ($p < 0.05$) against a 4.9-fold nitropropane-induced increase in the 8-oxodG level.

Oral administration of an aqueous extract of Brussels sprouts (corresponding to 6.4 g fresh vegetable per day) for three or seven days to groups of four male Wistar rats significantly increased the level of 8-oxodG in rat liver by 20–30% (Sørensen *et al.*, 2001). No effect on liver malondialdehyde levels was found. In a second experiment, groups of eight male Wistar rats were given Brussels sprout extract equivalent to 7 g per day of fresh vegetables by gavage for four days. No effect was observed on activity of CAT or GPX or on hepatic expression of γ-glutamylcysteine synthetase light and heavy chains in livers and kidneys removed 6 h after the last dose.

Two varieties of broccoli (Emperor and Shogun) grown under conventional or organic conditions were fed at a level of 10% in the diet to groups of 8–10 male Wistar rats during one week and hepatic, renal and colon glutathione reductase, GPX and SOD were determined (Vang *et al.*, 1997). Feeding broccoli overall decreased the level of glutathione in the colon and reduced the activity of SOD in liver. Significant, albeit minor, differences between the two varieties and between organically and conventionally grown broccoli were noted. [The Working Group noted that details of the statistical methods were not given.]

Onion oil (100 mg/kg bw), given daily for 21 days by stomach tube to groups of 15 male Sprague-Dawley rats treated with nicotine (0.6 mg/kg bw, daily) as a pro-oxidant, significantly decreased the level of TBARS, lipid hydroperoxides and conjugated dienes in the liver, lungs and heart (Helen *et al.*, 2000).

Groups of 4–5 male Sprague-Dawley rats fed low- or high-fat diets were given three weekly intubations of garlic oil (200 mg/kg bw) over seven weeks (Sheen *et al.*, 1999). Garlic oil increased hepatic glutathione reductase by 20–27% and erythrocyte glutathione by 51–70%, but did not significantly affect hepatic glutathione. Hepatic SOD was increased by 14–44%, whereas hepatic GPX decreased by 27–34%. Garlic oil did not affect hepatic TBARS or α-tocopherol. The fat content (5 or 20%) in

the feed did not significantly interact with the garlic oil treatment.

Lyophilized garlic fed at 2% in the diet to groups of eight male Wistar rats for three weeks decreased CAT activity and CAT protein levels in renal cortex, but did not influence CAT expression (Pedraza-Chaverri *et al.*, 2000). Treatment of rats with the nephrotoxic drug gentamicin (75 mg/kg by subcutaneous injection every 12 hours during the last six days) led to increased urinary excretion of lipid peroxidation products, decreased activity of Mn-SOD and GPX in the renal cortex and of plasma GPX and decreased activity and expression of CAT in the renal cortex in rats given ordinary chow. Gentamicin-treated and garlic-supplemented rats only experienced a decrease in renal cortex CAT activity similar to the action of garlic alone. A subsequent study by the same group indicated that the decrease in CAT activity in the renal cortex followed a garlic-induced decrease in tissue levels of H_2O_2 (Pedraza-Chaverri *et al.*, 2001).

Three months' daily feeding of a 5% bitter gourd extract to groups of eight female Swiss albino mice increased hepatic GPX, CAT and SOD by 110%, 100% and 57%, respectively [values read from diagram] and decreased the *ex vivo* susceptibility of hepatic microsomes to lipid peroxidation (>60%; read from diagram) and to lymphocyte DNA strand breakage (61%; read from diagram) (Ganguly *et al.*, 2000). Similar effects were found in mice treated with DMBA in croton oil.

In summary, the evidence from animal studies with respect to effects of fruit and vegetables on antioxidant enzymes and direct oxidative damage to DNA is inconsistent, whereas lipid oxidation seems in many cases to be reduced by such treatments.

Effects on mutation and DNA strand breaks

Groups of six Long-Evans male rats were allowed to drink *ad libitum* only fresh or boiled (100°C, 15 min) vegetable juices (500 g vegetable to 1 L juice, 7–17 mL juice per day) during one week and bone marrow micronucleus formation induced by DMBA was measured (Ito *et al.*, 1986). Fresh or boiled extracts of onion, burdock, egg plant, cabbage and Welsh onion and boiled pumpkin extract all reduced DMBA-induced clastogenicity by 40–68%. Fresh pumpkin juice increased clastogenicity, while fresh or boiled juices from lettuce, carrot, peaman (bell pepper) and celery were inactive.

Seven fruit and ten vegetable extracts, prepared with organic solvents, were tested for their ability to inhibit the clastogenic effects of cyclophosphamide and B[a]P in the mouse bone marrow micronucleus assay (Edenharder *et al.*, 1998). Groups of four 7–12-week-old male NMRI mice were treated intraperitoneally with B[a]P (150 mg/kg bw in 200 µL corn oil) or orally with cyclophosphamide (200 mg/kg bw in saline by gastric intubation) to induce micronuclei and simultaneously by gastric intubation with 0.5m mL suspension of freeze-dried fruit or vegetable extracts. Sweet cherries, strawberries, bananas, kiwi fruit, oranges and peaches all decreased the clastogenic effects significantly (10–40% decrease); a 39% decrease caused by apples was not significant. Among the vegetables, cucumber, radish, tomato, Brussels sprouts, asparagus, red beet, yellow-red peppers and spinach (22–79% decrease) had significant activity, but cauliflower and onions did not significantly decrease clastogenicity. Further fractionation of the orange extract revealed that several fractions contained active principles, and that different fractions contained activity against each of the two clastogens tested.

The influence of five days of grapefruit juice intake on PhIP-induced DNA damage in the colon was examined by the comet assay in groups of three male Fischer 344 rats given 60 mg/kg of PhIP by gavage three hours before sacrifice. DNA damage in the colon of rats allowed free access to grapefruit juice for five days was significantly reduced to 40% of the level in control rats (Miyata *et al.*, 2002). The effect was found to be unrelated to absorption and biotransformation of PhIP.

In summary, evidence from three studies with more than ten different fruits and vegetables points to a preventive effect of many on carcinogen-induced DNA damage and mutation.

Effects on DNA repair

No studies on modulation of DNA repair caused by treatment of experimental animals with combined fruits, vegetables or their extracts were available.

Groups of eight male Wistar rats were given an aqueous Brussels sprout extract equivalent to 7 g per day of fresh vegetable for four days by gavage and the livers and kidneys were removed 6 h after the last dose (Sørensen *et al.*, 2001). No effect on the activity of 8-oxoguanosine DNA glycosylase (OGG1) was observed in either organ.

Intermediary markers related to the cell cycle

A range of lyophilized vegetables were individually added to human-type diets [no details were given] at a level of 12 g per day and fed to groups of three male Fischer 344 rats and the mitotic index and proliferating cell nuclear antigen (PCNA) in colon cells were measured (O'Neill *et al.*, 1997). PCNA responded only marginally, whereas spinach, petit pois (green peas) and peppers decreased the mitotic index substantially. Only the effect of petit pois (41% decrease) was statistically significant. There was an inverse

relationship between colonic mitotic index and colonic GST activities across the test groups.

Mechanisms of cancer prevention

The epidemiological evidence for a cancer-protective effect of diets rich in fruit and vegetables and the ability of many extracts from fruits or vegetables to counteract carcinogenesis in experimental animals has prompted a range of studies into mechanisms that may underlie these effects. Whole plants, extracts and subfractions have been tested, as well as certain purified plant compounds. Relatively few experimental studies have tested the effect of diets mimicking human habitual patterns of fruit and vegetable intake. Rather, most studies in humans and animals have investigated the potential of single test components to influence intermediate markers related to mechanisms of carcinogenesis.

Proposals that antioxidant vitamins (Mirvish *et al.*, 1972; Anon., 1980), fibres (Wynder, 1985; Weisburger *et al.*, 1993) or enzyme inducers (Wattenberg, 1975; Das *et al.*, 1985; Prochaska & Talalay, 1988; Talalay *et al.*, 1988) present in fruit and vegetables might be responsible for preventive effects prompted early research into these areas. Subsequently, there has been much research on plants rich in nitrosation inhibitors, antioxidants or enzyme inducers, e.g., ascorbate and polyphenols (Bartsch *et al.*, 1988) or carotenoid-rich vegetables, garlic (Bianchini & Vainio, 2001) and cruciferous vegetables (van Poppel *et al.*, 1999).

Several reviews have described potential mechanisms behind the cancer-protective actions of fruit and vegetables (Wattenberg *et al.*, 1976; De Flora & Ramel, 1988; Hartman & Shankel, 1990; Dragsted *et al.*, 1993; Potter & Steinmetz, 1996; Lampe, 1999). This section summarizes the range of mechanisms through which fruit and vegetables might influence carcinogenesis. The end-points studied experimentally are largely intermediate biomarkers for carcinogen uptake, activation, damage and later cellular effects, which theoretically are related to cancer risk. In many cases, however, the relationships of these intermediate markers (e.g., oxidative damage, DNA-adduct formation or cell proliferation) to subsequent cancer outcomes are not well established. Surrogate markers used in human studies (e.g., damage to lymphocyte DNA in place of the target tissue DNA) often have not been well validated. Furthermore, the effects of high doses of single compounds on animal models of carcinogen-induced tumours are often difficult to extrapolate to humans.

In some cases, it has been shown that interactions between several dietary components increase the preventive activity, and the growth conditions of fruits and vegetables might directly influence such synergies (Vang *et al.*, 1999, 2001). The interactions between garlic and selenium in enzyme induction, prevention of genetic damage and cancer prevention in experimental systems illustrate the importance of many factors in the diet acting together in cancer prevention (Ip & Lisk, 1995; Amagase *et al.*, 1996; Ip & Lisk, 1997; Schaffer *et al.*, 1997). Therefore, whenever possible, studies on preventive mechanisms of whole fruits and vegetables or simple extracts and lyophilized preparations are used as examples in this chapter.

Inhibition of endogenous carcinogen formation

Nitrosamines, alkenes and reactive radical species are examples of potentially carcinogenic factors that are formed endogenously. Modulation of their formation might lead to an altered risk of cancer.

Inhibition of radical formation

Free radicals are formed in one-electron reactions by transition metals, ionizing radiation or endogenous enzymes such as xanthine oxidase and nitric oxide synthase. Their formation may be propagated by redox systems such as ascorbate/ferrous ion in the water phase or by transition metal-catalysed peroxide degradation in unsaturated lipids. Free radical formation may be counteracted by scavenging of radicals by antioxidants or by chelation of transition metals into less reactive complexes. Fruits and vegetables contain many natural primary (scavenging) or secondary (chelating) antioxidants that might directly prevent radical-induced damage to cellular structures, including DNA. The evidence for antioxidant actions of fruit and vegetables comes largely from studies with cell-free systems and to a lesser extent from experimental studies in animals and humans using assays of antioxidant capacity. In view of the wide range of phytochemicals with antioxidant activity and the difficulty of measuring each compound individually, several assays have been developed to assess total antioxidant activity. Serum total antioxidant capacity, determined *ex vivo*, can be measured by several assays: oxygen radical absorbence capacity (ORAC), ferric-reducing ability (FRAP) and Trolox equivalent antioxidant capacity (TEAC). However, these assays have been insufficiently validated (Crews *et al.*, 2001) and the relevance of these measures to cancer risk has not been established.

Formation of radicals is an important part of several physiological processes, including inflammation and metabolism of xenobiotics, both of which have dual roles in carcinogenesis. Direct evidence of primary or secondary antioxidant activity from animal and human experimental studies is

scarce; the indirect evidence of decreased oxidative damage is discussed later in this chapter. No long-term studies have investigated the relationship between markers of antioxidant capacity and cancer risk. In one small case–control study, increased serum total antioxidant status, measured by TEAC, was found to be associated with reduced breast cancer risk (Ching *et al.*, 2002); however, the case–control design limited the conclusions that could be drawn regarding temporality. To date, there is no evidence for a relationship between increased *ex vivo* antioxidant capacity of plasma and feeding with whole fruits or vegetables in experimental animals; the only study identified had a negative outcome (Aprikian *et al.*, 2002).

Inhibition of nitrosation

Some of the factors that contribute to oxidative damage and the production of reactive oxygen species can also lead to production of reactive nitrogen species. A wide range of nitrogen-containing compounds and nitrosating agents to which humans are exposed react *in vivo* to form potentially carcinogenic *N*-nitroso, *C*-nitroso and reactive diazo compounds. Nitrosating agents are also synthesized endogenously by bacteria and activated macrophages. High exposure to nitrate leading to increased endogenous nitrosation has been proposed as a possible risk factor for several cancers (Bartsch *et al.*, 1992). Therefore, interventions that reduce formation of nitroso compounds may lower risk, although evidence to support this directly is lacking (Bartsch & Frank, 1996; Hughes *et al.*, 2002).

Modulation of carcinogen bioavailability

Dietary carcinogens need to be absorbed from the gut or at least to enter the epithelial cell lining of the gastrointestinal tract in order to have an effect on cancer risk. In theory, fruit and vegetables may influence the bioavailability of carcinogens by inhibiting their uptake or by increasing their excretion. Carcinogens may adsorb to structures in fruit and vegetables such as fibres or chlorophyll or may be diluted by the increased bulk of material in the gastrointestinal tract after meals containing large amounts of fruit and vegetables.

Aflatoxins adsorb strongly to chlorophyllin (a water-soluble copper complex of chlorophyll used as a food colorant), making them less bioavailable and decreasing DNA binding and subsequent tumour development in trout (Breinholt *et al.*, 1999; Hayashi *et al.*, 1999). Chlorophyllin also reduces aflatoxin adduct formation in humans (Egner *et al.*, 2001). Although chlorophyll was less potent than chlorophyllin in adsorbing aflatoxins (Dashwood *et al.*, 1998), the ubiquitous presence of chlorophylls and other porphyrins in green fruits and green leafy vegetables suggests that such a mechanism may be relevant to cancer prevention by fruit and vegetables.

The bulking or carcinogen-adsorbing effect of plant-based fibre-rich foods, including fruit and vegetables, has been hypothesized to be important for protection against exogenous and endogenous cancer-enhancing factors, including secondary bile acids (Jacobs, 1986) and hydrophobic carcinogens (Harris *et al.*, 1996). Certain fibres may be able to inhibit carcinogenesis by heterocyclic amines (Ferguson & Harris, 1996). In humans, supplementation with dietary fibre from vegetable and grain sources lowers faecal bile acid concentrations in a dose-dependent manner as a result of faecal bulking (Lampe *et al.*, 1992), but there are no experimental studies to support such an effect of fruit and vegetables in general.

Modulation of enzyme systems

Many carcinogens need metabolic activation in order to elicit their effects. The oxidation (phase I) and conjugation (phase II) reactions involved in this process may be influenced by dietary fruit and vegetables. The enzyme systems responsible for these transformations also participate in steroid hormone metabolism and their modulation may therefore also affect risk of hormone-dependent cancers. The enzymes involved in antioxidative defence against reactive oxygen and nitrogen species are another group that may be modulated by dietary factors.

Phase I and II enzymes

Phase I enzymes such as the cytochrome P450-dependent monooxygenases (CYP) catalyse oxidation, hydroxylation and reduction reactions, but may also convert hydrophobic compounds to reactive electrophiles. Phase II enzymes such as UGT, sulfotransferases and GSTs catalyse conjugation reactions with water-soluble moieties to improve excretion. The balance between carcinogen activation and detoxification is potentially important for cancer risk. Both oxidation reactions and conjugation can lead to formation of either activated, DNA-reactive metabolites or less toxic metabolites. Modulation of phase I and II metabolism may therefore lead to increased or decreased risk of cancer, depending on the carcinogen in question. However, there are few examples of activation solely by conjugation and lack of ability to induce conjugating enzymes is associated with increased cancer risk in transgenic knock-out mice (Talalay & Fahey, 2001). Excessive induction of phase I enzymes has been associated with increased risk of cancer at several sites in humans (Lee *et al.*, 1994; Landi *et al.*, 1999; Mollerup *et al.*, 1999; Stucker *et al.*, 2000; Guen-

gerich, 2001). Therefore, induction of phase II enzymes alone (monofunctional action) is regarded in general as protective, whereas the effect of simultaneously inducing both phase I and II enzymes (bifunctional action) is less clear.

In animal studies, mixtures of fruits and vegetables at 20% in the diet had relatively weak and variable effects on CYP induction (Alink *et al.,* 1988). In contrast, potent GST induction was repeatedly observed in male rats (Alink *et al.*, 1988; Rijnkels & Alink, 1998). Several vegetables or vegetable extracts at levels of 7–20% in the diet have been shown to induce xenobiotic-metabolizing enzymes in rodents. Brassica vegetables appear to induce both phase I and II enzymes in liver, but apparently the induction of phase II enzymes is most pronounced. GST induction takes place in extrahepatic organs, including testis, small intestine, colon and kidney (Clapper *et al.*, 1997; Vang *et al.*, 1999, 2001). The bifunctional indole derivatives and the monofunctional isothiocyanates, formed during cutting or chewing of the fresh vegetables, seem to be the main active principles in this group of vegetables (Verhoeven *et al.,* 1997b).

The mode of induction by compounds from *Brassica* vegetables depends on their chemical structures, with indole derivatives and isothiocyanates having distinct effects. Binding of indole derivatives (e.g., diindolylmethane) to the aryl hydrocarbon receptor (AhR) leads to translocation of the AhR complex to the nucleus and interaction with xenobiotic response elements (XRE) in the Ah responsive gene promoter. Subsequent recruitment of co-activators and transcription factors results in transactivation (Safe, 2001). Induction of CYP1A, CYP1B, GSTA, NAD(P)H:quinone oxidoreductase (NQO1) and UGT is mediated through the AhR (Wolf, 2001). In contrast, isothiocyanates typically activate genes via the antioxidant or electrophile response element (ARE/EpRE) (Bonnesen *et al.*, 2001; Kong *et al.*, 2001). Regulation of NQO1, γ-glutamylcysteine synthase and several GSTs is mediated through the ARE/EpRE (Wolf, 2001).

Garlic preparations also increase GST and CYP2B1 activity in a dose-dependent manner in rat liver (Chen *et al.*, 2001a) and GST in breast tissue (Liu *et al.,* 1992) and decrease CYP activities, notably inducible CYP2E1 (Kwak *et al.,* 1995). Allyl polysulfides are the main active principles causing enzyme induction after treatment with the *Allium* species (Bianchini & Vainio, 2001) and cutting or squeezing of fresh garlic is important for their formation and activity. Data on other fruits or vegetables are sparse; the importance for drug interactions of the induction of CYP3A4 by grapefruit remains controversial (Bailey *et al.*, 1994).

Generally, induction of both phase I (e.g., XRE-driven) and phase II (e.g., ARE-driven) enzymes is thought to speed carcinogenic compounds through the metabolic pathway towards elimination, whereas agents that induce XRE-driven gene expression without stimulating ARE-driven expression are thought to enhance, rather than retard, chemical carcinogenesis (Bonnesen *et al.,* 2001). However, the picture is complex, for not all AhR ligands promote neoplastic disease and the promoter regions of some human biotransformation enzymes (e.g., *NQO1*) contain both an XRE and an ARE (Bonnesen *et al.,* 2001).

Numerous phytochemicals in fruits and vegetables, including flavonoids (Eaton *et al.*, 1996), isothiocyanates (Hecht, 1995) and allyl sulfides (Brady *et al.*, 1988), act as potent modulators of CYP activities *in vitro*; however, their effects are complex. Some have the capacity to inhibit certain enzymes at high concentrations of the compound, and to activate moderately the same enzyme at lower concentrations (Obermeier *et al.*, 1995). Others may act as competitive CYP inhibitors; even when present at low concentrations and in combination with other compounds, their actions can be significant (Yang *et al.*, 1994). Even slight differences in chemical structure can significantly alter activity. However, the concentrations of the individual compounds which have been shown to modulate CYP activities *in vitro* or in animal studies are still much higher than those likely to be achieved in humans at ordinary dietary levels of fruit and vegetables (Dragsted *et al.,* 1997). Good evidence that habitual dietary fruit and vegetable intakes modulate CYP activities in humans is still lacking. In animal models and cell systems, certain combinations of bioactive compounds may confer protection against genotoxic agents at levels that individual compounds do not achieve alone (Bonnesen *et al.*, 2001; Nho & Jeffery, 2001). Given that any particular *Brassica* species contains dozens of different glucosinolates (Fahey *et al.*, 2001), a mixture of glucosinolate-containing vegetables might also exert synergistic effects towards a lower-risk enzyme profile in humans.

Efforts to determine the effects of fruit and vegetable constituents on biotransformation enzymes in humans *in vivo* are hampered by lack of access to relevant tissues. Measurements of enzyme concentrations or activities in circulation or in peripheral leukocytes or of drug metabolites provide indirect support for the capacity of various vegetables, particularly *Brassica* species, to alter enzyme function in humans (Bogaards *et al.*, 1994; Nijhoff *et al.,* 1995a; Lampe *et al.*, 2000 a,b). Direct effects of vegetable diets on tissue levels of enzymes have been little explored, but Nijhoff *et al.* (1995b) showed that consumption of Brussels sprouts led to increased rectal GST-π.

Human studies of the effects of cruciferous vegetable supplementation on metabolism of carcinogens and promoting agents, such as estrogens, have also provided support for a protective effect through modulation of phase I and phase II enzymes. Watercress added to the diet of smokers significantly increased glucuronidation of nicotine and tobacco-carcinogen metabolites, but had modest effects on oxidative metabolism of these compounds (Hecht *et al.*, 1999; Murphy *et al.*, 2001). Similarly, broccoli and Brussels sprouts increased the metabolism (reducing the excretion) of heterocyclic aromatic amines derived from cooked meat; this implied induction of both CYP1A2 and relevant phase II enzymes (Murray *et al.*, 2001; Knize *et al.*, 2002).

Phase I and II enzymes that metabolize and/or are modulated by phytochemicals also contribute to inactivation of endogenous steroid hormones. They alter the potency of testosterone, estrogen and their derivatives via oxidation and hydroxylation reactions and conjugation with sulfate and glucuronide moieties (Aoyama *et al.*, 1990). Thus, induction or inhibition of these enzyme systems *in vivo* can modify the biological effects of hormones. Several studies have demonstrated that high dietary levels of cruciferous vegetables can increase 2-hydroxylation of estrogens in humans, probably by inducing CYP1A2 (Bradlow *et al.*, 1994; Kall *et al.*, 1996).

In conclusion, some mechanisms by which constituents of certain fruits and vegetables, notably *Brassica* and *Allium* species, induce phase I and II enzymes have been identified. However, the magnitude of effects in relevant human tissues remains unclear, because of the difficulties associated with accessing these tissues. Although induction may take place after consumption of several hundred grams of certain vegetables, effects of habitual dietary intakes of fruit and vegetables have received little attention.

Antioxidant enzymes

Modulation of antioxidant enzymes is hypothesized to affect protection against reactive oxygen species, but the cancer-preventive effects are not clear. An increase might be interpreted as a response to an oxidative challenge or as an increased capacity for antioxidative defence, depending upon the experimental design.

In aflatoxin B_1-dosed rats, CAT and SOD activity in blood decreased in relation to treatment time when the rats were treated with carrot, orange or tomato juice by gavage (He *et al.*, 1997). Since plasma glutathione levels and erythrocyte haemolysis also decreased, the simplest explanation for these results would be that the decrease in the enzymes was a response to a decreased need for degradation of hydrogen peroxide and superoxide. These reactive oxygen species were not measured in the study, however, and no feedback system is known for the regulation of antioxidant enzymes in erythrocytes, which have no capacity for *de novo* protein synthesis. In rats that were not pretreated with a carcinogen, treatment for two weeks with garlic led to a decrease in hydrogen peroxide in the renal cortex (Pedraza-Chaverri *et al.*, 2001), which coincided with a decrease in CAT, in support of a feedback regulation. Since CAT activity and protein levels were affected but not CAT mRNA levels (Pedraza-Chaverri *et al.*, 2000), post-translational regulation may take place. Short-term treatment with *Brassica* juices did not seem to influence GPX or CAT activity in liver (Sørensen *et al.*, 2001) or testes (Vang *et al.*, 1999). There is some evidence that the long-term effects of constitutive increases in GPX or SOD may be either protective against cancer (Zhao *et al.*, 2001; Shoichet *et al.*, 2002) or, conversely, increase cancer in transgenic animals (Lu *et al.*, 1997; Marikovsky *et al.*, 2002). Thus, in relation to cancer, changes in cellular antioxidant defence can have complex consequences.

In humans, expression and activities of SOD, CAT and GPX have been reported to be lower in tumours than in tumour-free adjacent tissue (Bostwick *et al.*, 2000; Ho *et al.*, 2001; Durak *et al.*, 1996), as well as in conditions associated with elevated cancer risk, such as chronic pancreatitis (Cullen *et al.*, 2003) and prostatic intraepithelial neoplasia (Bostwick *et al.*, 2000). These data support the hypothesis that inflammation and the associated decreases in antioxidant enzyme activity create an intracellular environment that favours DNA damage and the promotion of cancer (Ho *et al.*, 2001). This is likely to be a local tissue effect and causality remains to be established; however, antioxidant enzyme activities in blood may serve as surrogate markers of exposure and response to general oxidative stress. In healthy individuals, activities of CAT and GPX in whole blood haemolysates were significantly higher in those exposed to environmental tobacco smoke than in the unexposed, and levels of oxidative DNA damage were also higher in the exposed individuals (Howard *et al.*, 1998). The few studies that examined effects of fruit or vegetable interventions on antioxidant enzyme activities in humans restricted their measurements to erythrocytes or plasma. The responses varied widely with the fruit or vegetable type and dose, and only a few disparate foods were tested (Castenmiller *et al.*, 1999; Lean *et al.*, 1999; Nielsen *et al.*, 1999; Young *et al.*, 1999, 2000).

Inhibition of damage to macromolecules

Many carcinogens are activated to electrophilic metabolites, which react with cellular macromolecules, including DNA, proteins and lipids (Miller & Miller, 1981). Reactive radical species have a similar pattern of activity. Fruit and vegetables contain factors that decrease the damage to macromolecular structures, determined as decreases in oxidative damage, in adducts, or in the downstream consequences of adduct formation, such as mutations or repair.

Decreased oxidative damage to lipids, proteins and DNA

Experimental evidence is consistent with the view that increased oxidative DNA damage leads to elevated cancer risk (Halliwell, 2002). The 8-hydroxylation of guanine bases in DNA is a frequent type of oxidative DNA damage that can lead to GC to TA transversions unless repairs are made before DNA replication (Cheng *et al.*, 1992b). *In vivo*, when DNA is repaired by exonucleases, 8-hydroxy-2'-deoxyguanosine (8-OHdG) is subsequently excreted in the urine without further metabolism. Increased levels of urinary 8-OHdG are associated with conditions characterized by increased oxidative stress, such as smoking, whole-body irradiation and cytotoxic chemotherapy (Kasai *et al.*, 1986; Loft *et al.*, 1992; Tagesson *et al.*, 1995). Urinary levels of 8-OHdG also declined in response to intervention with Brussels sprouts (Verhagen *et al.*, 1997) or to a high-vegetable and fruit dietary intervention (Thompson *et al.*, 1999a), but tomato sauce or fruit juice supplements had no effect (Rao & Agarwal, 1998; Dragsted *et al.*, 2001). Raw Brussels sprouts did not affect urinary 8-OHdG excretion in rats, but cooked sprouts were effective and also significantly decreased nuclear 8-OHdG levels in bone marrow and kidneys (Deng *et al.*, 1998). Levels in the liver were unaffected. In another study, Brussels sprouts increased 8-OHdG levels in rat liver (Sørensen *et al.*, 2001).

As with many biomarkers associated with early events in carcinogenesis, direct and compelling evidence that 8-OHdG is a biomarker of subsequent cancer development in humans is not available. There are several explanations why elevated oxidative DNA damage may not be consistently associated with increased cancer risk (Halliwell, 2002). Measurement of 8-OHdG in urine and/or easily accessible tissues does not necessarily reflect damage in the target tissues of interest. For example, steady-state levels of 8-OHdG in rats can differ in different tissues (Devanaboyina & Gupta, 1996). The biomarker also does not adequately account for oxidative damage to RNA or to free deoxyguanosine and may be influenced by variations in DNA repair rates and by site of DNA oxidative damage. For example, unrepaired damage in genes encoding functional proteins crucial to tumour suppression such as p53 is likely to be more deleterious than damage in non-coding regions of DNA (Halliwell, 2002). Finally, another explanation for the lack of evidence from human studies may be insufficient statistical power due to the large inter-individual variation in 8-OHdG excretion levels and the relatively small sample sizes in many of the studies.

Tissue levels of oxidative damage remain difficult to measure, although recent improvements in DNA extraction have led to more reliable techniques (Ravanat *et al.*, 2002). Oxidative damage to DNA may also be determined by single-cell gel electrophoresis (SCGE) using restriction enzymes sensitive to oxidative damage to purines or pyrimidines. Protective effects towards DNA oxidation have been observed by this technique in several human studies after dietary modulation with fruits or vegetables (Duthie *et al.*, 1996; Pool-Zobel *et al.*, 1997; Collins *et al.*, 1998, 2001; Porrini *et al.*, 2002). However, the effects are generally not strong, and, as with other markers of oxidative DNA damage, the technique shows large inter-individual variation.

Animal and human evidence points towards decreased lipid oxidation with increasing fruit and vegetable intake (Miller *et al.*, 1998; Maskarinec *et al.*, 1999; Aprikian *et al.*, 2002). Lipid oxidation products have been observed to form adducts with DNA in several human organs, including oral mucosa, colon, liver and breast, leading to increased genetic damage, and have been implicated as a risk factor for human colorectal adenomas (Chaudhary *et al.*, 1994; Wang *et al.*, 1996; Zhang *et al.*, 2002a; Leuratti *et al.*, 2002). Adduct levels were similar to levels of 8-OHdG in human pancreas (Thompson *et al.*, 1999b), underlining their potential importance. Protection against lipid oxidation may therefore contribute to cancer prevention.

In conclusion, it appears that fruit and vegetables may decrease direct or indirect (through lipid oxidation products) oxidative damage to DNA, but the evidence linking such damage to decreased cancer risk is still very limited.

Decreased carcinogen–DNA binding or increased DNA repair

Many carcinogens bind to DNA and it is generally believed that changes in the DNA code resulting from such binding are the main cause of cancer initiation, constituting the core of subsequent heritable genetic damage from early precancerous lesions up to the development of malignancy. Any decrease in carcinogen–DNA binding is therefore important for the prevention of cancer. Decreased binding may

be a result of decreased absorption, decreased formation of activated carcinogen metabolites or increased detoxification and excretion. Many fruit and vegetables can influence these pathways, as discussed above. For instance, the potent inhibition of mammary DNA binding of DMBA in rats pretreated with garlic extracts (Liu *et al.*, 1992), the dependence of the effect on garlic crushing or ageing (Amagase & Milner, 1993; Song & Milner, 1999) and the synergy with selenite in eliciting this effect (Amagase *et al.*, 1996; Ip & Lisk, 1997; Schaffer *et al.*, 1997) are paralleled by similar actions of garlic and garlic constituents with respect to enzyme induction (Liu *et al.*, 1992; Ip & Lisk, 1997). This strongly implicates changes in the enzymatic activation and deactivation of DMBA in the prevention of DNA damage. Deactivation seems to be important, since urinary excretion products of polycyclic aromatic hydrocarbons have been observed to be less mutagenic after garlic supplementation in rats (Polasa & Krishnaswamy, 1997). Garlic preparations also decrease the activity of hepatic CYP2E1 (Kwak *et al.*, 1995), which is likely to account for the observed decrease in alkylation of DNA by nitrosamines and nitrosoureas (Lin *et al.*, 1994). Examples exist of bioactive components in fruits and vegetables which are able directly to scavenge electrophilic metabolites (Wang *et al.*, 1989; Athar *et al.*, 1989) or to shield sensitive sites in DNA (Teel, 1986; Barch & Fox, 1988). Such actions or other as yet unknown mechanisms may contribute to prevention of adduct formation by fruits and vegetables.

The evidence for a link between decreased carcinogen–DNA adduct formation and dietary fruit and vegetable intake in humans is very limited. In a cross-sectional study among 104 healthy Japanese men, no relationship was observed between total bulky adducts in human lymphocytes and plasma β-carotene, a marker of vegetable intake (Wang *et al.*, 1997). Evidence from human studies of polymorphisms in drug-metabolizing enzymes supports a link between carcinogen activation, adduct formation and cancer risk at several sites (Li *et al.*, 1996; Poirier, 1997; Peluso *et al.*, 1998; Li *et al.*, 2002; Chen *et al.*, 2002c), but clear evidence that dietary fruit and vegetables may reduce the risk of cancers specifically through this mechanism is still lacking.

Measurements of DNA binding reflect the balance between adduct formation and removal. Alterations in DNA repair will also influence this balance, and defects or polymorphisms in DNA-repair genes are known to affect cancer risk (Cheng *et al.*, 2000b; Matullo *et al.*, 2001; Bohr, 2002; Ito *et al.*, 2002; Tang *et al.*, 2002). However, there are no data indicating that fruit and vegetables enhance DNA repair. Thus, hepatic or renal expression of the DNA-repair enzyme OGG1 was not affected in rats after dosing with extracts of Brussels sprouts (Sørensen *et al.*, 2001). In a human study with complete dietary control, a 25-day intervention with 600 g of fruit and vegetables had no effect on expression of the repair enzymes OGG1 and ERCC1 in lymphocytes (Vogel *et al.*, 2002).

Decreased mutation or cytogenetic damage

Interaction of electrophilic compounds, including reactive oxygen or nitrogen species, with DNA bases can result in formation of DNA adducts or cross-links, which, during the course of attempted repair or replication, can lead to gene mutations, DNA strand breaks and other structural changes in DNA. Accumulation of genetic damage in crucial genes may contribute to the development of neoplastic cells. In animal studies, the majority of the twenty-odd different fruit and vegetable juices that have been tested counteracted cytogenetic damage to mouse bone marrow (Ito *et al.*, 1986; Edenharder *et al.*, 1998). The observation that inhibitory activity was found with the majority of preparations suggests that this effect may be important for the preventive effects of fruit and vegetables. Mutagenicity *in vivo* is generally regarded as a strong predictor of carcinogenicity in animal tests and decreased chromosomal damage may similarly be a predictor of protection against tumorigenicity. As already discussed, adduct levels seem to correlate closely with treatments which cause a decrease in carcinogen activation, and it is possible that the ability of many fruits and vegetables to influence drug-metabolizing enzymes underlies the surprisingly common ability of these foods to decrease cytogenetic damage in animals. In contrast, the effect of grapefruit juice on phase I enzymes does not seem to lead to any alteration of the metabolism of the heterocyclic aromatic amine PhIP. Neither does the juice cause changes in the bioavailability of PhIP, so the inhibition of PhIP-induced strand breakage in colon DNA by grapefruit juice must involve other mechanisms (Miyata *et al.*, 2002). Thus, links between the influence of dietary fruit and vegetables on carcinogen metabolism, adduct formation and decreased mutagenic or clastogenic effects in humans or in animals are still not clearly established.

Human studies give an equivocal picture of the ability of fruits or vegetables to decrease DNA strand breaks or micronuclei. Four studies used the comet assay without restriction enzymes or *ex vivo* oxidative challenge and one of them observed a decreased level of strand breaks after intervention with tomato and carrot juice or spinach powder (Pool-Zobel *et al.*, 1997). The others failed to show such an effect after intervention with

onion, kiwi fruit or a mixed-vegetable burger (Boyle *et al.*, 2000; van den Berg *et al.*, 2001; Collins *et al.*, 2001). Vegetable intake was negatively correlated with micronucleus formation in peripheral blood lymphocytes in a cross-sectional study in Hungary, whereas no effect of fresh fruit intake on micronucleated cells in the oesophageal mucosa was observed in young Chinese men and women (Chang-Claude *et al.*, 1992; Pastor *et al.*, 2002).

In humans, there seems to be a strong link between chromosomal aberrations and subsequent cancer risk (Hagmar *et al.*, 1998; Bonassi *et al.*, 2000), but no studies have provided a strong link between the other cytogenetic end-points and cancer risk.

In conclusion, there is good evidence from animal studies that fruit and vegetables decrease cytogenetic damage, but the human evidence is weak.

Post-initiation effects

The biokinetics of cell turnover are of central importance to cancer prevention, since a hallmark of cancer is dysregulation of the cell cycle. Effects on cell turnover are important early as well as late in the development of cancer. Toxic effects leading to enhanced proliferation increase the efficiency of cancer initiation. Many experimental co-carcinogens are irritants or agents causing inflammation. The same is true for many substances that act as promoters in two-stage carcinogenesis experiments and for factors that enhance human cancer but lack a potential to cause direct DNA damage. Inhibition of excess cell proliferation or increased apoptosis would consequently be expected to prevent cancer; however the picture is complex and it is necessary to gain better understanding of the underlying processes before generalizing from specific effects affecting the cell cycle to subsequent cancer prevention. Many specific compounds derived from plant foods affect cell turnover in cell culture or in animal studies, but relatively few studies have examined the effects of increased intake of preparations made from whole fruits or vegetables on cell turnover and they are all concerned with markers of cell proliferation, mitosis or apoptosis.

Fruit and vegetable preparations given after treatment with an initiator have been observed to inhibit tumour development and growth and to delay cancer onset in some experimental studies, but the evidence is equivocal. Garlic preparations had preventive activity against breast cancer when dosed after an initiator (Ip & Lisk, 1995). Lyophilized strawberries or black raspberries in the diet inhibited rat oesophageal tumorigenicity when given after initiation with NMBA (Carlton *et al.*, 2001; Kresty *et al.*, 2001). Feeding cabbage after initiation inhibited tumour development in the mouse colon in one of two similar studies (Temple & Basu, 1987; Temple & el-Khatib, 1987), but in a third study, feeding a fruit and vegetable mixture after azoxymethane treatment had only marginal effects on rat colon carcinogenesis (Rijnkels *et al.*, 1998). Likewise, pure mandarin juice did not significantly affect lung tumorigenesis when given to mice after initiation with NNK (Kohno *et al.*, 2001) and the post-initiation effects of Brussels sprouts or garlic powder on DMBA-induced rat breast cancer were also much weaker than dosing before and during initiation (Stoewsand *et al.*, 1988; Ip *et al.*, 1992). In adenomatous polyp patients, intervention with a diet low in fat and high in fibre, fruits and vegetables did not reduce the risk for recurrence of colorectal adenomas (Schatzkin *et al.*, 2000).

Modulation of cell proliferation or apoptosis

A range of different lyophilized vegetables decreased the mitotic index in the rat colon without affecting proliferating cell nuclear antigen (PCNA) (O'Neill *et al.*, 1997). However, in rats initiated with NMBA, feeding lyophilized raspberries decreased oesophageal levels of PCNA (Kresty *et al.*, 2001). Citrus products have been observed to enhance cyclin D1, apoptosis and activity of T killer cells in the colon and to decrease mucosal PCNA and the proliferation zone, but the effect was not consistently associated with decreased tumour incidence (Miyagi *et al.*, 2000; Tanaka *et al.*, 2000; Kossoy *et al.*, 2001).

There is no direct evidence for an effect of fruit and vegetable consumption on cell proliferation in humans. Although constituents of fruit and vegetables can affect indices of cell proliferation and turnover *in vitro*, there is little evidence from experiments with dietary change or from feeding studies with whole fruits or vegetable preparations.

In summary, the evidence for a post-initiation effect of fruit and vegetables is relatively weak.

Immune function

In vitro and *in vivo* studies suggest a possible role of immunological defence against cancer and its metastasis (outlined in Imai *et al.*, 2000). The mechanism of immunosurveillance (Burnet, 1970) is hypothesized to be non-specific, with natural killer cells, activated macrophages, K cells and NKT cells playing key roles (Kubena & McMurray, 1996). Although immune-compromised individuals are at higher risk for certain cancers such as Kaposi sarcoma, data on cancer risk in relation to immune function in the general population are sparse. One cohort study in Japan found that medium and high cytotoxic activity of peripheral

lymphocytes at study entry was associated with reduced risk of cancer (all sites combined) and that low activity was associated with increased risk of cancer at 11-year follow-up (Imai *et al.*, 2000). The relationship of single nutrients to immune function (Chandra & Sarchielli, 1993), as well as the effect of nutrient–nutrient interactions (Kubena & McMurray, 1996) in humans and in animal models support a role for fruits and vegetables in maintaining immune function, but the effects of whole fruits and vegetables and their constituents on cancer-related immune function parameters have been little studied.