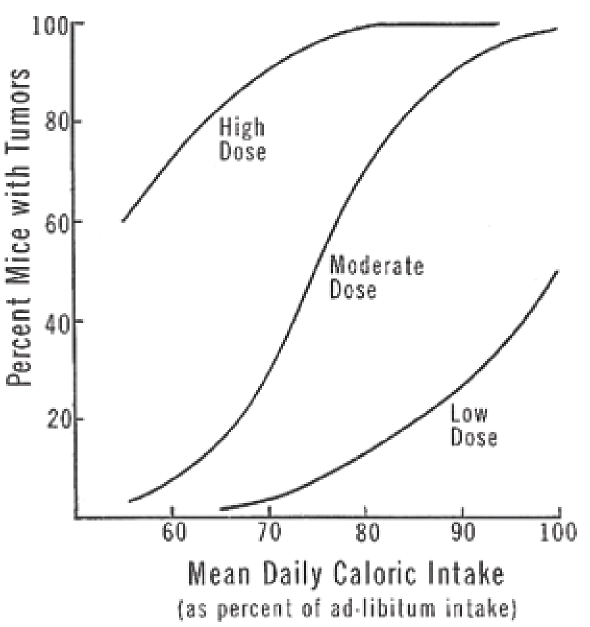
NUTRITION, METABOLISM, AND CANCER

NUTRITION, METABOLISM, AND CANCER

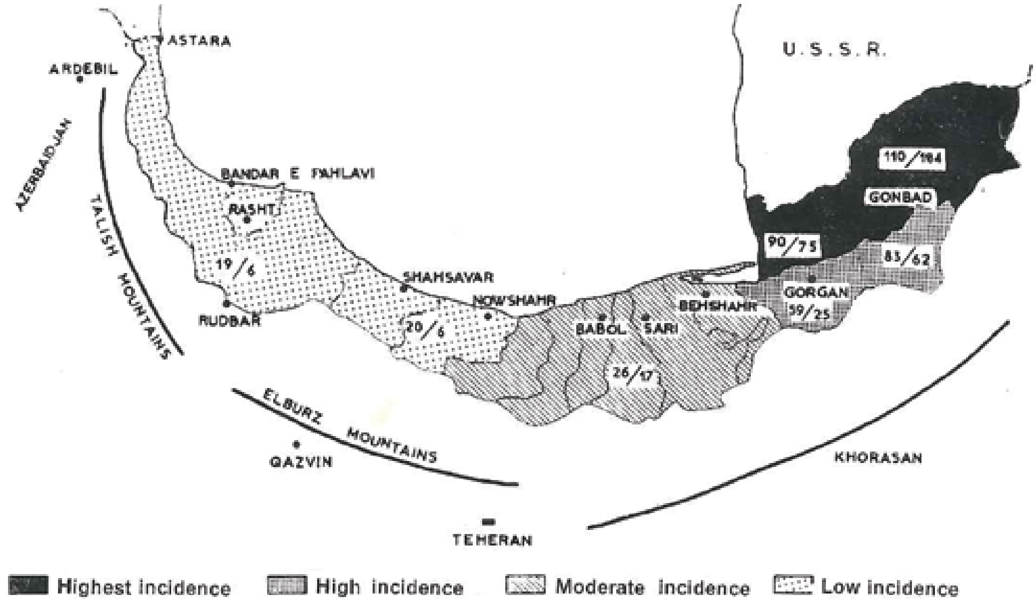
"Individuals who overeat and are overweight when past middle age are more likely to die of cancer than persons of average weight or less. ... It seems reasonable to expect that the avoidance of overweight would result in the *prevention* of a considerable number of cancers in man. ... Even moderate continued caloric restriction or control of body weight deters the development of neoplasms." The date of this text is startling: 1953. In the first volume of *Advances in Cancer Research*, published that year, Albert Tannenbaum and Herbert Silverstone contributed a review entitled "Nutrition in relation to cancer". It reported results from six studies using data on cancer mortality and body weight from insurance companies in the USA, and one questionnaire-based survey of dietary habits. More fundamentally, it presented the findings of the pioneering experimental studies conducted in the 1940s and 1950s in Tannenbaum's laboratory, which clearly showed that a restriction in caloric intake induced a sizeable decrease in the incidence of tumours in mice compared with an "eat as you wish" (ad libitum) diet. The reduction occurred both for cancers arising spontaneously in mice and for cancers induced by exposure to known carcinogenic chemicals. The scene was set to confirm these results in human populations using more accurate measurements, particularly of dietary assessment, and – much more challenging – to try and understand how caloric intake may influence cancer occurrence in different organs in humans.



Idealized relationship between degree of caloric restriction and tumour incidence: curves that can be obtained with low, moderate, or high doses of carcinogenic chemicals.

STEPPING UP THE EPIDEMIOLOGY OF NUTRITION AND CANCER

Diet is an obvious possible cause of digestive cancers, particularly those that exhibit wide variation in occurrence between populations. One example is oesophageal cancer. In the high-incidence areas of Brittany, rates are elevated mostly among men, and an early IARC study clearly indicated tobacco smoking and alcohol consumption as causal agents (see the chapter "Innovation in statistical methods"). Dietary factors, also explored in the studies in Brittany and Normandy, suggested a protective effect of citrus fruits, possibly related to their vitamin C content.



Incidence of oesophageal cancer in the Caspian littoral region of the Islamic Republic of Iran (1970). Numbers indicate rates per 100 000 people per year (males/females).

Unlike in Brittany and Normandy, a high occurrence of oesophageal cancer was reported for both men and women in the Caspian littoral region of the Islamic Republic of Iran, bounded to the south-west by the Elburz Mountains. To firmly document the reports, a population-based cancer registry was established in 1969 as a joint endeavour of Tehran University and IARC (see "The IARC diaspora" in the chapter "The birth of IARC"). The registry confirmed the high incidence of oesophageal cancer in the eastern part of the littoral, the area now known as Golestan Province, and particularly in northern Gonbad, a semidesert plain inhabited mainly by people of Turkmen ethnicity, where incidence was much higher in women than in men. Rates

Some inhabitants of the rural area in the Islamic Republic of Iran where the incidence of oesophageal cancer is high.

declined steadily towards the west, and 300 kilometres from Golestan they were one tenth as high, with a preponderance of cases in men.

To address the causes of this striking pattern of occurrence, several IARC collaborative studies were conducted in the 1970s. They pointed to different possible factors, in particular low socioeconomic status, thermal injury from consumption of very hot tea, and exposure to carcinogens in combustion products, including from opium use. However, none of these could be soundly established as causes. After a quiescent phase of two decades, a new cycle of investigation started in the 21st century. A key component is the Golestan Cohort Study, a prospective study of oesophageal cancer conducted by IARC in collaboration with Tehran University and the United States National Cancer Institute (see "Back into action: the Golestan Cohort Study").

Collecting information about diet on one or more occasions and then relating it to the subsequent occurrence of cancer, as is done in prospective cohort studies (like the Golestan Cohort Study), is much preferable to collecting dietary information in cancer cases and non-cancer controls, as is done in case–control studies, because it is less prone to biases and errors. People with cancer have often altered their diet because of the disease and may be very inaccurate in reporting what they were eating at earlier times, except for items that can be distinctly remembered, like alcohol consumption. However, prospective studies are much more difficult and lengthy than case–control studies. A large population needs to be assembled and dietary information collected for each person, so that an adequate number of cancer cases can be obtained – usually after at least 10 years – to explore the relationship between dietary items and cancer occurrence. A welcome opportunity to "warm up" for the task of embarking on prospective dietary studies came to IARC from an interested group of investigators in the city of Malmö, Sweden, where a pilot investigation was conducted collaboratively and demonstrated the feasibility of using complex dietary assessment methods (see "How good are dietary measurements?").

THE EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION

Beginnings

By the early 1980s, the scientific community had realized that convincing answers to diet–cancer hypotheses could be obtained only by investing in large population-based prospective cohort studies. The Harvard School of Public Health had started the Nurses' Health Study in 1976 and expanded it in the 1980s. In Europe, an excellent opportunity arose for IARC through the Europe Against Cancer programme, established in 1985 by the European Community. Within this programme, diet was earmarked as a key priority, provided that the research would involve a substantial number of European countries. This would mean mounting one very large project, organized in several countries, with coordinated and standardized protocols.

BACK INTO ACTION: THE GOLESTAN COHORT STUDY

The Golestan Cohort Study was launched in January 2004, a contemporary and technically advanced successor to the early IARC projects of the 1960s and 1970s. It has three primary aims.

The first aim is to identify risk factors for oesophageal cancer in a population with a high frequency of the disease, by a comprehensive assessment of personal characteristics, work and medical history, physical activity, body measurements, tobacco use, alcohol consumption, and opium use. Particular attention is given to diet, which is evaluated through a food questionnaire specially developed for use in this population. The questionnaire covers the consumption of more than 100 items, including bread and cereals, meat and dairy products, oils, confectionery, legumes, vegetables, fruits, and condiments, as well as cooking methods.

The second aim is to take advantage of IARC's experience in biobanking to establish a local or national repository for long-term storage of blood, urine, hair, and nail specimens to be used in molecular biology and genetic studies. Half of the frozen blood samples have been sent to Lyon for storage in the IARC Biobank.

The third aim is to provide a model for population-based studies in areas and countries in economic and social transition, based on collaborations between international institutions like IARC and local and national health workers, authorities, and research centres.

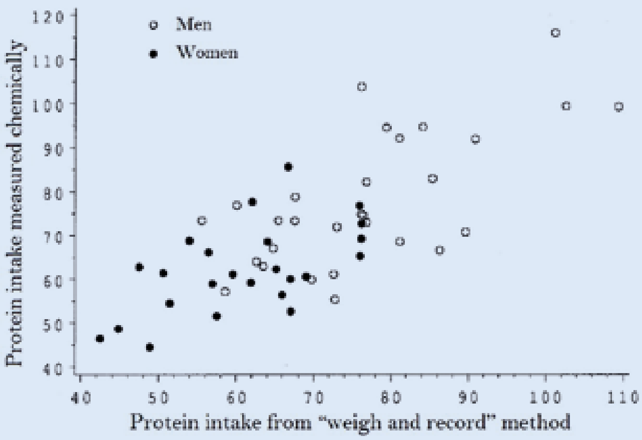
The project has progressed successfully, with Iranian investigators making a leading contribution. The plan involved the enrolment into the cohort of 50 000 people aged 45–75 years, 20% from urban areas (in the city of Gonbad) and 80% from rural areas, with equal numbers of men and women. The target number of participants was reached in 2008, and people are now actively followed up through annual telephone calls by local health workers and through a review of monthly death registration data to record causes of death and cases of cancer.

The full value of any prospective cohort study emerges only after many years of follow-up, when enough cancer cases have been recorded. However, the Golestan Cohort Study is already generating useful information, in particular on possible early biological markers of oesophageal cancer and on the determining factors of gastro-oesophageal reflux, which is today a common cause of discomfort not only in the Islamic Republic of Iran but worldwide, and in turn a potential cause of one type of oesophageal cancer.

The tower in the central part of the city of Gonbad-e Qabus in the Islamic Republic of Iran has been a UNESCO World Heritage Site since 2012. The 72-metre brick tower, built in 1006, is a decagonal building with a conic roof. Gonbad houses the Golestan Cohort Study Center, a research centre established specifically for the project.

HOW GOOD ARE DIETARY MEASUREMENTS?

In case–control studies, dietary assessment in cases may be distorted by changes in diet (or in the recollection of diet by the patient) due to the presence of the cancer, but even in healthy people dietary measurements are challenging and potentially subject to errors. Many meals vary in composition from day to day. An individual's diet may also undergo more general changes, in food types and quantity, over the long term because of ageing or changing personal circumstances, such as living alone or in a family.



Results from the Malmö food study. The mean daily intake of protein determined chemically from nitrogen output in samples of urine is plotted against the mean daily intake of protein estimated by means of food tables from the "weigh and record" method.

Other than in experimental and rigidly controlled conditions (as in laboratory studies of metabolism), there is no perfect method to measure what a person has eaten and drunk over a prolonged period. Methods that weigh and record all foods and beverages seem an optimal solution, but they are cumbersome and not applicable on a large scale. In the pilot study in Malmö, which involved 500 people, six 3-day periods of weighing and recording, supervised by a dietician, were evenly distributed over a 1-year period. These records, faithfully capturing what had been eaten and drunk during each of the 18 days, were considered to be representative of that person's typical diet.

Indeed, as the graph shows, for a nutrient like protein there is good agreement between the estimates of intake derived by the "weigh and record" method and the actual intake measured chemically. It was therefore reasonable to regard the results from the "weigh and record" method as the yardstick or reference against which to evaluate the validity of methods that are more practicable on the large scale, as are needed in a cohort study involving thousands of participants. Two such methods were tested. First, an extensive questionnaire, with the help of pictures of food portion sizes, was used to gather information on the frequency of consumption of more than 300 foods over the preceding 12 months. Second, a reduced questionnaire, involving only 130 foods, was used, supplemented by recording (but not weighing) all foods and beverages consumed over a 2-week period. Both methods provided satisfactory agreement with the reference method.

A further degree of complexity is inherent in any dietary study because the research questions concern not only what people eat and drink but also the specific nutrients, like proteins, sugars, fats, vitamins, and alcohol, contained in foods and beverages. Therefore, after a dietary assessment is performed, the intakes need to be converted into amounts of nutrients. This can be done using published conversion tables. These food tables indicate the amounts of nutrients present in each of a long list of typical foods and beverages, as actually measured by methods of analytical chemistry. However, food tables may be incomplete or out of date, or may not even have been developed for the foods commonly consumed in some countries. In fact, when the European Prospective Investigation into Cancer and Nutrition (EPIC) project began, the first step was to develop appropriate food conversion tables. IARC coordinated and assisted in this complex exercise of validating methods in each of the participating countries, including assembling the pertinent food tables and working towards their harmonization.

Establishing such a project was a major challenge, including all methods and procedures, from the recruitment of subjects and the design of questionnaires for collecting data on diet and many behavioural factors to the collection of biological samples and the controversial inclusion of anthropometric measurements. Moreover, the protocols established had to be as similar as possible, while maintaining adaptability to the languages and cultures of the different European countries. For most investigators, at IARC as well as in the individual countries, this was a novel experience that required a full, long-term commitment.

Elio Riboli led the conception and development of the European Prospective Investigation into Cancer and Nutrition (EPIC) project and the EPIC biobank. In 2005, after 20 years at IARC, he moved to Imperial College London as a professor of cancer epidemiology; he became director of the School of Public Health there when it was established in 2010.

Map showing the location of all EPIC collaborating centres, including the joint coordinating centres: IARC, in Lyon, and Imperial College London (ICL).

The project was also a new direction within IARC's overall research strategy. In the words of Elio Riboli, "At IARC, research on the causes of cancer had historically focused on chemical, physical, and biological carcinogens, and since its creation IARC has made major contributions to the identification of exogenous carcinogens. This makes even more innovative and forward-looking the leading role that IARC has played in the investigation of the role of nutritional, metabolic, and – more generally – endogenous host factors in cancer etiology. IARC was one of the first top-level research centres to establish a Nutrition, Hormones, and Cancer Programme, in the early 1980s, which led to the establishment of the largest nutrition- and metabolism-focused prospective cohort study with a biorepository of the 20th century. These achievements were made possible by the international standing of the institution, its visionary leadership, the dedication of its staff, and its ability to develop an extensive network of long-term collaborators."

The planning and piloting of the project that soon became known as the European Prospective Investigation into Cancer and Nutrition (EPIC) started with a series of methodological and feasibility studies. They included, in particular, testing the validity of dietary questionnaires within each country, along the same lines as the investigation previously carried out in Malmö, and developing the procedures for collecting and storing biological samples for the associated biorepository. These pilot studies provided very encouraging results, which supported the European Community's decision in 1992 to fund EPIC jointly with several national granting organizations. Recruitment of study participants and collection of data and biological samples started in 1993 in four countries (France, Italy, Spain, and the United Kingdom) and was extended between 1994 and 1998 to include six further countries (Germany, Greece, and the Netherlands and the three Scandinavian countries, Denmark, Norway, and Sweden, which adopted their own procedures for the storage of biological samples). Enrolment was completed in 1999, when the cohort included more than half a million people in 23 EPIC centres in the 10 participating countries.

MEASURING FOODS AND NUTRIENTS IN AN INTERNATIONAL CONTEXT

Assessing diet in a variety of populations poses a major methodological challenge. The diet of EPIC participants was assessed by different instruments that had been developed and validated previously in local methodological studies. The results of these studies, together with the need for a “flexible uniformity”, guided the choice of measurement methods. These methods needed to be as uniform as possible across centres, to allow results in different cohorts to be compared. At the same time, they needed to be flexibly adapted to local circumstances. For instance, in some places participants could easily complete a dietary questionnaire by themselves, while in others an interview appeared to be preferable. A major source of local variability is, of course, diet itself: foods and dishes that are eaten frequently in some places may seldom or never be eaten in other places. The questionnaires had to be suitable for use under these variable circumstances.

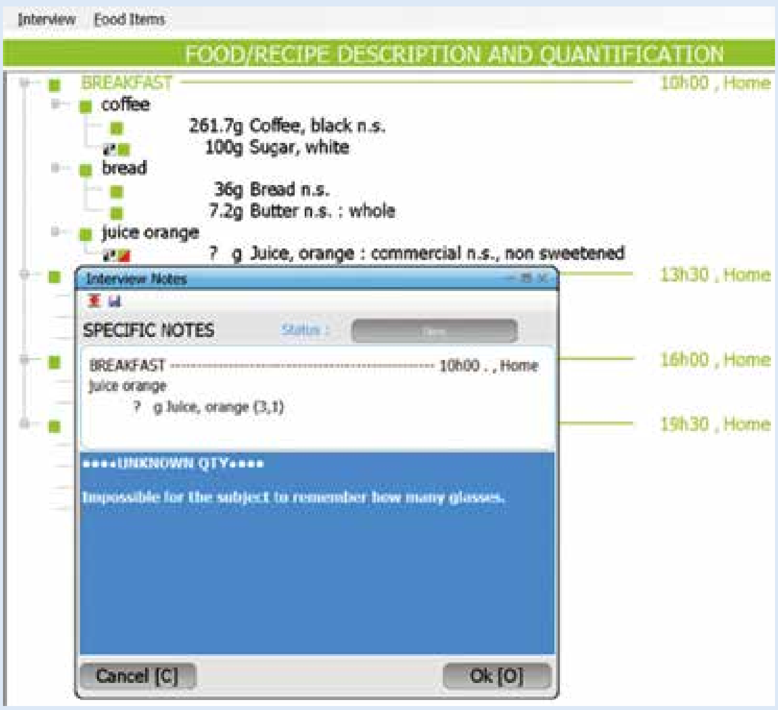
Three dietary assessment methods were eventually adopted. The first was *quantitative dietary questionnaires* containing up to 260 food items and systematically estimating individual average portions. They were used in six countries (France, Germany, Greece, Italy, the Netherlands, and Spain). To improve the reliability of the acquired information, centres in two countries (Italy and Spain) performed a face-to-face dietary interview using a computerized dietary program. The second method was *semiquantitative food frequency questionnaires*, in which a list of food items was compiled for each participant and the same fixed portion size for each food item was assigned to all participants. These were used in three countries (Denmark, Norway, and Sweden). Third, *combined dietary methods* were used in the United Kingdom and in Malmö (Sweden), following the principle of the method developed in Malmö, which combined a questionnaire on the frequency of food consumption with a detailed record of diet for a fixed number of days.

Agreeing on just three methods for 23 centres went a long way towards uniformity, but the issue remained of ensuring that these methods were comparable. To this end, additional dietary measurements were collected through a newly developed instrument of recall of diet over a 24-hour period (EPIC-Soft) in representative subsamples of 8% of participants in each cohort (see “Novel instruments for studies of diet worldwide”). In total, as many as 37 000 EPIC-Soft measurements were collected from EPIC participants. These were used as a reference to align on a common scale the food and nutrient estimates obtained by the three different methods in the 23 centres. Within EPIC, the estimates of amounts of several nutrients, like proteins, lipids, sugars, and vitamins, were derived from the food consumption data by using a conversion table that provides the amount of each nutrient present in each gram of each food. A specific project, the European Nutrient Database (ENDB), was required to develop a common conversion table – in fact, a common food composition database – standardized across the 10 participating European countries.

Examples of photographs of different portion sizes, used to support the quantification of consumed foods.

NOVEL INSTRUMENTS FOR STUDIES OF DIET WORLDWIDE

EPIC-Soft, recently renamed GloboDiet, is a computerized tool for detailed recall of all items a person has eaten and drunk during the previous 24 hours. This interview-based dietary assessment instrument has been successfully used and has been shown to increase the accuracy of dietary data measurements in international settings. It was developed and is maintained by IARC. It was first used within the EPIC study, for which it was initially designed, and is currently in use or planned to be used in several different national and international studies in Europe. Today, GloboDiet is the only available software package that has been constructed to provide standardized individual food consumption data for adults in different European populations. GloboDiet enables the description and quantification of all items consumed, selected from 1500–3000 foods and 150–450 recipe ingredients specific to each country. The software automatically codes food items and recipe ingredients and calculates nutrient intake. This results in an extremely detailed description of the type and amount of all items that have been eaten or drunk by a person during the previous 24 hours.



An example of a note file generated during a GloboDiet interview.

GloboDiet has been used in several projects, in particular in the European Food Consumption Survey Methods (EFCOSUM) Project and the European Food Consumption Validation (ECOVAL) Project. An adaptation for food records in children has been positively evaluated within the Pilot Study for the Assessment of Nutrient Intake and Food Consumption Among Kids in Europe (PANCAKE) Project. Like the European Nutrient Database, development of the GloboDiet methodology was prompted by the needs of the EPIC study. Both of these tools have enabled far wider progress in epidemiological investigations of diet and disease and in surveys monitoring the evolution of dietary habits across populations worldwide. GloboDiet is now a key instrument of a joint IARC-World Health Organization Global Nutrition Surveillance initiative aimed at improving nutritional surveillance for the control of noncommunicable diseases.

> *EPIC was – and still is – among the biggest international studies available. It was a very ambitious programme, and it started at IARC at a time when these types of big projects were not as common, so this is what makes it very special.*
> – Manolis Kogevinas, former IARC scientist

An extensive data collection

At each EPIC collaborating centre, detailed information was collected on each participant with respect to diet, anthropometric measurements (weight, height, waist and hip circumference), medical history, and a spectrum of lifestyle habits (see "Measuring foods and nutrients in an international context"). This included items related to education and socioeconomic status; current job, and current and past occupations, which might have led to exposure to carcinogens; history of previous illnesses, disorders, or surgical operations; lifetime history of tobacco smoking; lifetime history of alcohol consumption; physical activity (occupational, walking, cycling, gardening, housework, physical exercise, climbing stairs); menstrual and reproductive history; and use of exogenous hormones for contraception and postmenopausal hormone replacement therapy. At most EPIC centres, blood pressure was also measured at recruitment. Biological samples including plasma, serum, white blood cells, and red blood cells were collected at recruitment from about 400 000 participants. A unique feature was the "split sample" storage of biological samples, at IARC and at the EPIC centres (see "The EPIC repository of biological samples").

Waist circumference, an indicator of fat distribution within the body, is one of the anthropometric variables measured in EPIC study participants.

THE EPIC REPOSITORY OF BIOLOGICAL SAMPLES

A key resource of the EPIC project is the availability of blood samples taken from participants at the time of recruitment into the cohort. For each participant, blood plasma, blood serum, white blood cells (containing DNA), and red blood cells were collected for long-term storage. The storage procedure differed between the three Scandinavian countries and the other seven participating countries (France, Germany, Greece, Italy, the Netherlands, Spain, and the United Kingdom).

For the seven countries, IARC designed, tested, and developed a novel storage system, which was capable of satisfying the requirements of optimal storage conditions and of dividing samples into small aliquots (so that when a sample is analysed for a specific research question, only a small aliquot is consumed). Each sample was aliquoted into 28 plastic straws containing 0.5 millilitres each. To ensure a high degree of standardization, the materials (syringes, straws, etc.) were purchased by IARC and distributed to the centres. Each sample was then split into two identical sets of 14 aliquots each. One set was stored locally and one was sent to IARC to be stored in a central biorepository in liquid nitrogen at −196 °C, an optimal freezing temperature for inhibiting reactions of biochemical decay. A very similar approach was followed in Norway, whereas in Denmark and Sweden blood samples were stored in 2-millilitre tubes and kept only in local repositories (since the containers at IARC were unsuitable for storage of tubes). In Denmark the samples are stored at −150 °C in nitrogen vapour, and in Sweden they are kept at −70 °C in freezers.

When it was established, the EPIC storage system housed a combined total of nearly 9 million aliquots, centrally at IARC and at national facilities, constituting one of the largest collections in the world for biochemical and genetic investigations of cancer and other chronic diseases. Since then, more than 10% of these aliquots have been used for research projects.

The complex structure of the central IARC biorepository. Plastic straws have proven well suited for storing blood in the EPIC project. Each straw is labelled with the participant's identification code and is colour-coded to indicate its contents: red for plasma, yellow for serum, blue for white blood cells, and green for red blood cells. Their tiny size enables storage of small quantities of fluid (0.5 millilitres), and the plastic material permits sealing with an automatic device once a straw is filled. All the straws containing samples from the same participant are stored together in a coloured visotube. The visotubes are placed inside a goblet (each goblet contains 14 visotubes), which in turn is stored in a canister. Canisters are arranged in concentric circles inside each of 33 liquid nitrogen containers. When a sample needs to be retrieved, a software package indicates the sample's container, canister, goblet, and visotube.

The challenge of following up more than half a million people

In the mid-1990s, regular follow-up of EPIC study participants began, to ascertain whether a participant was alive and whether he or she had been diagnosed with any kind of cancer. Additional follow-up to measure changes in lifestyle, health conditions, diagnosed diseases, and related treatment was conducted a few years after recruitment, at least once in all EPIC study centres. The number of cancers developing in the cohort by 2016 is estimated to be more than 96 000. This large number of incident cancer cases with prospectively collected lifestyle data and blood specimens enables EPIC to address state-of-the-art scientific hypotheses about the etiology and prevention of several forms of both common and rare cancers with a high degree of precision and confidence.

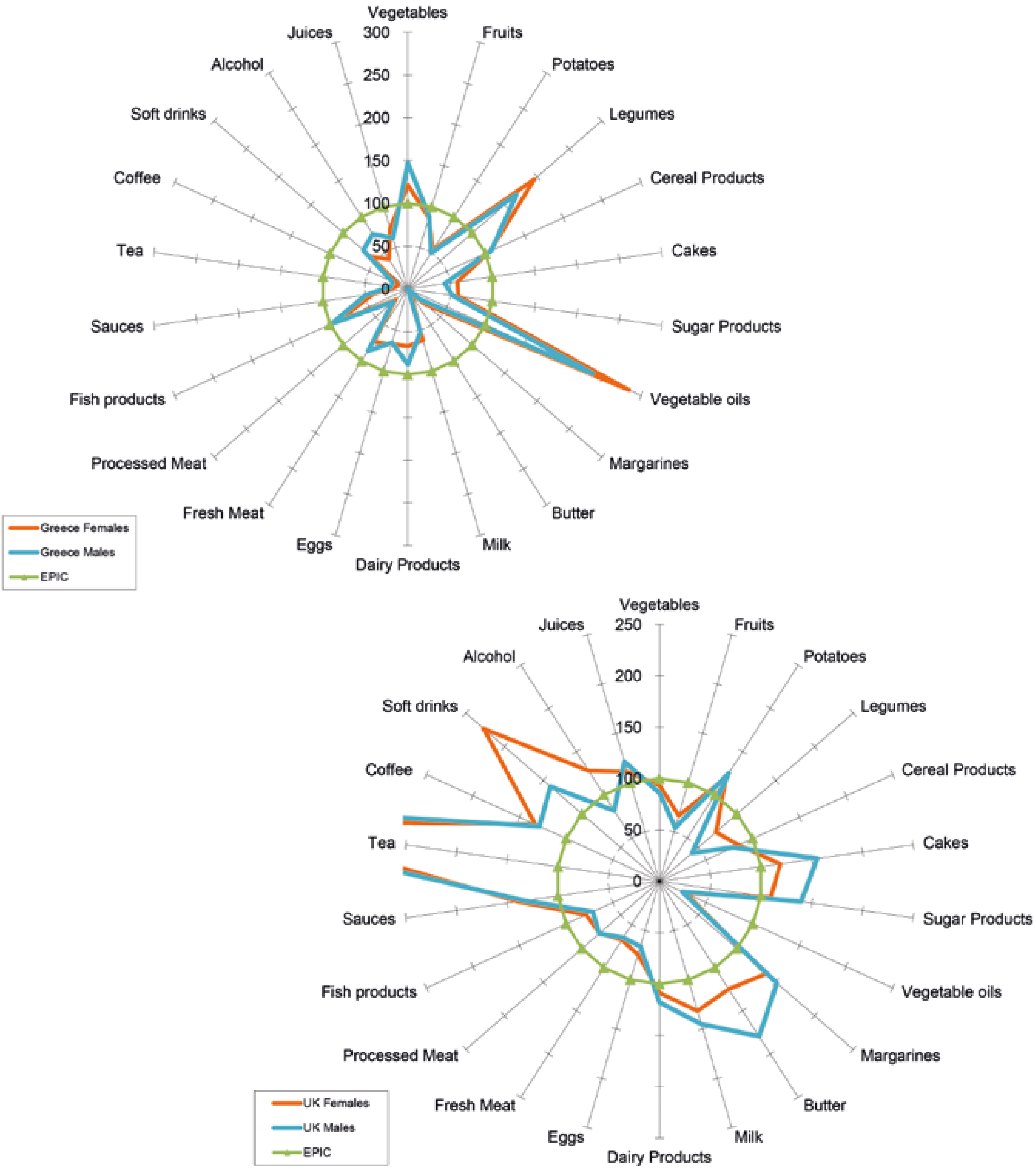
Sex-specific expected frequency of major cancer sites in the EPIC cohort by 2016

Sex	Site					
	Breast	**Colorectum**	**Lung**	**Prostate**	**Stomach**	**All cancers**
Men	50	4907	4152	10 771	1198	32 334
Women	24 899	7669	3852	0	1010	64 242
Total	24 949	12 576	8004	10 771	2208	96 576

A RICH AND EXPANDING HARVEST OF SCIENTIFIC RESULTS

Early results

EPIC started to produce results as soon as recruitment of the cohort was completed in 1999. The first published reports provided a full picture of the populations of the 10 countries included in the cohort. Physical traits (e.g. weight, height), physical activity, and lifestyle habits like tobacco smoking and alcohol consumption were seen to vary within and between countries. These observed variations underscore the rationale for the initial selection of European regions from north to south and from east to west, aimed at capitalizing on the variability in diet and lifestyle to maximize the power of the study to identify relationships with cancer risk. For instance, large differences in alcohol consumption were found between countries: total alcohol consumption ranged from 3–4 grams per day among women in Greece to about 20 grams per day among women in Denmark and about 40 grams per day among men in Spain. Of particular importance were the differences in food consumption and dietary patterns, notably between the southern European countries and those in central and northern Europe. These differences were described with greater accuracy than in any previously available study. These initial results from EPIC raised the standard of investigation and contributed to a better knowledge of personal and nutritional characteristics relevant to health in 10 European populations.



A multidimensional comparison of dietary patterns from the EPIC study. The average consumption for a country of each of 22 foods is expressed as a percentage of the average for all countries, indicated by the green reference circle of radius 100%. A point inside the green circle indicates that people in the country eat less of that food than the all-country average, and a point outside the circle that they eat more. Joining the 22 points generates a "dietary profile" for a country that provides a visual representation of the difference in dietary habits between different countries. For example, the profile for Greece shows "spikes" of high consumption of vegetable oils, legumes, and vegetables, whereas the profile for the United Kingdom shows a very high consumption of tea together with an above-average consumption of butter, margarines, and soft drinks.

Follow-up results

Studies of specific cancers started when a sufficient number of cases of a particular cancer had accrued. These studies were, and are, conducted by international and multidisciplinary Working Groups, each focusing on a topic to be investigated (e.g. breast cancer in relation to consumption of fats, or colon cancer in relation to fibre consumption). Working Groups have a variable composition of members, depending on the interest that individual researchers have in participating in a group, and are coordinated and led by any of the researchers actively involved in EPIC at IARC or in the collaborating countries. Investigators not belonging to the EPIC network are often included in Working Groups, especially when they contribute particular types of expertise.

Two main types of studies are implemented. The first type is for investigations that require only the use of data collected through questionnaires (as is the case for diet, lifestyle habits, or physical exercise) or anthropometric measurements (like weight and height). These analyses are performed on the whole cohort of more than half a million people, with subanalyses by centre, country, sex, and so forth. The second type of study is for investigations that require measurements on blood samples, such as determining plasma concentrations of vitamins or genotyping genetic variants in DNA from white blood cells. In these studies, the laboratory measurements are compared between cancer cases and a random sample of subjects in the cohort. This type of design is known as a case–control study nested within a cohort study. It provides essentially the same information as a study on the entire cohort of more than half a million people, while enabling conservative use of precious blood specimens, of which only a few hundreds or thousands need to be analysed in the laboratory.

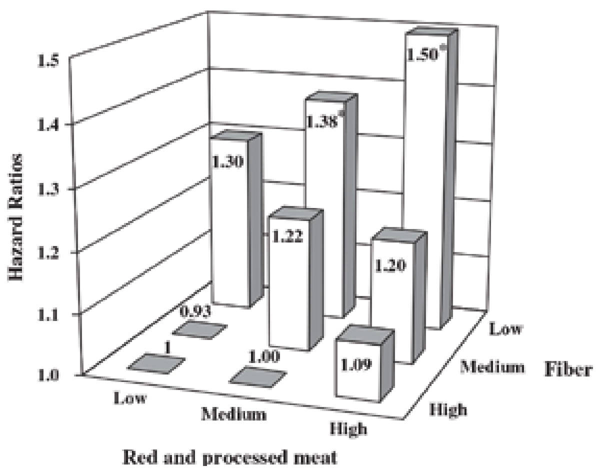
The EPIC infrastructure has produced almost 1000 peer-reviewed publications (see epic.iarc.fr), and EPIC studies have received nearly 30 000 citations in the scientific literature. The results from EPIC steadily add to the evidence – still incomplete – on the role of nutritional, metabolic, and genetic factors in cancer development. The relevance of nutritional factors for cancer development is supported by several specific results. (For more on metabolic and genetic factors, see the chapter “From laboratory to population”.)

Stomach, breast, and prostate cancers

High plasma levels of vitamin C, some carotenoids, retinol, and alpha-tocopherol, as well as high intake of cereal fibre and high adhesion to a Mediterranean diet have been found to be associated with a decreased risk of stomach cancer, whereas consumption of red and processed meat is associated with an increased risk. High intake of saturated fats and high alcohol consumption are associated with an increase in breast cancer in women. A high intake of dairy protein and calcium from dairy products is linked to an increased risk of prostate cancer.

Colorectal cancer

A clear pattern of risk has emerged for colorectal cancer. As shown in the graph, the risk increases with increasing consumption of red and processed meat, whereas risk decreases with increasing consumption of fibre. These findings were regarded as key evidence by the expert panels of the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) in their judgement that there is convincing evidence that red and processed meat causes colorectal cancer. They also considered as convincing the evidence of a preventive role of consumption of fibre, as contained in plant foods.



Relative risk of colorectal cancer in the EPIC study. The height of the columns expresses the value of the risk relative to the baseline of 1 for intakes of red and processed meat and fibre. The risks were computed after adjusting for 10 influential factors, including age, sex, and smoking status. (Asterisks indicate statistically significant differences relative to the group of subjects with low intake of red and processed meat and high intake of fibre.)

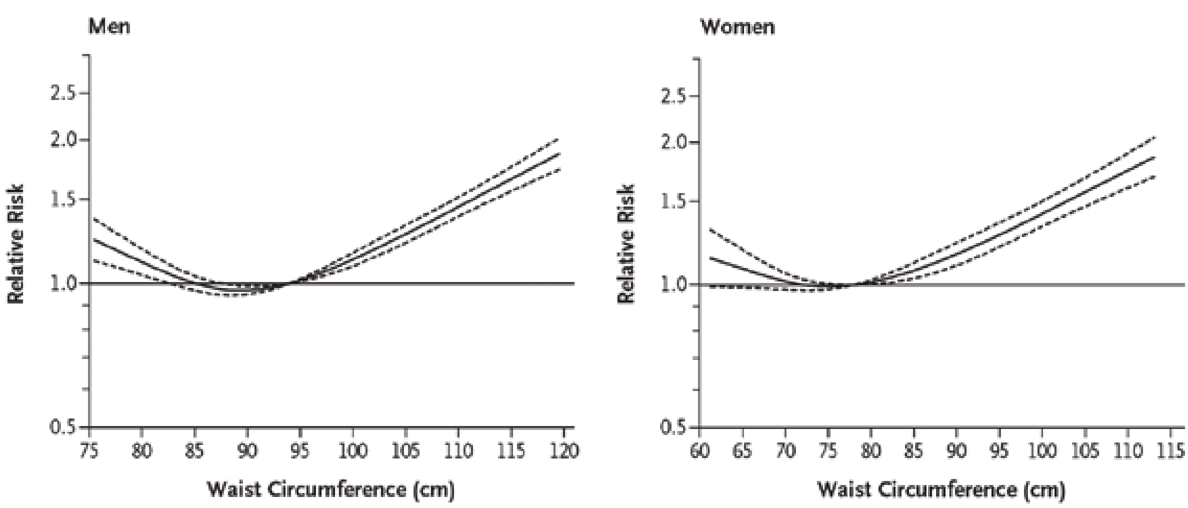
DIET CAN PREVENT CANCER

More results from EPIC

Beyond the specific findings on colorectal cancer, two other results from EPIC have major relevance for cancer prevention. First, a clear relationship was found between body fat (measured by the body mass index) as well as abdominal fat (measured by the waist circumference or the ratio of the waist to hip circumferences) and the relative risk of dying from any cause. This resulted from increased mortality for all cancers, cardiovascular diseases, and respiratory diseases, a finding consistent between sexes and countries.

The paper in the *New England Journal of Medicine* reporting these analyses has been widely cited as contributing key information on the adverse influence of body fat on all-cancer mortality. In particular, it showed that the smaller the waist the lower the mortality. Results from EPIC challenged a long-held concept in medicine – that of "the ideal weight" – by showing that the apparent increase in mortality in subjects who are very lean in terms of body mass index is an artefact due to people with a low body mass index but a relatively large waist. This novel finding has since been confirmed by other epidemiological investigations and by a recent IARC study of the global burden of cancer attributable to obesity (see the chapter "Cancer patterns, trends, and burden"). Obesity results from an imbalance between caloric intake through the diet and caloric expenditure. However, diet can also affect cancer occurrence via factors other than obesity.

WCRF/AICR had issued a series of diet-related recommendations for cancer prevention, condensed into six points, concerning body fat, physical activity, foods and beverages promoting weight gain, plant foods, animal foods, and alcoholic beverages (for women, there was a seventh point, concerning breastfeeding). Numerical scores were developed to reflect the degree of adherence to each of the recommendations of every participant in EPIC. For instance, with respect to plant foods, people eating on average more than 400 grams of fruits and vegetables per day got a score of 1, people eating 200–400 grams per day got a score of 0.5, and those eating less than 200 grams per day (one third of the participants) got a score of 0. When all of a participant's scores were added up, it was found that for people with the highest composite scores, mortality was reduced by one third compared with people with the lowest composite scores. This reduction applied to death rates for all cancers, cardiovascular diseases, and respiratory diseases.



Relative risk of dying from any cause among men and women in the EPIC study. The risk increases markedly with increasing body fat as measured by the waist circumference. The dotted lines indicate the range of uncertainty around the solid trend line.

From knowledge to action

Results from EPIC-based investigations have major implications for the prevention of cancer as well as of other chronic diseases. First, they point to the adverse influence of body fat and caloric imbalance, which involves both diet and physical activity, on the risk of death from cancers. They also indicate that, in addition to caloric imbalance, the risk is more broadly affected by factors in the diet. Second, these influences extend to other noncommunicable diseases, notably diabetes, cardiovascular diseases, and respiratory diseases (see "EPIC and chronic noncommunicable diseases"). Therefore, a substantial scope has been opened for prevention of noncommunicable diseases via diet-related intervention. However, it is paramount to recognize that prevention of noncommunicable diseases cannot be effectively achieved only through laudable recommendations made to individuals or through interventions by health services. As Margaret Chan, Director-General of the World Health Organization, has stated, "The health sector has no control over the cheap and convenient availability of processed junk food, the consumption of tobacco and alcohol, and the weight problems that go with sedentary city lives. ... The striking rise of noncommunicable diseases illustrates

EPIC AND CHRONIC NONCOMMUNICABLE DISEASES

From the very beginning, EPIC was conceived as a dual system. First, it would be a prospective cohort study to explore and test several specific hypotheses about dietary factors in cancer etiology, for instance the possible role of fats in the causation of breast cancer. Second, it would also provide an open resource not only for studies of cancer but also for etiological explorations of other chronic noncommunicable diseases. Two examples of such studies are already well developed: the InterAct and EPIC-CVD research programmes.

InterAct (www.inter-act.eu) was funded by the European Union FP6 programme to investigate how genetic factors and lifestyle behaviours, particularly diet and physical activity, interact (hence the name of the programme) in their influence on the risk of developing type 2 (so-called adult-type) diabetes. Of particular relevance are the findings that moderate physical activity appreciably reduces the risk of type 2 diabetes in both people of normal weight and overweight people, whereas consumption of sugar-sweetened foods increases the risk.

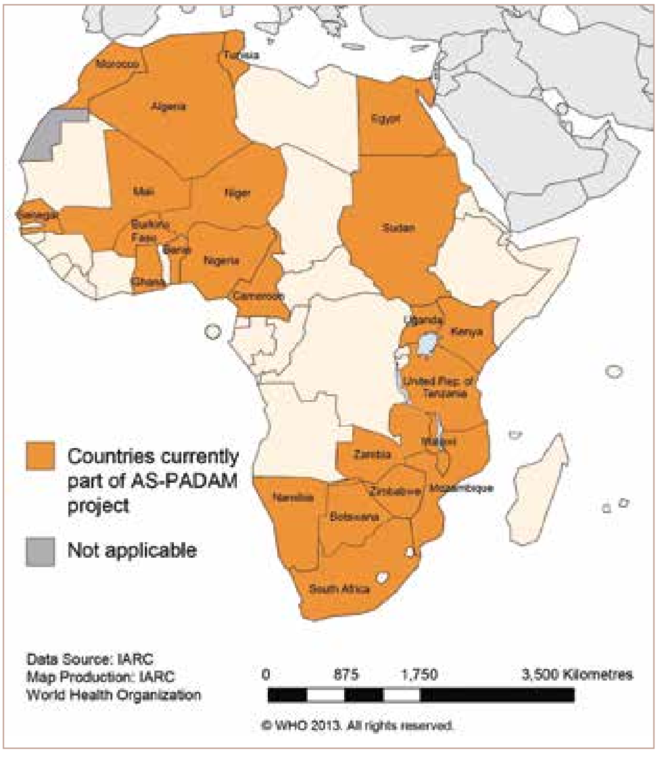
EPIC-CVD (www.epiccvd.eu) is dedicated to the investigation of cardiovascular diseases, in particular coronary heart disease – the focus of the EPIC-Heart project – and stroke. More than 10 000 EPIC participants have developed heart disease since they joined the study in the 1990s. Studies are in an early phase, with the ultimate objective of improving the identification of people at particularly high risk of developing myocardial infarction or other acute coronary syndromes.

Thus, EPIC is making a contribution well beyond cancer. In this context, the opportunity to look at comorbidities with other chronic diseases and to focus on healthy ageing is providing fresh impetus to this 20-year-old project.

the vast collateral damage to health caused by policies made in other sectors and in the international systems. Knowing the right policies is easy, but putting these policies in place is an enormous challenge. Establishing and enforcing health-promoting policies means pushing for fairness against some extremely powerful and pervasive commercial interests." Pushing for fairness can take very different and successful forms, provided that researchers and health professionals are firmly committed to it, using scientific evidence not as an end in itself, however noble, but as an instrument for action.

FROM DEVELOPED COUNTRIES TO DEVELOPING COUNTRIES

When IARC began its research activities, in the late 1960s, the less-developed countries were facing problems of under-nutrition, not over-nutrition and obesity. Concerns with respect to diet and cancer were focused in these regions on food contaminants rather than food constituents. Consequently, there was a natural orientation to study the effects of diet and metabolism in the more-developed countries, notably through EPIC. Over the history of IARC, however, a transition has occurred such that many developing countries now face problems of both over- and under-nutrition as lifestyles more typical of industrialized countries are adopted. As a consequence, IARC is extending its studies of diet into different regions of the world, where there is often also an associated need to provide training and expertise in dietary methodology. Notably, IARC has started to work with a network of nutrition groups across Africa in the Africa's Study on Physical Activity and Dietary Assessment Methods (AS-PADAM) project to develop methodology and capacity for joint research.



The map shows the countries that are participating in the Africa's Study on Physical Activity and Dietary Assessment Methods (AS-PADAM) project. The aim of the project is to carry out an inventory of the availability, quality, and challenges of dietary and physical activity methodologies and cancer registries in different African regions and to evaluate the possibility of using GloboDiet as the reference methodology for future pan-African monitoring surveillance. The African network includes representatives from four geographical areas (north, south, east, and west) and currently comprises 23 countries.