Introduction

Section A1: Objectives and methodology

1. Background

Many factors, whether genetic, or related to lifestyle or the environment, have been identified over the past 50 years as being associated with cancer occurrence.

About 2 to 4% of all cancers seem to have a genetic origin, i.e., gene defects known to be associated with these cancers can be transmitted from parents to their offspring. Moreover, genetic polymorphisms and epigenetic phenomena may enhance or reduce the risk associated with endogenous or exogenous carcinogenic factors. During the past two decades, it has been assumed that most cancers are due to lifestyle or to environmental risk factors. Very many epidemiological studies have been reported, but they are often contradictory or of debatable value because of methodological problems or lack of sufficient statistical power. Hence, their results have to be critically reviewed. In parallel, our understanding of carcinogenesis has markedly progressed, but the data are still insufficient to fully establish the different steps of carcinogenesis and the interaction between the various endogenous or exogenous factors. In many fields, further research is clearly required. Nevertheless, the strategy of cancer prevention must be based on the latest estimates of the relative weight of the various lifestyle and environmental risk factors. The aim of this report is to estimate the proportions of cancer attributable to such risk factors and also to evaluate the weight of each factor in the burden of cancer. This report distinguishes solid data from those which are still dubious or controversial; the former may be considered and taken into account in decision-making in cancer prevention and for prioritizing public health and research efforts.

Discussions about the roles of lifestyle and of the environment in cancer are often hindered by confusion over the meaning of the term “environment”, which is variably interpreted to encompass quite different types of factor ranging from pollutants to behaviours. Also, this term (or its equivalent) is given different meanings in different languages. In this report, we use the term “environment” as meaning “environmental pollutants”, an expression that includes pollutants of water, air, soil and food.

The first estimate of the relative importance of genetic and environmental factors in the global burden of cancer was made by Richard Doll and Richard Peto (1981), based on US cancer mortality data. Since then, only a few studies have tried to estimate the relative importance of cancer risk factors (see Section E2, General Discussion for a review). In 1981, a number of risk factors were still unknown and good qualitative and quantitative information on exposure of populations to risk factors was rare. Many nations have now entered the era of “information societies.” In this respect, in 2007, we have more information on exposure patterns and thus should be able to estimate better the burden of cancer that can be attributed to known causes, and to provide an evaluation of their relative importance.

At the beginning of 2005, the IARC created a “think-tank” on this topic, with the aim of developing methods for first obtaining estimates of the proportions of cancers attributable to known causes and second estimating the number of cancers that could be avoidable. In July 2005, a workshop at IARC brought together cancer epidemiologists who concluded that studies on attributable causes of cancer should start by examining a few selected countries in the five continents.

In September 2005, the French Académie Nationale de Médecine and the French Académie

des Sciences proposed to IARC to collaborate on a study on attributable causes of cancer in France. The present report is the product of this collaboration.

2. Objectives

The purpose of this report is to provide an assessment of the number of cancer cases and cancer deaths in France in the year 2000 attributable to factors of demonstrated carcinogenicity or with a demonstrated association with carcinogenic processes.

Ionizing radiation is a well established risk factor for cancer at many sites. There is fairly good knowledge of the cancer risk due to exposure to moderate and high doses of ionizing irradiation. However, the vast majority of exposure to ionizing radiation in France consists of low and very low doses. The specific effects of low-dose ionizing radiation on cancer risk are still controversial and difficult to quantify properly. Therefore, it was decided not to present data on cancer cases and deaths possibly attributable to radiation for the whole country. Following the same argument, no estimate was made for residential exposure to radon decay products. Section D1 on ionizing radiation addresses this issue in more detail.

For a number of factors, the evidence of a role in human cancer is suggestive but not demonstrated; these factors are reviewed in a separate section of the report (Section D3), but no estimates of attributable fraction are provided for them.

3. Methodology

Estimation of attributable causes of cancers was performed by calculating the proportions of specific cancers occurring in France in 2000 attributable to specific risk factors. The proportion of cancers in the total population that can be attributed to a risk factor is called the *attributable fraction* (AF) (Armitage and Berry, 1987) and is expressed as a percentage.

For cancer risk factors that can be avoided or completely suppressed, at least in theory, the most straightforward way to estimate the attributable fraction is to calculate the fraction of all cases (exposed and unexposed) that would not have occurred if exposure had not occurred (Rothman and Greenland, 1998). For this approach, the alternative scenario to current exposure is the absence of exposure.

For cancer risk factors that cannot be completely avoided or suppressed, a suitable approach consists of estimating the avoidable fraction of cancer, that is the fraction of cancer that would not occur if an alternative scenario of attainable exposure level or exposure intensity were considered (Murray and Lopez, 1999).

Most estimates of AF in this report are based on the scenario of *no exposure*, as this does not require assumption of minimal levels of exposures to carcinogens that would represent realistic targets for the French population. However, “total absence” is not a realistic alternative scenario for several risk factors, notably the number of children a women has (for breast and ovarian cancer). For such factors, it was deemed best to choose an alternative scenario that was historically realistic, i.e., exposure levels that had existed in France in the past.

4. Incidence data

France does not have nationwide cancer registration that would allow the monitoring of cancer incidence at the national level. There are, however, registries operating in several departments, some of which focus on specific cancers. For the year 2000, estimates of cancer incidence in France were obtained from a study that estimated the nationwide burden of cancer for the period 1997–2000 (Remontet et al., 2002). This report presented estimates of the incidence of cancer at the main sites for the period 1978–2000, using incidence data from departmental registries and the national mortality data for the period 1978–1997. Cancer incidence in France in 2000 was derived by age–cohort modelling of (i) incidence from cancer registries, (ii) mortality in populations covered by cancer registries, and (iii) incidence-to-mortality ratios in populations covered by cancer registries. This model was applied to predicted national mortality for the year 2000 so as to estimate the national cancer incidence in 2000.

Some specific cancer sites were not reported by Remontet et al. (2002):

(1) For **sinonasal cancer** incidence (ICD 10: C30, C31), we calculated the ratio of incidence of sinonasal to lung cancer in nine cancer registries that record sinonasal cancers (Parkin et al., 2002: Bas-Rhin, Calvados, Doubs, Haut-Rhin, Hérault, Isère, Manche, Somme and Tarn) and applied that ratio (0.019 for

men and 0.033 for women) to lung cancer incidence in France, which yielded estimates for sinonasal cancer incidence for France of 453 cases for men and 151 cases for women. Mortality data were available directly from CepiDc data: 99 deaths for men and 42 deaths for women.

(2) For the incidence of **pharynx cancer** (ICD 10: C09–14), we estimated the proportion of pharynx cancer among oral cavity and pharynx cancers (ICD 10: C00–14) in French registries (Parkin et al., 2002: Bas-Rhin, Calvados, Doubs, Isère, Somme and Tarn). The proportion of pharynx cancer among oral cavity and pharynx cancers was 57% for men and 35% for women. We applied this proportion to data reported by Remontet et al. (2002) for oral cavity and pharynx combined, and obtained figures of 7396 cases of pharynx cancer for men and 833 cases for women. Mortality data were available directly from CepiDc data: 2558 deaths for men and 312 deaths for women.

(3) For **colon cancer** (ICD 10: C18), we estimated the proportion of colon cancer among colorectal cancers (ICD 10: C18–21) in French registries (Parkin et al., 2002: Bas-Rhin, Calvados, Doubs, Isère, Somme and Tarn). We estimated that colon cancer represents 57% of colorectal cancers for men and 63% for women. We applied these proportions to data reported by Remontet et al. (2002) for colon and rectum combined, and obtained figures of 11 132 cases of colon cancer for men and 10 606 cases for women. Mortality data were available directly from CepiDc data: 6092 deaths for men and 5719 deaths for women.

(4) For **adenocarcinoma of the oesophagus**, we had recourse to a European study that used data from the cancer registries of Bas-Rhin and Calvados and reported separately the incidence of oesophageal adenocarcinoma (Botterweck et al., 2000). Proportions of adenocarcinoma were estimated as 17.6% of all oesophageal cancers in males, and 34.7% in females. We applied these proportions for incidence and mortality data of oesophagus (ICD 10: C15), which led to estimates of 711 cases for men and 322 for women. The corresponding figures for mortality were 612 deaths for men and 241 for women.

5. Mortality data

Mortality data were provided directly by the Institut National de la Santé et de la Recherche Médicale, Centre d'Epidémiologie sur les Causes Médicales de Décès (INSERM-CepiDC) for the year 2000 by five-year age groups and by sex for each ICD 10 code (International Classification of Disease, 10th revision).

Fifty-six per cent of all uterus cancers were coded as "uterus not further specified" (ICD 10 code C55). Mortality data for cancers of the cervix and corpus uteri would be underestimated unless this "not specified" category is redistributed among the two sites. Therefore, we estimated for each age group the proportion of deaths due to cervix or corpus uteri cancer (ICD 10 codes C53 or C54). We applied these proportions to the "not classified" uterine cancer deaths and reallocated these to either cervix uteri cancer or corpus uteri cancer.

6. Issues in the classification of diseases and causes of death

Remontet and co-workers (2002) compiled cancer incidence and mortality data using the 9th revision of the International Classification of Disease (ICD 9), and estimated cancer incidence in 2000 using projections of mortality for 2000. INSERM mortality data for 2000 were classified using the 10th revision of the ICD. Differences between the two ICD classifications could have affected the mortality estimates, notably for uterus and prostate cancer, multiple myeloma and leukaemia. However, Pavillon and co-workers (2005) estimated that differences in the two classification systems did not induce discrepancies greater than 10% in causes of deaths. Therefore, we did not correct the incidence data for 2000 compiled by Remontet and co-workers to match the INSERM mortality data for 2000. Table A1.1 summarizes cancer incidence and mortality in France in the year 2000 for males and females.

7. Risk factors for cancer in France

Risk factors considered in this report were those for which there is evidence for a causal association with cancer.

The first type of risk factor considered comprises those agents classified by the IARC as Group 1 carcinogens, i.e., agents for which there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity[1]. Since 1971, the International Agency for Research on Cancer has provided evaluations of the carcinogenic potential of substances based on epidemiological and biological evidence. The term "substance" encompasses single physical, chemical, or biological agents, and mixtures of physical chemical, biological and physical agents, and also places or circumstances concentrating still unknown carcinogenic agents. Table A1.2 summarizes the list of carcinogenic agents considered in this report.

The second type of risk factor includes individual conditions known to be causally associated with cancer occurrence. These factors are not evaluated in IARC Monographs but some have been evaluated by working groups convened by the IARC. An IARC working group came to the conclusion that there was sufficient evidence in humans for a cancer-preventive effect of avoidance of weight gain (IARC, 2002), and thus this report estimates AFs associated with overweight and obesity. The same IARC working group reported that there was sufficient evidence for a protective effect of physical activity on the risk of breast cancer and colon cancer (IARC, 2002).

Reproductive factors (e.g., number of children, age at first birth, duration of breastfeeding) have never been evaluated by an IARC working group. However, a large body of evidence supports strong associations between reproductive factors and breast and ovarian cancer (CGHFBC, 2001). We therefore included these factors in this analysis.

A number of IARC Group 1 carcinogens were not included in this report, either because exposure is very rare in France or because they are insignificant. For instance, parasitic infestation with *Schistosoma haematobium* (involved in bladder cancer) and *Opisthorchis viverrini* (involved in liver cholangiocarcinoma), and intake of nutrients such as aflatoxins (involved in liver adenocarcinoma) (see Section D2).

8. Prevalence of exposures in France

The burden of cancer observed in the year 2000 reflects past exposure to risk factors. Usually, exposure to a risk factor is spread over many years, and cancer may occur long after cessation of the exposure (e.g., lung cancer in ex-smokers, mesothelioma in retired shipbuilding workers). For most cancers and risk factors, the average latency between first exposure and diagnosis is about 15 years. Hence, for evaluating the burden of cancer in 2000, we took into account exposures that occurred in or around 1985.

Data on prevalence of exposure to risk factors in France were assembled by scrutinizing many different sources, publications, reports and relevant information publicly available on governmental organization web-sites.

The most representative exposure data for the population at risk came from population surveys that evaluated the prevalence of specific exposures in France, and were conducted using quota methods on age, sex and socioeconomic characteristics (e.g., INSEE surveys). For most exposures, however, prevalence surveys were not available for the year 1985, but only for other years. In this case, we calculated a linear interpolation of survey results that used a similar method for years before and after 1985, with weighting for sample sizes and, when relevant, for age and sex distribution. When similar surveys before and after 1985 were not available, we selected the best available survey describing the situation around 1985. When no survey was available, we used proportions of exposed subjects reported in observational studies conducted in France.

Attributable fraction is very sensitive to misclassification of subjects who could have been exposed (even minimally) as unexposed subjects (Wacholder et al., 1994). For instance, the error in an estimate of AF due to tobacco smoking is greater when occasional smokers are categorized as never-smokers than when they are included in the ever-smoker category. Therefore, the simplest and most robust method for estimating the attributable risk from several exposures is based on division of subjects into

[1] http://monographs.iarc.fr

two groups, a baseline consisting of those unexposed and a group including everyone who was exposed.

9. Calculation of the attributable fraction (AF)

The AF can be calculated as a function of the relative risk (RR) of cancer associated with exposure to a risk factor and the prevalence of exposure (P) of a population to that risk factor. This method was originally described by Levin (1953):

$$AF = \frac{P^* (RR-1)}{[P^* (RR-1)] + 1}$$

The relative risks we used were based on estimates from the most recent meta-analyses or from best estimates available in published literature.

When a risk factor was reported in the literature in multiple exposure categories (i.e., exposures classified in more than two categories), we used Levin's formula adapted by Hanley (2001). Because of the distributive properties of the AF, multi-level exposures could be reduced to a simple dichotomous situation (i.e., ever vs. never exposed) or to an average exposure of the whole population at risk when the relative risk was related to an exposure level greater or lower than a pre-determined level. These ways of grouping or averaging strata of exposure do not affect AF estimations (Hanley, 2001).

Data on exposure prevalence were sometimes available only as continuous variables. For these continuous-scale exposures, starting from relative risks estimated for several exposure categories, we derived the risk of cancer per unit increase in exposure (e.g., the increase in risk of oesophagus cancer per unit gram per day of alcohol consumption). Assuming a log-linear relationship between exposure and risk of cancer, we estimated the average risk for the whole French population using the average level of exposure of the whole population. This was done by applying the following formula:

$$Risk = Exp\,[Ln\ (\text{Risk per unit}) * \text{average level of exposure}]$$

Because this log-linear relationship supposes that each individual has experienced a similar average exposure, we can use the simplified Levin's formula for direct calculation of the AF:

$$AF = \frac{Risk - 1}{Risk}$$

This formula is valid when the risk of cancer per unit of exposure was estimated in a model using log transformation. This is the case for logistic regression or Poisson regression, which are models widely used in case–control and cohort studies respectively. We checked that the risks per unit we used were all based on models with a log transformation of the risk.

It should be stressed that the dose–effect relationship is in fact rarely linear (or log-linear) over the whole range of exposures, but this method is considered to be the best approximation available in this respect.

10. Sensitivity analysis

For exposures having a large impact on cancer burden, in order to check the robustness of AF with respect to latency time between exposure and cancer occurrence, we took different lag-times between first exposure and cancer diagnosis (10 and 20 years) when prevalence data were available for these periods.

When for a risk factor, the alternative hypothesis was not total absence of exposure, the sensitivity analysis was performed taking different alternative exposure scenarios.

A more comprehensive description of this sensitivity analysis is presented in Section C2.

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Table A1.1 - Incidence of and mortality from cancer in France in 2000

		Incidence **				Mortality ***			
		Males		Females		Males		Females	
Site	**ICD 10**	**Number of cases**	**Rate***	**Number of cases**	**Rate***	**Number of cases**	**Rate***	**Number of cases**	**Rate***
Breast	C50	-	-	41845	138.5	-	-	10950	36.3
Central nervous system	C70-72	2697	9.5	2602	8.6	1609	5.6	1290	4.3
Cervix uteri	C54			3387	11.2	-	-	1463	4.8
Colon-rectum	C18-21	19431	68.1	16826	55.7	8345	29.3	7604	25.2
Corpus uteri	C53	-	-	5064	16.8	-	-	1360	4.5
Gallbladder	C23-24	815	2.9	1272	4.2	519	1.8	938	3.1
Hodgkin disease	C81	736	2.6	631	2.1	168	0.6	117	0.4
Kidney	C64	5306	18.6	2987	9.9	1888	6.6	1107	3.7
Larynx	C32	3865	13.6	361	1.2	1702	6.0	149	0.5
Leukaemia	C91-95	3609	12.7	2634	8.7	2694	9.4	2352	7.8
Liver	C22	5014	17.6	962	3.2	5019	17.6	1600	5.3
Lung	C33-34	23152	81.2	4591	15.2	20585	72.2	4246	14.1
Melanoma	C43	3066	10.8	4165	13.8	706	2.5	643	2.1
Mesothelioma	C45	671	2.4	200	0.7	606	2.1	162	0.5
Multiple myeloma	C88,C90	1942	6.8	1645	5.4	1352	4.7	1309	4.3
Non-Hodgkin lymphoma	C82-85,C96	5527	19.4	4381	14.5	2281	8.0	2185	7.2
Oesophagus	C15	4040	14.2	928	3.1	3477	12.2	695	2.3
Non-melanoma skin cancer	C44	-	-	-	-	212	0.7	211	0.7
Oral cavity and pharynx	C00-14	12990	45.6	2398	7.9	3911	13.7	732	2.4
Ovary	C56	-	-	4488	14.9	-	-	3210	10.6
Pancreas	C25	2701	9.5	2186	7.2	3631	12.7	3205	10.6
Prostate	C61	40309	141.4	-	-	9080	31.8	-	-
Stomach	C16	4520	15.9	2606	8.6	3156	11.1	2011	6.7
Thyroid	C73	821	2.9	2890	9.6	140	0.5	251	0.8
Urinary bladder	C67	8986	31.5	1785	5.9	3250	11.4	1007	3.3
Other		10827	38.0	6394	21.2	12406	43.5	8110	26.8
All cancers	**C00-97**	**161025**	**564.8**	**117228**	**388.1**	**86737**	**304.2**	**56907**	**188.4**

* Crude rate per 100 000 person years. ** From Remontet et al., 2002 *** From Inserm-CepiDC

Table A1.2 - Selected agents causally associated with cancer (IARC Group 1 carcinogens)

Agent	Risk factor	IARC Monograph volumes and year*	
Alcohol	Alcoholic beverages	Vol. 44	1988
Chronic infection	*Helicobacter pylori*	Vol. 61	1994
	Hepatitis B virus	Vol. 59	1994
	Hepatitis C virus	Vol. 59	1994
	Human papillomavirus	Vol. 64	1995
Hormonal therapy and oral contraceptives	Hormonal therapy Oral contraceptives	Vol. 72, 95 § Vol. 72, 95 §	1999, 2006 § 1999, 2006 §
Occupational exposures	Aromatic amines	Vol. 1 & 4, (7) †	1987
	Asbestos	Vol. 14, (7)	1987
	Benzene	Vol. 29, (7)	1987
	Boot and shoe manufacture and repair	Vol. 25, (7)	1987
	Cadmium	Vol. 58	1993
	Chromium (VI)	Vol. 49	1990
	Mineral oil	Vol. 33, (7)	1987
	Nickel	Vol. 49	1990
	Painters	Vol. 47	1989
	Polycyclic aromatic hydrocarbons (combustion fumes, tar, pitch)	Vol. 35, (7)	1987
	Radon decay products	Vol. 78	2001
	Rubber industry	Vol. 28, (7)	1987
	Silica	Vol. 68	1997
	Wood dust	Vol. 62	1995
Pollutants	Non-occupational exposure to asbestos	Vol. 14, (7)	1987
	Radon decay products	Vol. 78	2001
	Secondhand smoking	Vol. 83	2004
Radiation	Background exposure, terrestrial gamma and cosmic rays	Vol. 75	2000
	Medical diagnosis radiations	Vol. 75	2000
Solar radiation	Sun exposure	Vol. 55	1992
	UVA and psoralens	Vol. 24, (7)	1987
Tobacco	Tobacco smoking	Vol. 83	2004

*http://monographs.iarc.fr.
§ In press.
† (7) refers to the last update of evaluation reported in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7, Lyon, 1987.

Section A2: Temporal trends in cancer incidence and mortality in France

This section examines temporal trends in cancer incidence and cancer mortality in France. It has been known for many years that incidence and mortality of most human cancers steeply increase with the ageing of populations. The worldwide phenomenon of population ageing is therefore, in most countries, the principal cause of the increasing number of cancer cases and cancer deaths over time. Population ageing is particularly significant in Europe and so most of the change in the numbers of patients diagnosed with or dying from cancer is due to the increasing number of people in older age strata.

We first examine the effects of population ageing on mortality trends. Next, we examine the residual incidence and mortality trends after the influence of ageing is removed by statistical adjustments. Finally, we examine the reasons other than ageing that are likely to underlie the observed changes in incidence and mortality of specific cancers.

1. Data on cancer incidence and mortality in France

For incidence, we combined the data from cancer registries that have reported since 1978 or 1979 and published data in the *Cancer Incidence in Five Continents* (CI5) series (Parkin et al., 2005); namely Bas-Rhin (1978–1997), Calvados (1978–1997; except for leukaemia, because of the incomplete reporting of the disease [see CI5 Vols. VII and VIII]), Doubs (1978–1997), and Isère (1979–1997). These registries cover only 5.6% of the French population, but provide data covering at least 20 years, which is a reasonable time window for appraisal of trends.

For mortality, we used data from Hill et al. (1989, 1990, 1991, 1993, 2001) for mortality before 1968, and the WHO mortality database for mortality between 1968 and 2003 (WHO, 2006). The French population figures for the period from 1968 to 2003 were those provided for 1 January of each year by the INSEE. All incidence and mortality rates have been standardized on age, using the standard World population defined by Segi (1960), and introduced in CI5 volume I by Doll et al. (1966).

2. Temporal trends in cancer incidence and mortality in France

Decrease in age-adjusted cancer mortality over time

Before looking at changes in any specific cancer, we examined how population increase and ageing have influenced cancer mortality in France. Table A2.1 shows that in a period of 35 years, from 1968 to 2003, the number of cancer deaths in France increased by 50% in men (from 58 914 to 88 201) and by 26% in women (from 46 865 to 59 033). However, the computations detailed in Table A2.1 show that the increase in the number of cancer deaths over time is entirely due to the increase in population size and to ageing.

Applying the cancer mortality rates observed in 1968 to the population of 2003 (the “expected deaths” in Table A2.1), we see that the numbers of cancer deaths observed in 2003 were 6.9% lower in French men and 18.9% lower in French women than if the 1968 rates were still valid in 2003. Hence, relative to 1968, the burden of cancer deaths in France has actually decreased by 6.9% in men and by 18.9% in women.

Age-adjusted cancer mortality is decreasing but age-adjusted cancer incidence is increasing

Figure A2.1 displays temporal trends in age-adjusted incidence in the four registries that had data from 1978 until 1997, and the age-adjusted mortality rates for the whole French population from 1950 until 2004.

The trends in cancer mortality rates observed in the four departments from which the incidence data originate were similar to those observed in the entire French population.

Most cancers that occurred in 1950, the year from which the earliest mortality data exist, were initiated in the 1930s, when a large part of the French population was living in rural areas, with low numbers of motorized vehicles and less chemical substances than after the Second World War.

Over a twenty-year period, cancer incidence rates have increased by 23% in men and by 20% in women. Because the rates in Figure A2.1 are adjusted for age, the increases in incidence are real, and not related to the ageing of the French population. In contrast, the cancer mortality rate in males reached a maximum around 1985 and decreased steadily thereafter, down to the level it was in the early 1950s.

To properly interpret the discrepancy between age-adjusted incidence and age-adjusted mortality trends, we need to examine the reasons for changes in trends for specific cancers.

3. Reasons for changes in incidence and mortality of specific cancers

Figures A2.2 to A2.8 display trends in age-adjusted incidence and mortality rates of the most common and selected less common cancers in French men (Figures A2.2, A2.3, A2.4) and women (Figures A2.5, A2.6, A2.7, A2.8). Figure A2.9 displays trends in mortality from cancer in children and adolescents. Cancer incidence data in children could not be used because French childhood cancer registries include data covering different periods of time, which made difficult the production of temporal trends.

Reasons for changes in cancer incidence and mortality other than ageing, described by Doll and Peto (1981), are summarized below:

1. Administrative and demographic reasons:
   a. Changes in histological classification;
   b. Changes in disease classification;
   c. Changes in completeness of registration;
   d. Changes in populations: changes in denominators for calculation of rates, or significant immigration of populations having different cancer epidemiological profiles;
2. Changes in competing causes of death;
3. Changes in disease diagnosis;
4. Changes in earlier detection and screening practices;
5. Changes in exposure to risk or to protective factor(s) associated with cancer occurrence:
   a. Changes in nature of risk factors (qualitative change);
   b. Changes in exposure to risk factors (quantitative change).
6. For mortality: changes in efficacy of treatments and availability of efficient treatments.

The remainder of this section examines the influence of these various reasons on trends in cancer incidence and mortality in France associated with factors other than ageing. As a note of caution, the reasons outlined below by no means explain the totality of the observed time-trends, but the available data suggest that they have played an important role in changes in incidence or in mortality rates.

In cancers with high fatality rates, for which no efficient treatment yet exists, changes in incidence will be paralleled by equivalent changes in mortality, but with a time lag that is proportional to the average survival of these patients.

Incidence of a cancer may increase while mortality remains stable or decreases. Persistence over time of a discrepancy between increasing age-adjusted incidence and stable age-adjusted mortality rates is usually a result of increasing diagnosis of cancers with low malignant potential, some of which would probably never have surfaced as clinical cancers. Such increased detection of slow-progressing, non-aggressive cancers will not affect mortality unless the increased detection includes diagnosis at an earlier stage of cancers that would have been life-threatening if diagnosed later. Cancer screening activities may affect mortality only if the latter condition is true.

A discrepancy between incidence and mortality trends may also be due to an increase in the incidence of cancer, including cancers at an advanced stage, due to changing prevalence of risk factors in the population while efficient treatment is available to limit cancer mortality. When efficient treatment exists, these two situations can be distinguished by looking at trends in incidence of cancer by stage at diagnosis, or by other indicators of cancer progression, such as tumour size, lymph node involvement, tumour differentiation or biomarkers of aggressiveness.

Unfortunately, only very few registries record these parameters of cancer progression.

(1) Changes due to administrative reasons

Part of the change in incidence and mortality from haemato-lymphatic cancers probably results from changes in classification. For instance, some leukaemias are increasingly considered as sub-types of non-Hodgkin lymphoma (NHL). In addition, some haematological disturbances are now considered as cancer when previously they were not, such as some mild forms of NHL. The increase in multiple myeloma is probably due to better diagnosis and changes in the histological classification of sub-clinical haematological disturbances, mainly in the elderly.

The increase in bladder cancer incidence is not paralleled by a similar increase in mortality. Bladder cancer incidence is subject to great variability due to inclusion of pre-cancerous lesions in registry files. Earlier detection may also play a role (e.g., cystoscopic examinations).

(2) Changes due to competing causes of death

Competing causes of death refers to the decrease in one cause of death that leaves the road open for other causes of death, that may or may not be associated with the same risk factor(s). For instance, primary liver cancer in France is often associated with cirrhosis, a disease mostly due to high alcohol consumption. The latter is far more common in men than in women (see Section B2). It is hypothesized that part of the increase in the incidence of primary liver cancer observed in populations unexposed to aflatoxin and in which the incidence of viral hepatitis infection has not increased is due to more effective treatment of liver cirrhosis. As a consequence of greater survival of patients with cirrhosis, the later development of liver cancer would become more likely (Tubiana et Hill, 2004).

Prolongation of life expectancy has given time to lung cancer to emerge in workers exposed to silicosis, who would previously have died from obstructive chronic bronchitis. Similarly, primary prevention efforts and the availability of efficient treatments have led to drastic decreases in mortality from cardiovascular diseases, particularly ischaemic heart disease. The decrease in mortality from cardiovascular disease associated with smoking may have resulted in subsequent diagnosis of a lung cancer that would have remained undetected if smokers had died from cardiovascular disease.

Congenital malformation is a risk factor for childhood cancer, for example in the urinary tract. Better survival of children with congenital malformations may have led to greater incidence of several childhood cancers that would otherwise not have occurred.

(3) Changes due to changes in detection methods

The continuous increasing trend in prostate cancer mortality before 1988 was probably due to steadily better identification of elderly patients suffering from prostate cancer (e.g., more systematic blood measurement of alkaline phosphatases and bone X-ray examinations in older patients), that led to increasing certification and registration of prostate cancer as the underlying cause of death (Levi et al., 2004).

Increases in kidney cancer incidence in males and females is mainly attributable to increased incidental detection of these cancers during medical investigations, for instance, abdominal X-ray before surgery, assessment of causes of high blood pressure, or iterative echography of abdominal organs.

For liver cancer, mortality data are not always reliable because the liver is an organ frequently involved in metastatic dissemination of cancers of other organs. As a consequence, many cases of “primary liver cancer” or of death from “liver cancer,” are in fact related to other (sometimes undiagnosed) primary cancers.

The increase in tumours of the central nervous system is most probably due to better disease ascertainment made possible by continuous improvements in non-invasive imaging technologies (e.g., CAT scan, MRI, PET scan). These have permitted the detection of health conditions that in the past remained undiagnosed.

Changes in ultrasound examinations and diagnostic procedures such as fine needle aspiration have contributed to the increase in thyroid cancer incidence (see Section D1).

Diagnosis of pancreatic cancer has been much improved with the advent of new imaging technologies and endoscopic techniques.

Better imaging methods have also played a role in the better identification of causes of death in children, including brain tumours and rarer cancers.

(4) Changes due to early detection and screening

Early detection may follow, and be a result of, the introduction of new detection methods, but is also due to greater disease awareness among patients and doctors, who pay more attention to early symptoms or early clinical signs of cancerous processes. Screening denotes the systematic search for a specific cancer while it is clinically silent.

(4.1) Earlier detection and screening when precursor cancer lesions exist

Cancer mortality can decrease because of higher curability of cancers diagnosed at an earlier stage or because numbers of incident cases are lower. Lower incidence results from the removal of cancer precursor lesions such as polyps in the colon, and intraepithelial neoplasia in the cervix. This scenario appears to apply to colorectal cancer and cervical cancer.

The incidence of and mortality from cervical cancer have steadily decreased because of widespread use of screening modalities able to identify preneoplastic lesions that can be removed. Other factors also play a role, such as lower parity (number of children per mother), gynaecological hygiene and protection against sexually transmitted diseases.

Increasing trends in colorectal cancer incidence contrast with decreasing mortality. Reasons for increases in incidence (e.g., obesity, lack of physical activity) are discussed further below. Until recently, decreasing mortality due to earlier detection and downstaging of cancer was in part driven by greater disease awareness (Autier et al., 2003) and in part by progress in treatment (see below). Implementation of screening for colorectal cancer (e.g., with the faecal occult blood test, FOBT) is likely to further reduce mortality. Also, use of screening methods that can lead to the removal of polyps (i.e., endoscopy and virtual colonoscopy) should reduce both incidence and mortality from this cancer.

(4.2) Earlier detection and screening when precursor cancer lesions do not exist

Early detection and screening that does not involve a cancer precursor lesion and can only aim for earlier detection of cancerous lesions, can still lead to a lowering of cancer mortality because of the greater curability of patients with screen-detected cancer. However, incidence may increase because of increased detection of indolent cancers that would have never (or very slowly) progressed to clinically apparent disease and would probably never have become life-threatening. This scenario appears to apply to breast, prostate and thyroid cancer.

Age-adjusted breast cancer incidence in France has increased by 65% over a 20-year period (the increase in incidence was 82% in women 50 years old or more, and 55% in women below 50 years old), contrasting with a small permanent increase in all-age breast cancer mortality until 1994, after which a decrease of 11.6% occurred between 1995 and 2003 (calculated using joinpoint analysis from US-SEER Programme) (Figures A2.5 and A2.6).

Mammographic screening has played a major role in the increase in incidence of breast cancer, but the rise started well before such screening became available to many women. The increasing trends observed before around 1995 are due partly to greater disease awareness, partly to greater detection by physical breast examination (either self-examination or by a physician or a nurse), partly to changes in reproductive factors, partly to increasing use of hormone treatment (HRT) after menopause, and partly to increasing rates of obesity (see below).

Prostate cancer incidence in France has increased by a factor of 2.6 over 20 years, largely because of the use of testing for prostate-specific antigen (PSA). Mortality from prostate cancer reached its peak in 1988. A slight decline in mortality is observable just after 1988, and between 1989 and 2002, it decreased by 16%. Attribution of this slight mortality decrease to PSA screening is questionable; the peak in mortality of 1988 corresponds to the start of PSA testing and the following upswing of the incidence. It is difficult to assess the contribution of PSA testing that started in 1988 because of the rather long lag-time existing between prostate cancer diagnosis and death. Other factors may have contributed to improving the prognosis of prostate cancer, such as earlier diagnosis (non-PSA-based) and therapeutic progress, including hormonal treatments (see below).

(5) Changes due to changes in exposure to risk or to protective factors

In men, lung cancer incidence and mortality have been decreasing since the late 1980s. In women, incidence and mortality are rising sharply and lung

cancer has almost overtaken colorectal cancer as the second most important cause of cancer death after breast cancer. In men, these trends are mostly attributable to the decreasing number of smokers and also to control of occupational carcinogens. In women, trends are entirely due to the increasing number of French women who smoke.

Cancers of the mouth, pharynx, larynx and oesophagus are strongly related to alcohol consumption and tobacco smoking. A decrease in smoking and alcohol consumption among French males since 1950 (see Sections B1 and B2) was followed by marked decreases in the incidence of and mortality from these cancers. Mortality probably further decreased because of greater disease awareness, leading to earlier diagnosis and more effective treatment.

The increase in primary liver cancer incidence is – at least in part – explained by the increasing number of people in France (and in Europe) infected with hepatitis C virus (HCV). However, the contribution of HCV to liver cancer in France remains to be assessed. Introduction of systematic testing of blood donations for the presence of HCV is likely to curb the epidemic of HCV infection.

Stomach cancer incidence and mortality have dramatically decreased in France and in many other industrialized countries since 1950. The incidence of this cancer continues to decrease but in 2000, it still caused 4940 deaths in France. The decrease in gastric colonization by *Helicobacter pylori* induced by widespread use of antibiotics and more recently, the possibility to detect the presence of that bacterium and to eradicate it, should contribute to further decreases in stomach cancer incidence and mortality. Other possible factors contributing to the temporal changes include food preservation methods (refrigeration instead of salting and smoking) and the availability of fresh fruits and vegetables. However, we still have no firm data confirming the existence or importance of such nutritional factors in relation to stomach cancer burden.

Colorectal cancer incidence is still on the rise, mainly in men, probably because of increases in overweight and obesity and in physical inactivity. Still unidentified dietary risk factors are probably also involved.

Changes in risk factors implicated in the increase in breast cancer incidence include the use of hormone replacement treatment (HRT) and oral contraceptives, changes in reproductive factors, increasing prevalence of overweight and obesity, and decreasing levels of physical activity. The cumulative effects on breast cancer incidence of HRT use and mammographic screening have been described for other countries, such as the USA (California), Sweden, Denmark and Switzerland (Geneva) (see Bouchardy et al., 2006 for a review).

In addition to HRT use, since 1980, a wide variety of progestin-based drugs have been prescribed in France to premenopausal women for treatment of many “female disorders” (e.g., the so-called “luteal insufficiency”, Lowy and Weisz, 2005), and the impact of this practice on breast cancer risk is unknown.

Oral contraceptive use has recently been classified as a Group 1 carcinogen by the IARC (see Section B7), but its use accounts for few breast cancer cases. In contrast, use of oral contraceptives decreases ovarian cancer incidence (see below).

Ovarian cancer incidence and mortality have been decreasing slowly since the late 1980s, probably because of the widespread use of oral contraceptives. It is unknown to what extent the practice of hysterectomy has contributed to these favourable trends in France.

Until the mid-1990s, incidence of and mortality from non-Hodgkin lymphoma (NHL) have doubled over 20 years. Reasons for these increases remain unknown, although current research is focusing on viral and immune factors. Ultraviolet radiation could also be involved, but data are contradictory. The role of chemical pollutants, which were incriminated earlier, has not been supported by more recent data. It should be recalled that the incidence of Hodgkin lymphoma (HL) has markedly decreased and a number of lymphomas previously classified as HL are now classified as NHL. Hence, the incidence of both HL and NHL combined probably deserves more attention than the incidence of NHL alone.

Similarly to most populations of European descent, testis cancer incidence is rising steadily in France for unknown reasons, probably related to changes in lifestyle or in some exogenous risk factor. One current hypothesis focuses on exposure *in utero* to a substance triggering dormant pre-cancerous testicular lesions. After the start of adolescence, under the influence of androgens, these lesions would progress into cancer.

As in other light-skinned populations, incidence of cutaneous melanoma in France has seen a dramatic two-fold increase in the last two decades. Mortality has risen at a lower pace, as most of the increasing incidence concerns early-stage melanomas curable by surgery. Melanoma incidence and mortality in France are still generally on the rise, probably because of delays in the implementation of effective prevention campaigns based on sun protection (Severi et al., 2000).

(6) Changes in mortality due to availability of efficient treatment

Efficient treatment modalities combining chemotherapy, hormone therapy, radiotherapy, surgery and supportive care are now available for most cancers (e.g., Hodgkin lymphoma, leukaemia, breast cancer, colorectal cancer, testicular cancer). These modalities have contributed to the decrease in mortality observed in the last thirty years for a large number of cancers.

Effectiveness of cancer treatments has particularly improved for childhood cancer, resulting in sharp decreases in the mortality due to these cancers in France (Figure A2.9).

(7) Summary of factors likely to be involved in increasing cancer incidence

Table A2.2 summarizes factors known or suspected to be associated with the incidence of common and less common cancers in France. Competing causes, changes in detection and diagnosis and screening effects play important roles in the increase in incidence, whereas it seems that air, water, soil and food pollutants have had little demonstrable impact on cancer occurrence, with the exception of mesothelioma, for which the causal agent (asbestos) is clearly established.

4. Summary graphical representation of temporal trends

Figures A2.10 and A2.11 summarize temporal trends in age-adjusted incidence and age-adjusted mortality of most common cancers (drawings done after Pepin, 2006). The size of the lozenges is related to the incidence rates of cancers in 1997. Notable increases in both incidence and mortality are seen for cutaneous melanoma (in both sexes), liver cancer (in men), NHL (in both sexes), multiple myeloma (in both sexes), lung cancer (in women), kidney cancer (in both sexes), and pancreatic cancer (in both sexes). Increases in incidence and mortality are moderate for lung cancer in men, and for the central nervous system in both sexes.

For breast and prostate cancer, increases in incidence are not paralleled by changes in mortality.

Dramatic decreases in incidence and mortality are observed for stomach cancer (both sexes), cancers of the mouth, pharynx, larynx and oesophagus in men, and cervical cancer in women.

The availability of efficient treatment for testicular and colorectal cancer and leukaemia is manifested in decreases in mortality while incidence was still on the rise in 1997.

As described earlier, mortality data for liver cancer are not always reliable, as many cases of “primary liver cancer” or of death from “liver cancer,” are in fact related to metastasis of other (sometimes undiagnosed) primary cancer.

5. Discussion

This section offers a complementary view to the work done by Remontet and co-workers (2002, 2003), that explored in much more detail cancer incidence and mortality trends in France. The main difference is that this section relies only on data from cancer registries and official mortality statistics and no modelling approach was used to estimate recent mortality or incidence rates at the national level. Interested readers may find detailed statistics on cancer mortality in France on the web-site of the Institut de veille sanitaire (www.invs.sante.fr/cancer_1983_2002/default.htm). The “Atlas de la Mortalité en France” displays in great detail the geographical patterns of mortality from cancer and from other causes (Salem et al., 1999a, b). A comparison between European countries of projections of cancer incidence and mortality data for the year 2006 may be found in Ferlay et al. (2007).

With the ageing of the French population, annual absolute numbers of cancer cases and deaths will continue to increase steadily. The increase in incidence due to ageing is further increased by early detection and screening. Thus, to compare changes in the overall burden of cancer over time that is not due merely to ageing or to screening, the best indicator remains the age-adjusted cancer mortality rate.

Temporal trends in all-cancer mortality in France for men and women resemble those observed in most European countries (Boyle et al., 2003).

Decreasing age-adjusted mortality is due mainly to decreases in the incidence of cancers with high fatality rates, such as lung cancer and cancer of oesophagus in men, of cancer of the cervix uteri in women, and of stomach cancer in both sexes. The decreases in mortality from these cancers in France are attributable mainly to temporal changes in exposure to risk or protective factors, notably smoking and alcohol drinking in men, oral contraceptives in women, and possibly reductions in *H. pylori* infection in both sexes.

Earlier detection has also contributed to decreasing mortality from many cancers, for instance breast cancer, colorectal cancer, cervical cancer, and also cancers for which no systematic screening is organized but diagnosis tends to occur at steadily earlier stage, for instance head and neck cancers.

Most of the increase in cancer incidence is driven by breast and prostate cancer. Increasing breast cancer incidence is induced by changes in reproductive factors, use of HRT and screening. Increasing prostate cancer incidence is largely attributable to PSA screening that detects mainly prostate cancers that are not life-threatening and should not be treated.

Changes in occupational exposures have contributed to the trends in morbidity and mortality due to selected cancers in men, such as mesothelioma and sinonasal cancer. These factors have also contributed to a proportion of lung and bladder cancer, but their influence on trends in incidence of and mortality from these cancers is far less important than that of tobacco smoking.

The available evidence does not allow any temporal trend in cancer occurrence to be attributed with confidence to changes in exposure to pollutants. However, given that levels of exposure to many known carcinogenic agents have drastically decreased during recent decades, one could argue that these agents might have played a role (if any) in cancers with decreasing incidence, rather than in cancers with increasing incidence (e.g., non-Hodgkin lymphomas).

For more frequent cancers such as breast, prostate and colorectal cancers, no or few data exist to support a contribution of occupational factors or pollutants to temporal changes in incidence or mortality.

The decline in cancer mortality observed in France parallels the general decline in cancer mortality in the European Union (EU) in recent decades. Examination of trends in cancer mortality in Europe over the past 30 years has shown that, after long-term increases, age-standardized mortality from most common cancers has fallen since the late 1980s (Quinn et al., 2003).

Progress against cancer in Europe has been the focus of the Europe against Cancer programme of the European Commission that was launched in 1985. It was expected that this programme would foster cancer control efforts in EU Member States and achieve a 15% decline in cancer mortality all over Europe (Boyle et al., 2003). In this respect, the situation in France seems particularly positive, as here, between 1985 and 2002, cancer mortality declined by 21% in men and by 12% in women. It must be noted, however, that for some cancers, the decline in mortality occurred for causes largely independent of coordinated cancer control efforts, for instance, the secular decline in stomach cancer mortality and the secular decline in alcohol consumption in France.

Survival data are often used as an indicator of the severity and of the management of cancers diagnosed in a population. However, survival data do not replace mortality data, as survival may vary considerably over time and between countries for reasons unrelated to treatment or to earlier detection of cancer that would otherwise be diagnosed at a more advanced stage (Boyle and Ferlay, 2005). Survival is considerably influenced by the so-called lead-time bias, that is, the additional time of observation of a cancerous patient due to diagnosis of the cancer at an earlier moment in its progression. Ignoring lead-time gives a biased impression of longer survival that is in fact due to a longer period of observation. Increased detection of more indolent cancers of good prognosis by screening is another source of bias, called length-time bias, that artificially increases survival because proportionally more cancers of good prognosis are included for the calculation of survival duration. One way to control these biases is to take into account stage at diagnosis of cancers registered over time or in different countries. Availability of data on stages often leads to better explanations of cancer survival observed over time or across areas (Sant et al., 2003;

Ciccolallo et al., 2005); this requires registration of stage by cancer registries.

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Table A2.1 - Numbers of cancer deaths in France in 1968 and 2003 with application of cancer mortality rates observed in 1968 to the French population in 2003 *

	1968						2003							
	Observed deaths		Population figures		Crude rates		Observed deaths		Population figures		Expected deaths †		% change	
Age-group	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
All ages	58,914	46,865	24,210,936	25,500,088	243.3	183.8	88,201	59,033	28,976,913	30,658,067	94,725	72,765	-6.9%	-18.9%
00-	197	150	2,166,950	2,079,115	9.1	7.2	61	50	1,918,140	1,831,438	174	132	-65.0%	-62.2%
05-	127	109	2,119,613	2,040,697	6.0	5.3	36	37	1,830,796	1,743,294	110	93	-67.2%	-60.3%
10-	130	95	2,095,984	2,021,547	6.2	4.7	52	40	1,943,024	1,852,514	121	87	-56.9%	-54.1%
15-	180	136	2,174,178	2,090,862	8.3	6.5	82	60	1,967,871	1,890,078	163	123	-49.7%	-51.2%
20-	197	116	1,814,075	1,719,705	10.9	6.7	123	76	1,972,712	1,926,700	214	130	-42.6%	-41.5%
25-	216	123	1,475,148	1,387,106	14.6	8.9	149	131	1,915,844	1,899,546	281	168	-46.9%	-22.2%
30-	291	270	1,609,256	1,540,519	18.1	17.5	251	291	2,132,747	2,134,875	386	374	-34.9%	-22.2%
35-	599	570	1,723,373	1,664,195	34.8	34.3	506	641	2,156,834	2,189,424	750	750	-32.5%	-14.5%
40-	1,246	1,142	1,660,855	1,652,799	75.0	69.1	1,286	1,186	2,103,150	2,161,745	1,578	1,494	-18.5%	-20.6%
45-	2,184	1,800	1,388,534	1,423,625	157.3	126.4	3,249	2,135	2,052,795	2,119,910	3,229	2,680	0.6%	-20.3%
50-	2,544	1,862	1,056,750	1,122,283	240.7	165.9	5,918	3,156	2,079,055	2,116,724	5,005	3,512	18.2%	-10.1%
55-	6,044	3,670	1,348,559	1,470,495	448.2	249.6	7,677	3,641	1,676,949	1,706,731	7,516	4,260	2.1%	-14.5%
60-	8,971	4,759	1,219,614	1,403,213	735.6	339.2	7,885	3,739	1,256,452	1,327,729	9,242	4,503	-14.7%	-17.0%
65-	11,076	6,097	998,190	1,284,705	1109.6	474.6	10,743	5,422	1,211,021	1,395,287	13,438	6,622	-20.1%	-18.1%
70-	9,334	7,051	634,909	1,055,863	1470.1	667.8	13,882	7,524	1,095,059	1,408,138	16,099	9,403	-13.8%	-20.0%
75-	7,432	7,468	397,653	775,466	1869.0	963.0	14,599	9,223	844,725	1,251,812	15,788	12,055	-7.5%	-23.5%
80-	5,040	6,273	220,908	486,490	2281.5	1289.4	12,068	9,456	517,013	895,489	11,796	11,547	2.3%	-18.1%
85+	3,106	5,174	106,387	281,403	2919.5	1838.6	9,634	12,225	302,726	806,633	8,838	14,831	9.0%	-17.6%

* Mortality data from the CpiDC, INSERM (2005), Demographic from INSEE

† Expected numbers of deaths calculated from applying cancer age-specific mortality rates in 1968 on numbers of people in each age-group in France in 2003. The numbers of deaths in 2003 divided by the expected numbers of deaths in 2003 (as if rates of 1968 were still valid for 2003), gives the % change in cancer mortality in France between these two periods

Table A2.2 - Factors other than ageing associated with increases in incidence of selected cancer in France

The influence of risk factors displayed in the five columns on the right on cancer incidence and mortality in France is estimated in the remainder of this report.

Keys: (+/–) factor suspected but not confirmed to be involved in a change in incidence; (+) factor moderately associated with a change in incidence; (++) factor involved in change in incidence; (+++) factor strongly associated with change in incidence; (+?) or (++?) association suspected but not proven (?) indicates that there is no evidence for a specific risk factor belonging to the relevant risk factor category

Cancer site	Administrative or demographic reasons	Competing causes	Changes in diagnostic method	Screening effect	Changes in behaviours (a)	Individual risk factors	Reproductive factors	Infectious factors	Air, soil, water, food pollutants
Prostate		+	+	+++					
Thyroid			+++	+++		+/_ (b)			
Breast				+++	+	++ (c, d)	+		
Colorectal				+	++	++ (d)			
Cutaneous melanoma				++	+++				
Lung in women		+			+++				+(i)
Mesothelioma		+			++			?	+++ (e)
CNS tumours			+++						
Hepatocarcinoma		+	+		+			+	
Bladder	+		+						
Multiple myeloma	+		+		+?			++ ?	
Pancreas			+		+			?	
Childhood cancers	+	+ ? (f)	+			?	++ ? (g)	+?	
Testis					?	?	?	?	?
NHL	+		+		?	?		++ ?	?
Kidney			++ (h)		+	+ (d)		?	?

(a) e.g., Tobacco smoking; alcohol; lack of physical exercise; UV exposure; (b) Radiation; (c) Hormone treatment; (d) e.g., obesity; (e) Asbestos; (f) Better survival of children with congenital malformations; (g) e.g., aged mother; prematurity (1.5–2.4 kg), high prematurity (<1.5 kg), and high birthweight (> 4 kg); (h) Mainly incidental detection during medical investigations; (i) Second-hand smoking

Figure A2.1 - Evolution of incidence (1978-1997) and mortality (1950-2004) from cancer in France
Mortality trends in the départements of Bas-Rhin, Calvados, Doubs and Isère are displayed as dotted lines.

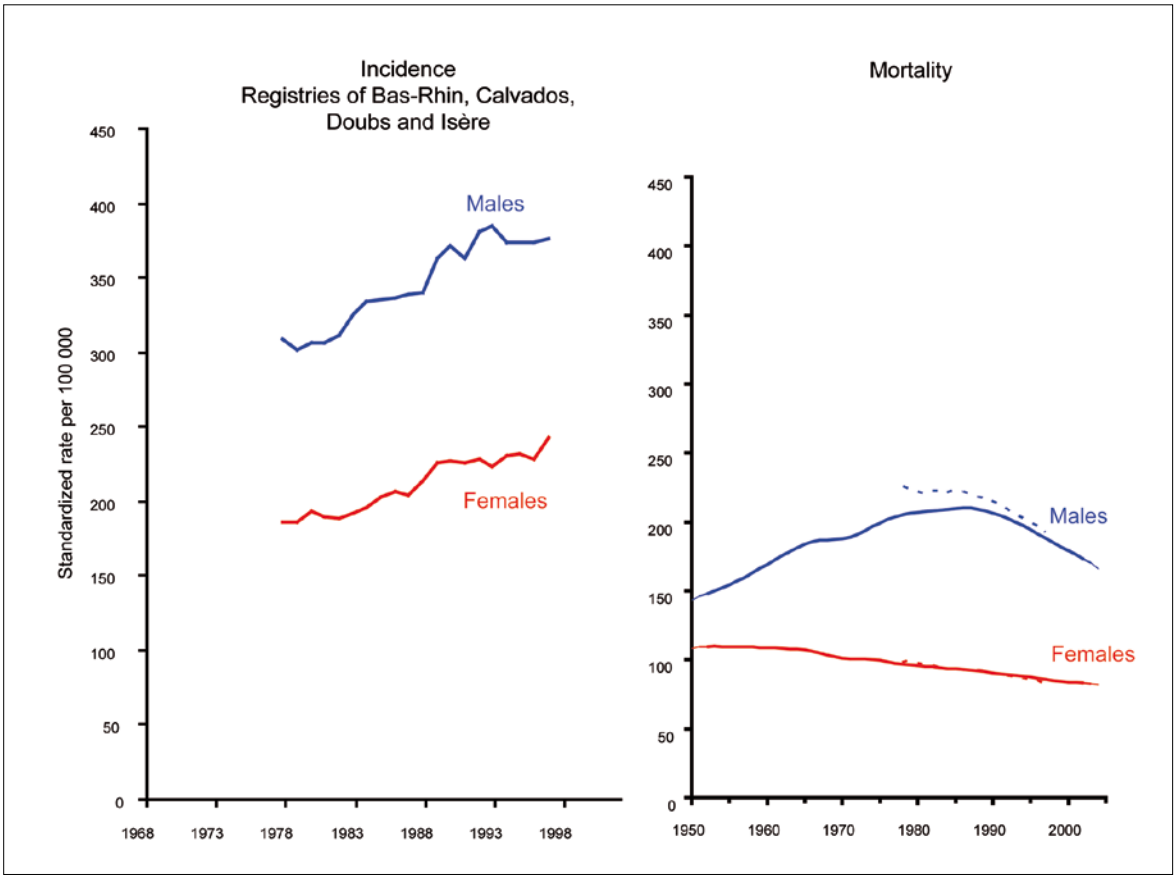

Figure A2.2 - Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Most frequent cancers - Males

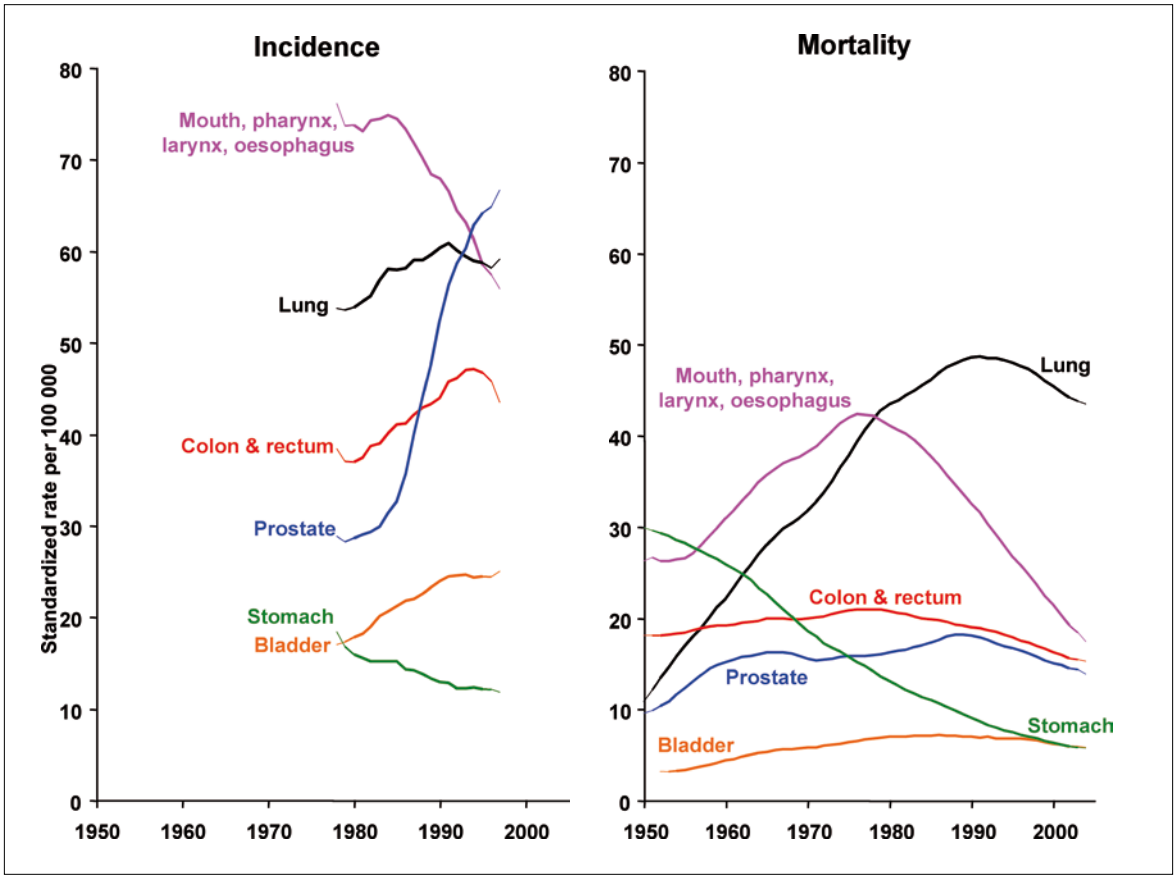

Figure A2.3 – Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Cancers of intermediate frequency - Males

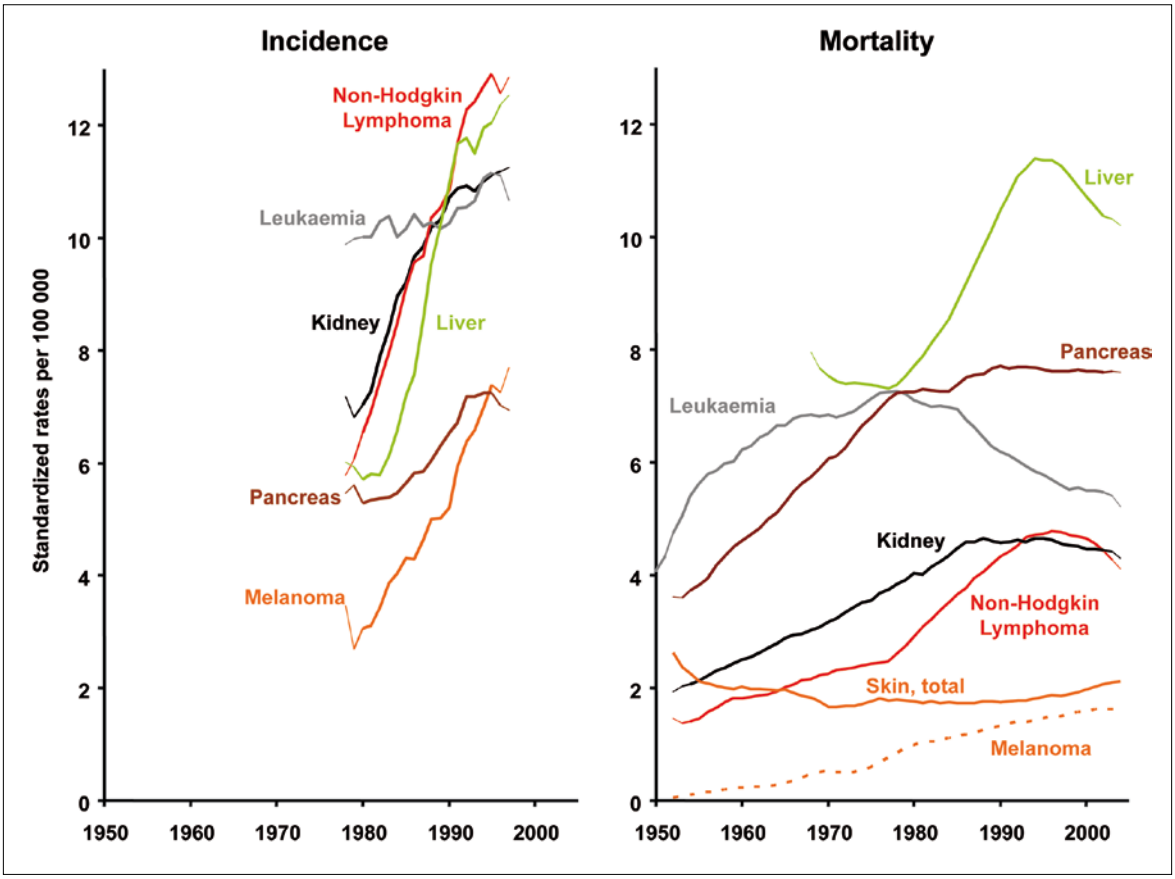

Figure A2.4 – Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Less frequent cancers - Males

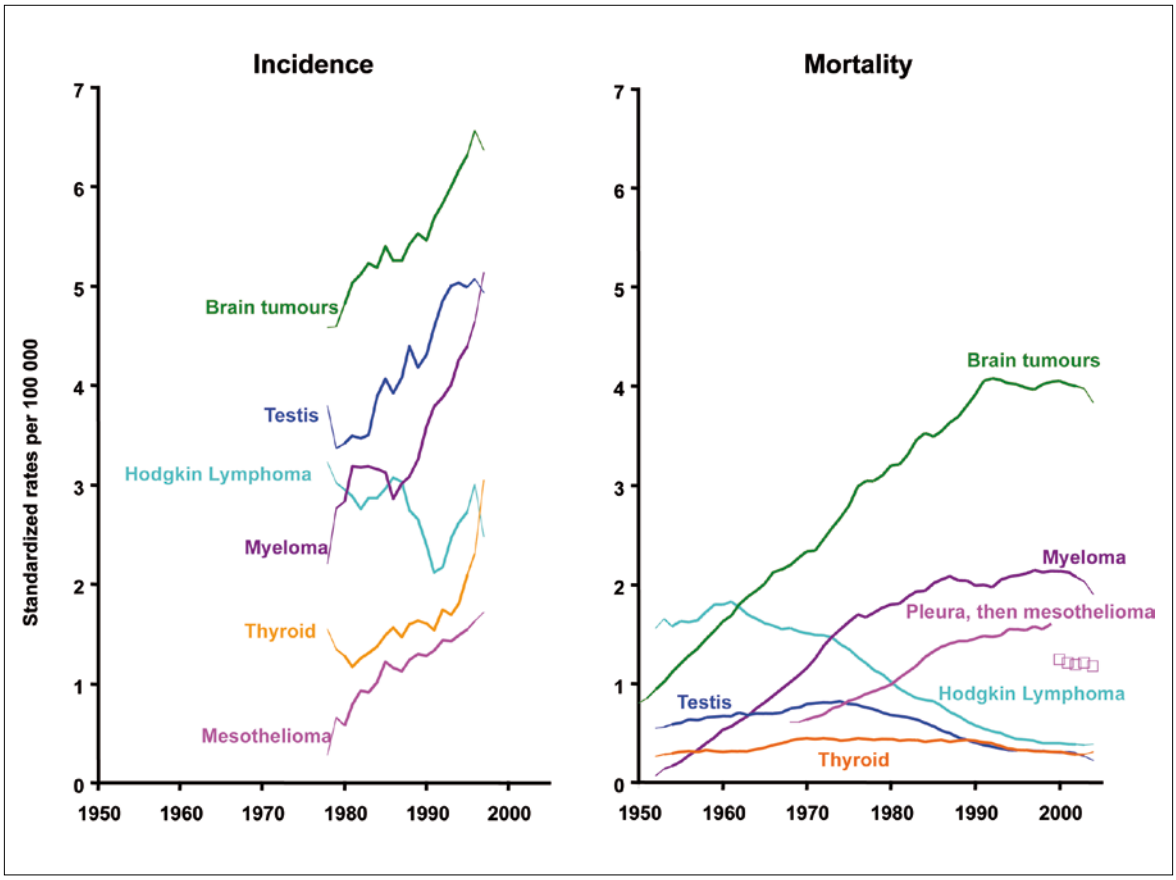

Figure A2.5 - Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer France
Most frequent cancers - Females

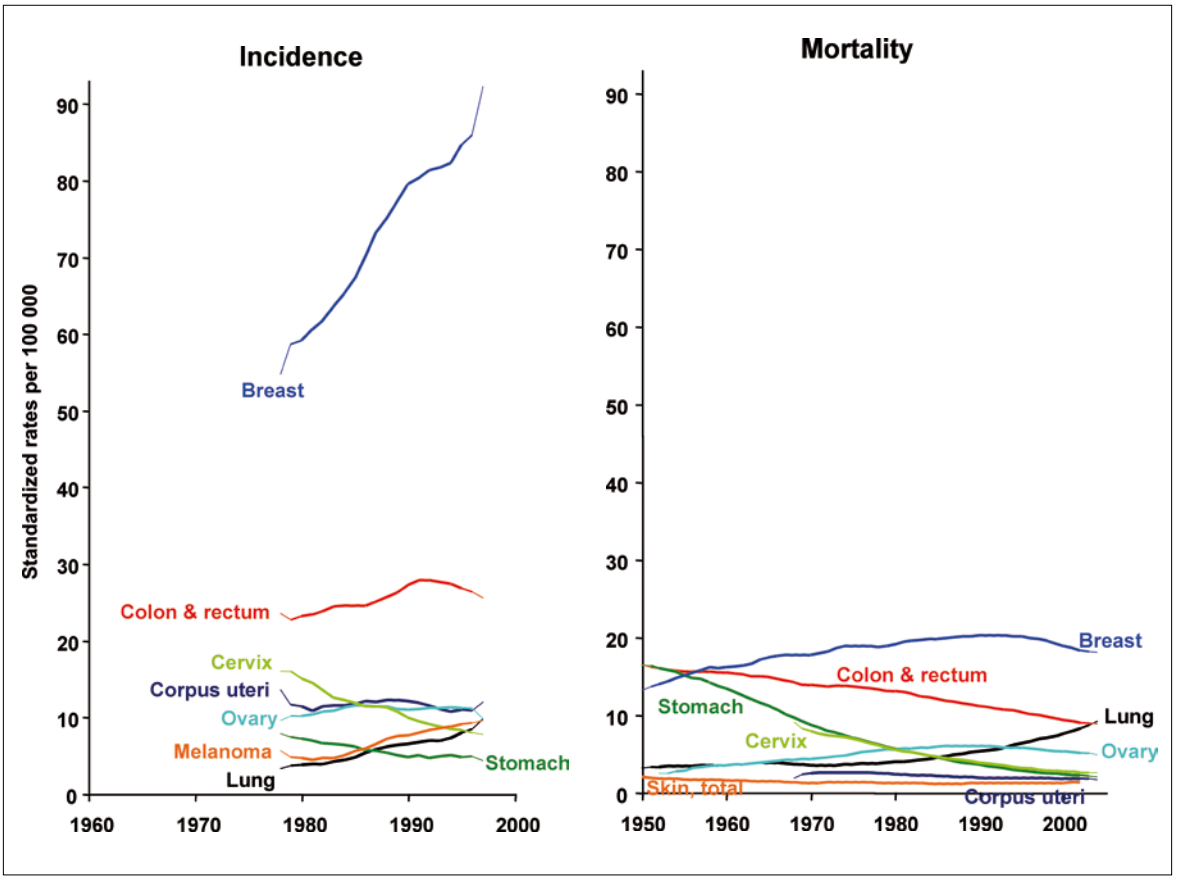

Figure A2.6 - Evolution of incidence (1978-1997) and mortality (1968-2004) of breast cancer in France
Over a 20 year period, breast cancer incidence has increased by 82% in women 50 and older
and by 55% in women younger than 50

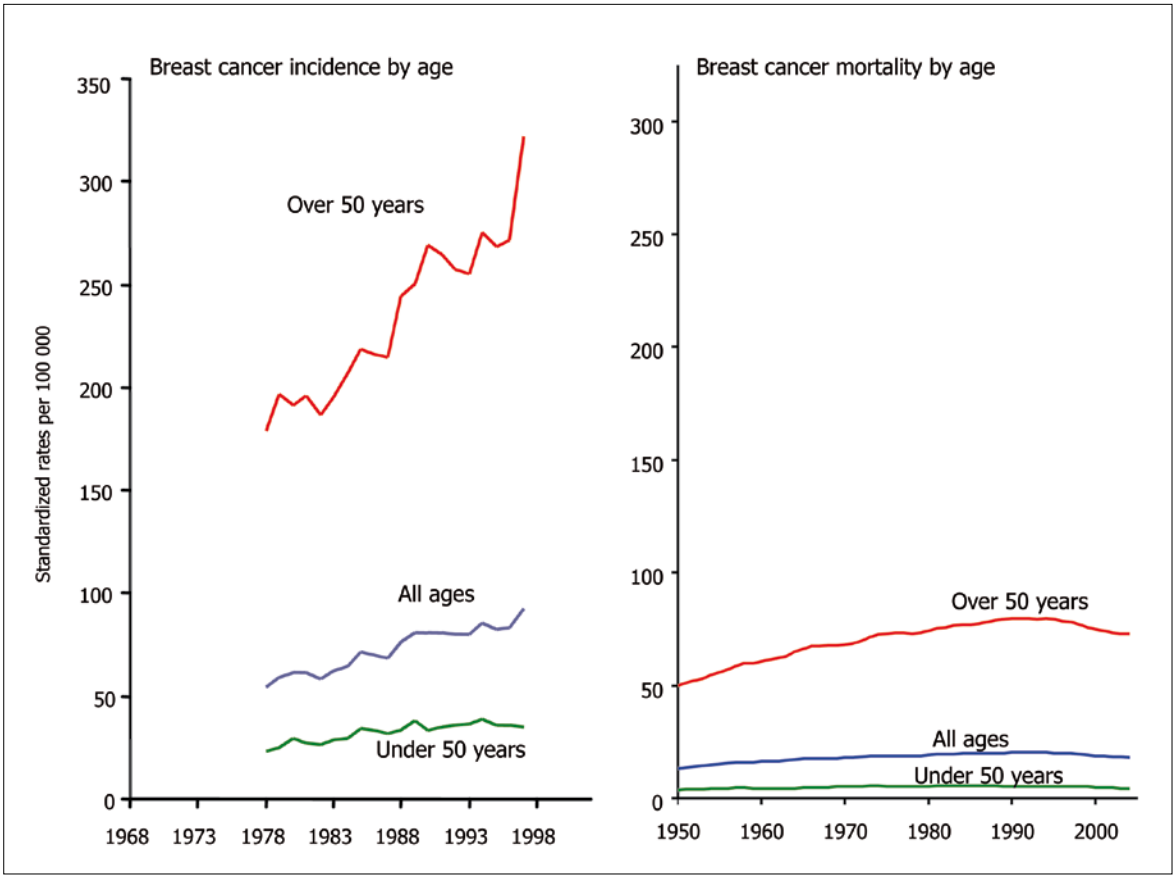

Figure A2.7 – Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Cancers of intermediate frequency - Females

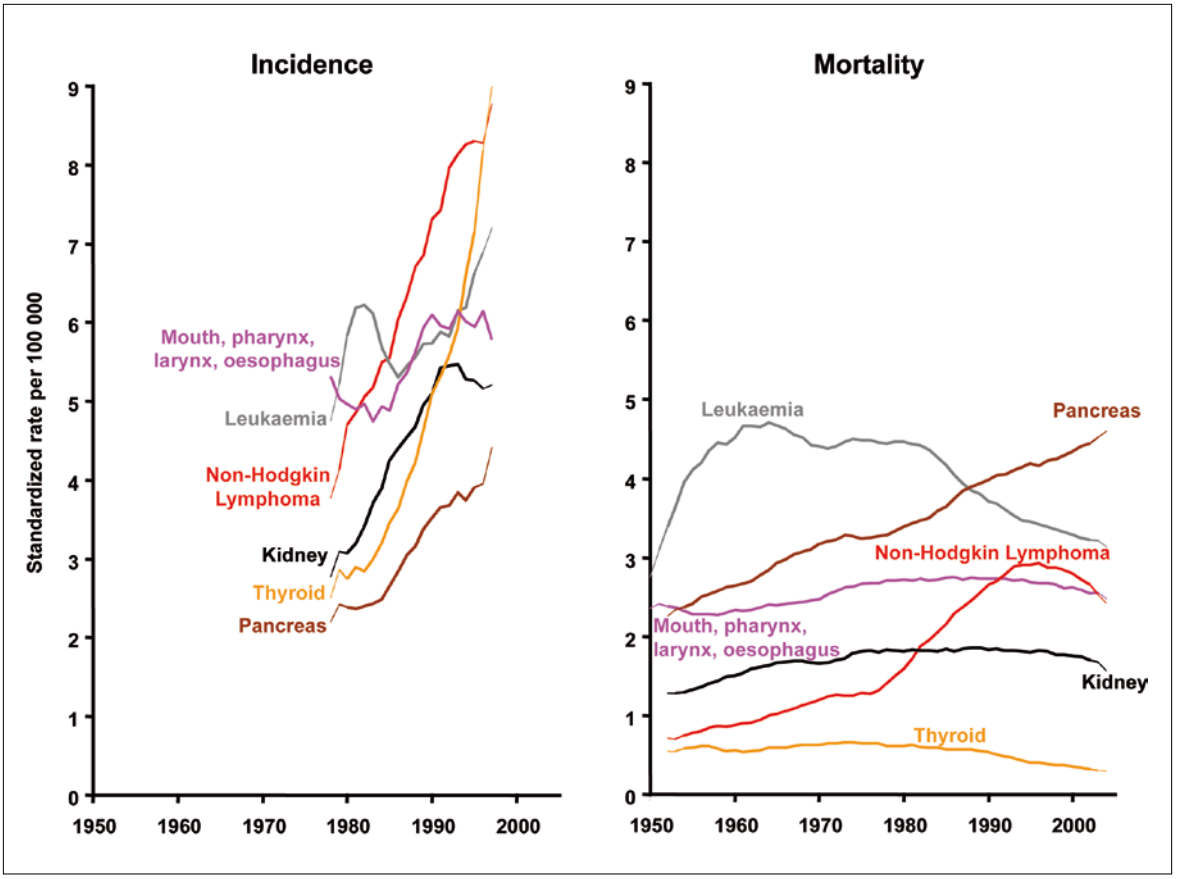

Figure A2.8 – Evolution of incidence (1978-1997) and mortality (1950-2004) by cancer in France
Less frequent cancers - Females

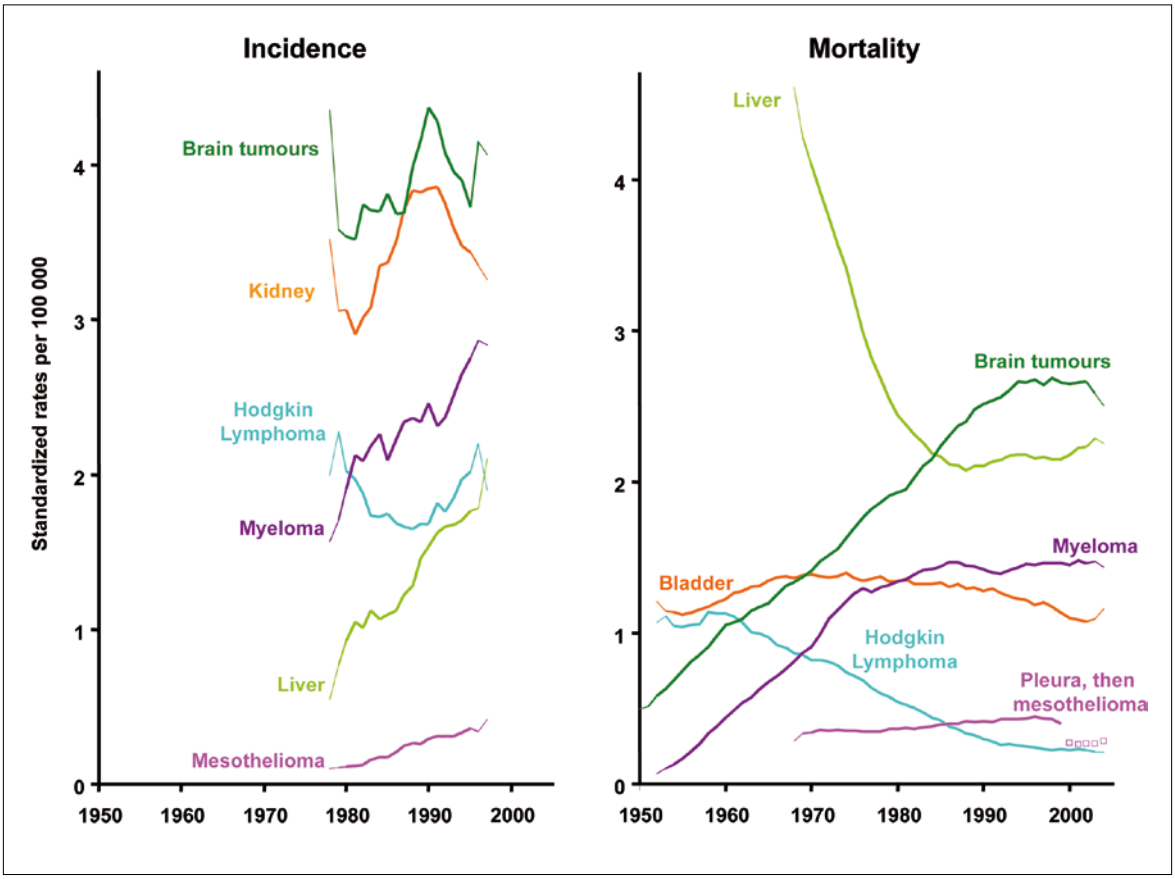

Figure A2.9 – Evolution of mortality (1950-2004) by cancer in France
Cancer in Children (0-14)

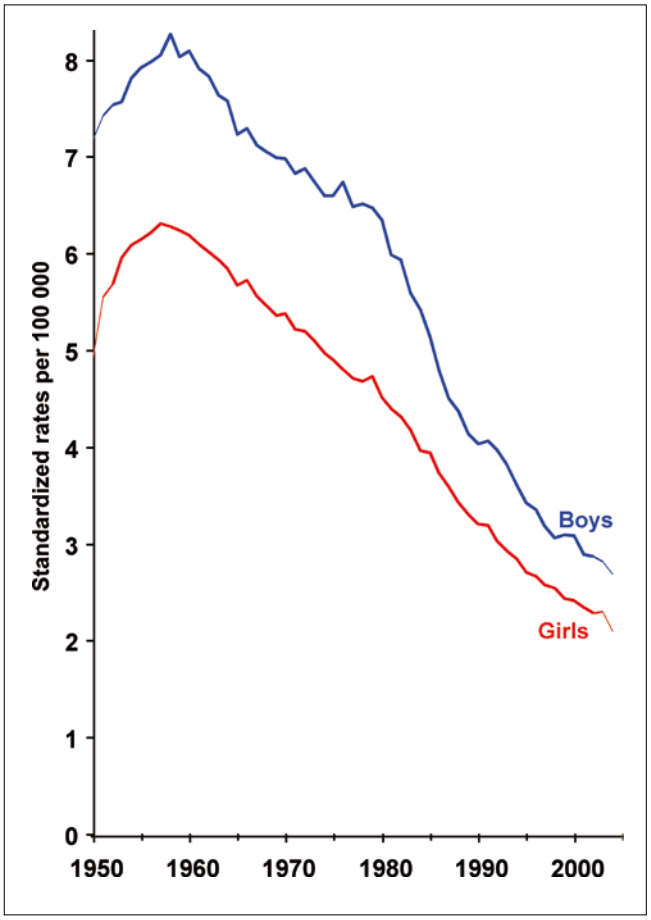

Figure A2.10 - Synthesis of the evolution of the incidence and the mortality from cancer in France, in males, between 1978 and 1997 (rates adjusted by age). The percentages on the ordinate (incidence) and on the abscissa (mortality) indicate the annual average change in the rates of incidence and mortality over the period 1978 to 1997. The size of the points is proportional to the rate of incidence of the cancers

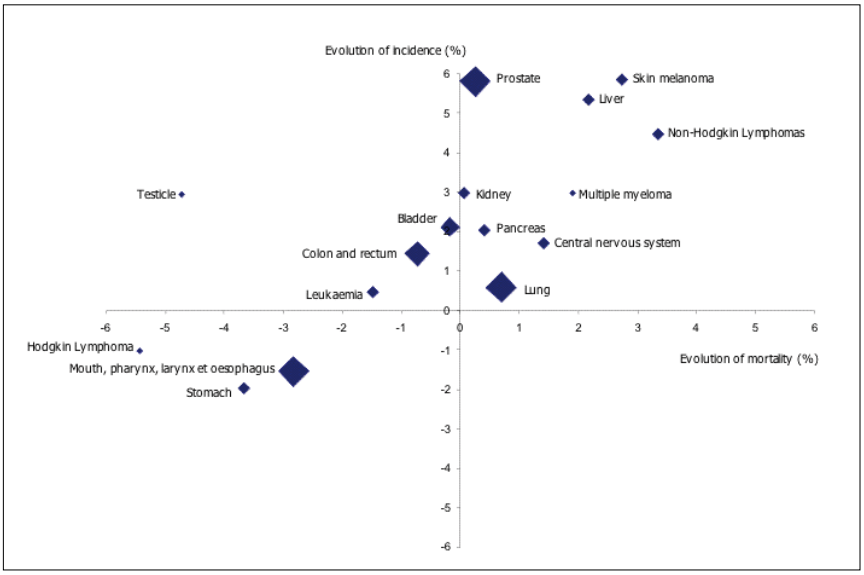

Figure A2.11 - Synthesis of the evolution of the incidence and the mortality from cancer in France, in females, between 1978 and 1997 (rates adjusted by age). The percentages on the ordinate (incidence) and on the abscissa (mortality) indicate the annual average change in the rates of incidence and mortality over the period 1978 to 1997. The size of the points is proportional to the rate of incidence of the cancers