Collective Expert Report

Cancers

Long-term prognoses

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Inserm

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This document presents the work of the expert group formed by Inserm in the context of the collective expert procedure in response to the request from the French Authority General of Health (DGS) and French National Cancer Institute (INCA) with respect to the long-term prognoses for neoplastic diseases.

The document is based on the scientific data available as at the first half of 2005. Over 400 articles and documents constituted the document base for this collective expertise report.

The Inserm collective expertise center ensured coordination of this collective expert report.

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Foreword

The access to insurance of patients having undergone cancer treatment is a subject that concerns both patients and public authorities. The difficulties encountered in this area by patients and former patients impact their social and professional lives. The agreement dated September 19, 2001 concluded between the French State, patient representatives, and insurance and credit establishments, was designed to increase the insurance access of people presenting with an increased health risk, and provides for an attentive and specific review of the expectations of those involved.

In order to determine the 'additional premiums for increased risks', it would appear necessary to review our knowledge of the life expectancies of patients treated for cancer at a given time taking into account the main parameters with an impact on life expectancy (age, gender, cancer stage, therapeutic progress, etc.). The provision of recent and validated life expectancy data for the various disease sites should enabled enhanced scientific pertinence with respect to the modalities of premium determination.

In 2004, the Inter-Ministerial Mission to Combat Cancer (MILC) and the General Authority of Health (DGS) asked Inserm to implement, in accordance with the collective expert report procedure, a detailed analysis of the national and international literature on the life expectancy of patients affected by cancer and the main prognostic indices. Only the risk of death, and not that of morbidity, was to be evaluated. This analysis is designed to provide scientifically found data to contribute to decision making by insurance professionals.

In response to that request, Inserm set up a pluridisciplinary group of experts with skills in public health and clinical practice in the field of neoplastic diseases. The expert group addressed the following questions:

- What sources of population data (cancer registries) are available in France, Europe, and worldwide for 5-, 10- and 15-year (and over) survivals for the various tumor sites?
- How is an annual excess mortality to be calculated from the population data available? How does the annual excess mortality vary for men and for women as a function of age at the time of diagnosis? How does the annual excess mortality vary as a function of diagnosis period, i.e. from the oldest cohorts to the most recent cohorts?
- What prognostic factors other than age and gender affect the annual excess mortality for each type of cancer? What is the impact of therapeutic progress on survival data?

In the course of 9 working sessions, the expert group reviewed the data on long-term survival available at national European and international level. The expert group defined the modalities for analysis of the data, calculation of the annual excess mortality, and result presentation in order to propose, for each disease site, components for the assessment of the excess risk that would be of value to the patients and professionals involved. It should be noted that long-term quantitative data are not available for factors other than age, gender and period of diagnosis. In addition, the survival data presented are those for former patients and do not forecast how the prognosis will evolve in the future. It is therefore necessary to remain very cautious in extrapolating from the results. Shortly, survival data for all the cases recorded in the cancer registries in France will become available as a complement to the results herein, mainly derived from European and North American data.

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Data sources

Survival information on a population in which neoplastic disease has been diagnosed is derived from three main types of sources: population studies (registries and other population studies), hospital series and clinical trials.

Although the analytical methods used are reasonably similar, the three types of study do not have the same objectives and do not reflect the same reality. They are therefore to be interpreted and used differently.

Cancer registries in France and Europe

The only databases specifically compiled with a view to studying neoplastic disease at population level are the cancer registries. The primary objectives of the latter are to supply epidemiological indicators (incidence, prevalence, survival, etc.). Survival studies conducted on registry data may be used to assess the overall efficiency of the healthcare system, i.e. both the quality of disease management and healthcare system use habits, which condition, in particular, the earliness of diagnosis. Such studies, by comparing several successive periods, provide information on the improvement in management system performance.

In Europe, the first population studies were conducted using the registries of the Northern European countries (Hakulinen, 1983) and Scotland (Black, 1993). A further large-scale study used the data collected by the English and Welsh registries from 1970 to 1990 and was published in 1999 (Coleman, 1999). The objective of the study was not only to compare the survivals in the various regions of England and Wales but also to compare survivals as a function of patient socioeconomic level and to study the time course of survival from 1975 to 1995.

In Europe, the most complete information on survival is derived from the 'Eurocare' study. The project, initiated in 1990, was designed to describe the survival of a population in which neoplastic disease had been diagnosed on the basis of the data supplied by the cancer registries of the European countries. The study enabled the definition, in three stages, of the survival rates for the various countries, first for the cases diagnosed in the period 1978-1985 (Berrino, 1995), then for the period 1985-1989 (Berrino, 1999) and finally for the period 1990-1994 (Sant, 2003). All the data were updated as at January 1, 2000 (table 1.I).

Table 1.I: Eurocare study recruitment

	Eurocare 1	Eurocare 2	Eurocare 3
Diagnosis period	1978-1985	1985-1989	1990-1994
Number of cases	800 000	1 296 063	2 202 169
Number of registries	30	45	56 + 11 pediatric registries
French registries	4 including 3 specialized	5 including 3 specialized	4 including 2 specialized + 3 pediatric registries

In 2005, the Eurocare study included data from 67 cancer population registries in 20 countries. The sample studied constituted a different proportion of the population in each country. For instance, for the last period (1990-1994), the sample accounted for 63% of the UK population, 24% of the population of the Netherlands and 15% of the population of Italy. In France, due to lack of resources for patient follow-up, only 4 to 6 French registries including data by disease site and period were able to supply data to the Eurocare study. That was equivalent to 2.9 to 5.6% of the population. The proportion also differs as a function of disease site and the specialized or non-specialized nature of certain registries. In France, a study is ongoing on the overall survival of the cases reported from 1988 to 1997 (table 1.II). The results of the study will be available in 2006.

Table 1.II: List of cancer registries in France

Type of registry	Region
General	Bas-Rhin, Calvados, Doubs, Haut-Rhin, Hérault, Isère, La Réunion, Loire Atlantique, Manche, Martinique, Somme, Tarn, Vendée
Gastrointestinal	Calvados, Côte d'Or, Finistère
Gynecological	Côte d'Or
Hematological	Côte d'Or, Gironde
Thyroid	Marne and Ardennes
National registry of childhood leukemia	National
National registry of childhood solid tumors	National
Francim network	Toulouse

The Eurocare study supplied the observed and expected survival data from which the relative survival was calculated. Relative survival is the ratio between the observed survival rate in the group of cancer patients and that expected for the same period and in the same region for a population of the same age and gender. The various neoplastic diseases were defined as per the 10th revision of the International Classification of Diseases (ICD-10; Fritz, 2000). In the Eurocare study, survival was analyzed by gender, age, period of diagnosis and country.

In the context of the survival analyses conducted on the entire Eurocare database, it is not possible to present studies by cancer stage. The cancer registry managements consider that the stage information routinely collected is not sufficiently reliable and standardized to be used in survival studies. Despite a commitment to simplification, staging remains relatively complicated. The stage is the resultant of a set of information enabling classification of the various dimensions of tumor spread and the evaluation of those dimensions is highly dependent on the investigations conducted.

The improvement in certain diagnostic techniques enables enhanced staging of a tumor. This phenomenon, known as stage migration, was described in an article entitled, 'The Will Rogers phenomenon' (Feinstein, 1985). The author used lung cancer to show how the improvement in diagnostic methods enabled demonstration, as of diagnosis, of metastases that had hitherto been overlooked. Depending on the investigations conducted, the same patients may thus be classified in various disease stages. The study of survival by stage, in order to compare two different periods, thus gives rise to a false improvement in prognosis. Since that phenomenon was evidenced, it is generally recommended that, for all survival comparisons taking into account stages, adjustment variables should be used in order to minimize the biases related to stage migration which is in turn related to the improvement in diagnostic techniques. The same problem arises when two geographic zones with different medical habits or resources are compared.

Those problems have been taken into account in specific studies of certain frequent cancer sites. Those studies took into account the stage and diagnostic workup. The studies, known as the 'Eurocare high-resolution studies', particularly addressed breast cancer and colorectal cancer diagnosed in 1990. The studies were conducted on representative sub-samples that were the subject of complementary investigations in order to enhance the standardization of the information collected. The results have yet to be published.

Other population data

Other registries are available. In particular, the American Surveillance Epidemiology and End Results (SEER) program is noteworthy. The SEER program is the best source of information on cancer incidence and survival in the United States (Ries, 2002). The program has been regularly presenting the data from 11 population registries and 3 hospital registries since 1973. The registries cover about 14% of the population of the United States. The geographic zones were selected on the bases of their representative nature, in particular from an ethnic point of view, but also for their ability to implement high-quality records. The program generates relative 10-year survival data as a function of tumor spread. Three grades are defined: localized tumor, tumor with regional spread (lymph nodes involvement) and tumor with remote spread (metastatic tumor).

Data close to population data

The studies implemented in France by certain health insurance organizations have an intermediate status between population studies and hospital registries. The health insurance studies monitor all the patients affiliated to the various health insurance organizations in a given area and having requested exoneration from the financial contribution to cancer treatment (ALD 30)[1]. The patients included in those studies are therefore not selected as a function of disease management site. However, the patients cannot be considered representative of the overall population in that a non-negligible fraction of patients do not request ALD status. Although studies of the representativeness of ALD status beneficiary cases are not numerous, it is agreed that certain types of cancer are less frequently the subject of an ALD status application. Those cases are situated at both prognostic extremities. One extremity consists in cases in which the disease is not very serious and the treatment duration is short. In contrast, at the other extremity, the scenario includes cases that die

[1] ALD 30: Long-duration disease (the number 30 denotes cancer)

quickly from an already very advanced disease and cases occurring in the context of another chronic disease for which ALD status has been granted.

Hospital series or hospital registries

Hospital registries are rare in Europe but more frequent in the United States where patient follow-up has long been one of the evaluation obligations of hospitals (Ederer *et al*., 1961). In the United States, the initial form of the SEER program included several hospital registries associated with population registries.

France has one of the largest hospital registries in Europe: the Permanent Cancer Survey (EPC) which collects information on all new cases of cancer treated in the Cancer Treatment Centers (CLCC). Since 1975, a computerized system set up by the National Federation of Cancer Treatment Centers (FNCLCC) has ensured the collection and processing of data from the 20 CLCCs in France. The survival studies based on the EPC data only address the cases entirely managed by the anti-cancer centers (FNCLCC, 1986; FNCLCC, 1993). This restriction is due to the fact that the information on patients managed secondarily is not very reliable, in particular with regard to tumor stage and diagnosis date. The EPC population, particularly that which is the subject of survival studies, is thus a population deriving from highly selective recruitment and for which highly-specific management is implemented. The population therefore cannot be considered a true reflection of the situation in France as a whole. The follow-up of the patients in that base, currently being updated, has therefore not been taken into account herein.

Clinical trials

Clinical trials are designed to test new treatments or new therapeutic strategies with a view to demonstrating that they are more effective or more efficient that those considered to be reference treatments or strategies. A small proportion of patients take part in clinical trials: the proportion varies depending on disease management site and structure. A much higher proportion of children are included in such trials. This is related to the fact that pediatric disease management is generally conducted in specialized pediatric centers (Tejeda, 1996).

Clinical trials do not enable extrapolation of the survival results obtained to the overall population but nonetheless generate important information on the parameters influencing the prognosis. Clinical trial patients undergo rigorous follow-up, enabling standardized evaluation of disease progression.

In France, trials are mainly conducted by specialized structures. The public sector or sector assimilated thereto (CLCC and university hospitals) predominate, even though cancer is treated in numerous other healthcare centers.

A further limitation on the use of data generated by clinical trials resides in the fact that certain types of patient are almost always excluded: in particular those presenting with marked comorbidity and elderly patients.

In conclusion, population studies provide fundamental data on mean survival in the past. They thus enable evaluation of the impact of care practices on survival over time. As a complement to registry data, hospital series, although subject to selection bias, may enable a finer degree of evaluation of the prognostic factors for survival. Clinical trials yield detailed information on the gains in terms of survival associated with the most recent treatments. In

the context of this collective expert report, the population data were derived from the Eurocare study, including the French data available. Shortly, the population data of the French network of cancer registries (Francim) and the hospital data from the Permanent Cancer Study (EPC) will provide further information.

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Methodology

The aim of this chapter is to present the method selected to calculate the estimates of the annual excess mortality risk related to cancer itself, remotely from the diagnosis, i.e. when the patient has survived for a certain time. The method was selected since it proved to be immediately applicable across all disease sites, using the data from the reference European study, the Eurocare study.

For certain cancer sites, data on the prognostic factors are available as a complement to the presentation of the risk estimates derived from the Eurocare study.

Sources of information for calculation of the annual excess risk

The data used are derived from the Eurocare 3 study. The data and publications are available in electronic form and can be downloaded from http://www.eurocare.it. The indicators available are: observed survival, expected survival and relative survival for each year post-diagnosis, by country and for Europe (22 countries), the period of diagnosis, disease site, gender and age group at the time of diagnosis. In addition, the database enables calculation of certain indicators specific to the objectives of the expert report since it states the patient populations, annual mortality and number of patients lost to follow-up.

Countries selected for the data analysis

In the context of this collective expert report, the French data were enriched with other data derived from European countries in order to enable more precise estimates of the long-term annual excess mortality.

The seven countries selected on the basis of the quality of their data and for the similarity of those data to the French data were Spain, Italy, the Netherlands, Switzerland, Sweden, Finland and Norway.

The data selected were on patients aged less than 75 years at the time of diagnosis. For prostatic cancer, the diagnostic age limit was extended to 84 years.

Disease sites studied

In the context of the expert report, 22 disease sites in adults and 9 sites in children were selected. Tables 2.I and 2.II list the disease sites for adults and children.

Table 2.I: Adult disease sites studied

Gynecology
Breast (women)
Ovaries
Cervix
Corpus uteri
Gastrointestinal
Colon
Rectum
Urology
Prostate
Testes
Kidneys
Lungs
ENT
Larynx
Hypopharynx
Oropharynx
Nasopharynx
Melanoma
Thyroid
Malignant blood diseases
Acute lymphoblastic leukemia
Acute myeloid leukemia
Chronic lymphocytic leukemia
Chronic myeloid leukemia
Hodgkin's disease
Non-Hodgkin's lymphoma

Table 2.II: Child disease sites studied

Malignant blood diseases
Acute lymphoblastic leukemia
Acute myeloid leukemia
Hodgkin's disease
Non-Hodgkin's lymphoma
Tumors of the central nervous system
Neuroblastoma
Nephroblastoma
Soft tissue tumors
Bone tumors

Data on other disease sites are also available from the Eurocare 3 study but those sites were not selected for the expert report.

Data extracted from the Eurocare 3 study to estimate the annual excess mortality risk

For the eight countries selected (including France) and for each disease site selected, the data presented in table 2.III were extracted from the Eurocare study data in order to calculate the annual excess risk estimate.

Table 2.III: Data extracted from the Eurocare 3 study data to estimate the annual excess mortality risk

Diagnostic cohort (1983-1985, 1986-1988, 1989-1991, 1992-1994)
Gender (men, women)
Age group: 15-44, 45-54, 55-64, 65-74 (except for prostatic cancer: 15-54, 55-64, 65-74, 75-84)
Number of years (1, 2,…, 12) since diagnosis, each year constituting a time interval
Total number of cases diagnosed
Number of survivors at the start of the interval (alive)
Number of deaths over the interval (dead)
Number of subjects lost to follow-up over the interval
Hakulinen estimate (1982) of the expected survival by interval of one year (esi)

The Eurocare 3 study has generated grouped data and not individual data. The expected survival estimates by interval are thus only available for certain groups defined by the diagnostic cohort, gender or age group[2].

The diagnostic period mainly influences the survival in the first years and very little the excess annual risk remotely from the diagnosis (Talbäck *et al.*, 2004) as has been confirmed on most of the Eurocare study data. The data for all the periods available were thus pooled in order to more precisely estimate the excess mortality remote from the diagnosis.

Period analysis method

The period analysis method (Brenner, 2002) takes into account, for calculation of the long-term cumulative relative survival, the survival observed over the first years post-diagnosis for the most recent periods. The method is of value in estimating the long-term cumulative relative survival since the method takes into account potential improvements in short-term survival liable to occur over time. However, this method does not generate additional information and hence is not beneficial for estimation of annual risk remotely fron the diagnosis. This is illustrated in table 2.IV.

[2] During data extraction, data line replicates were observed and corrected for the calculations. The survival estimates in the last time interval, 12-13 years, for each diagnostic cohort are not reliable. They were therefore not taking into account in the calculations.

Table 2.IV: Annual excess risk by the classic cohort method and by the period analysis method

	Follow-up years									
Year of diagnosis	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986
1977	0.61	0.81	0.91	0.96	0.95	0.90	0.95	1.00	0.98	0.97
1978		0.67	0.83	0.92	0.93	0.96	0.94	0.96	0.95	0.95
1979			0.67	0.79	0.90	0.94	0.95	0.94	0.92	0.96
1980				0.69	0.82	0.92	0.89	0.96	0.97	1.00
1981					0.77	0.78	0.90	0.88	0.94	0.94
1982						0.72	0.84	0.89	0.98	0.97
1983							0.73	0.82	0.92	0.91
1984								0.70	0.84	0.88
1985									0.74	0.81
1986										0.73

Relative survival by interval (Source: Finnish registry - colon cancer)

	Classic cohort method (cohort: 1977)	Period analysis method (period: 1986)
5-year survival	0.41 (0.61×0.81×0.91×0.96×0.95)	0.46 (0.73×0.81×0.88×0.91×0.97)
5-year survival after having survived 5 years	0.81 (0.90×0.95×1.00×0.98×0.97)	0.84 (0.94×1.00×0.96×0.95×0.97)
10-year survival	0.33 (0.61×0.81×0.91×0.96×0.95×0.90×0.95×1×0.98×0.97)	0.39 (0.73×0.81×0.88×0.91×0.97×0.94×1×0.96×0.95×0.97)

For example, for the cohort of patients whose disease was diagnosed in 1977, the 5-year survival is the product of the survivals in each 1-year interval for the first 5 years of survival and is equal to 41%. In comparison, the 5-year survival in 1986, using the period method, is equal to 46%. The survival is the product of the survivals per 1-year interval over the 5 years from diagnosis.

The period analysis method enables estimation of the long-term survival by using the survivals by interval for the most recent years. This has a strong impact on the cumulative relative survival at 5 or 10 years due to the differences in survival in the first years post-diagnosis depending on whether diagnosis took place in 1977 or 1986. This no longer applies when a patient has survived 5 years. Beyond those 5 years, the survivals by interval differ little irrespective of whether the year of diagnosis was recent or not.

It is legitimate to consider that the remote excess mortality data generated by the Eurocare study remain of value in the absence of data on the initial stage of the disease. The latter has a major impact on early excess mortality but probably much less impact, or no impact, depending on site, on the late excess mortality.

Principles of the methods of evaluating excess mortality

The net survival, for instance at 10 years, of a group of patients is the 'net' probability of being alive 10 years after the diagnosis of cancer with the hypothesis that all other causes of death are eliminated. The complement to 1 of the net probability of survival is the net probability of dying due to the cancer 'alone' within 10 years. This probability therefore reflects the excess mortality to which the patient group is subject.

Because it is not possible to warrant a distinction between mortality by cancer and other causes of death, the net probability of survival is difficult to estimate. Consequently, two methods are conventionally proposed to estimate the corrected probability of survival for other causes of death: the specific survival method and the relative or corrected survival method.

The specific survival method requires knowledge of the cause of death. The method only takes into account deaths related to cancer in the calculation of survival; deaths due to other cause are censored, i.e. follow-up stops at the date of death (when death due to cancer has not yet occurred). In the context of clinical trials in which data acquisition and patient follow-up are implemented in a precise and scheduled manner, the cause of death may be known. The method is therefore frequently used in such situations. It is, however, associated with two major questions: the reliability of the cause of death information (that datum appears to be of superior quality in recent years) and the difficulty of taking account of deaths indirectly related to cancer (in particular, adverse reactions to treatment). Whatever the case may be, collecting that information is impossible in the context of a population registry.

In consequence, the relative or corrected survival method is habitually used in the context of a population registry. The method does not require knowledge of the cause of death. An initial approach to calculating the relative survival rate consists in determining the ratio, in a given time t, between the observed survival probability in a population of subjects presenting with cancer and the expected survival probability in a general population of subjects not presenting with cancer, of the same gender, in the same age group, in the same region and at the same time. Relative survival is an estimate of net survival. The excess mortality, the complement to 1 of the net survival estimate, is deduced. The Eurocare study uses that approach to calculate the relative survival. The approach has also been used to conduct new analyses of the Eurocare data in the context of the present expert report.

There is however a second approach to calculating the relative survival (Estève *et al.*, 1990; Estève *et al.*, 1993; Dickman *et al.*, 2004). This approach is based on statistical modeling of the mortality rate added by the disease. Conceptually, the approach consists in estimating the parameters of a survival model and thus avoids the question of correcting the heterogeneity of the group under study for the covariables influencing survival. That question is repeatedly raised with the previous approach. The method has been adopted for the ongoing analysis of the data generated by the French cancer registry network (Francim network). The estimates, at 5 years, will be available in 2006. It is necessary to stress the importance of such estimates, which may subsequently be implemented over a longer term, in the context of updating the present expert report.

In this document, the net probability of death due to cancer was thus calculated on the basis of the Eurocare data. Hereinafter, it is referred to as 'excess mortality' and expressed as a percentage. The excess mortality was determined on an annual basis and is to be interpreted as follows: an annual excess mortality of 1% between 7 and 8 years means that at time t=7 years after diagnosis, the probability of dying of cancer or its consequences in the following year is 0.01.

It is doubtless of value to draw attention to the fact that the net probability of death due to cancer takes into account all the cofactors influencing the occurrence of the cancer. Let us take, as an example, a known cancer such as cancer in a smoker: the observed survival in the population of patients presenting with that cancer results from the fact of having had a cancer but also from the morbidity induced by smoking. If the observed survival is corrected by the expected survival in order to obtain the net survival, as indicated above, all the factors (cancer and co-morbidity induced by smoking) will be taken into account. It is thus appropriate, in any evaluation of the excess risk of death for a patient, not to incorporate the concept of smoking in the calculation again since this would mean taking the same risk factor into account twice.

The annual mortality rates by gender and age for the overall French population in 2002 are appended (source: Insee) for information.

Methods of estimating the excess risk of mortality

This section presents the methods used to evaluate the various indicators necessary for estimation of the excess annual mortality risk.

Observed survival

The first stage consists in estimating the observed survival by interval for a group of patients. The observed survival, *osi*, for the interval, *j*, is estimated as follows:

$$\mathrm{osi}_j = 1 - \frac{dead_j}{arisk_j}$$

where $arisk_j = alive_j - \frac{lost_j}{2}$ is the population at risk over the interval *j* (estimated by the actuarial method) and $dead_j$ is the number of deaths during the interval *j*.

Expected survival

When the observed survival has been estimated, the proportion of survivors that would have been observed for the same period, in the same country, region or department, in a population of the same age and same gender is to be estimated. The proportion is known as the expected survival.

The expected survival for an interval *j* (esi_j) is constructed as a mean of the estimates for each subgroup, weighted by the number of patients alive at the start of each interval. For each time interval *j* and for each subgroup *k* (*k = 1,…, K*), expected survival estimates (esi_{jk}) are calculated. The overall estimate (all groups considered) of expected survival (esi_j) for interval *j* is obtained as follows:

$$esi_j = \frac{\sum_{k=1}^{K} alive_{jk} \times esi_{jk}}{\sum_{k=1}^{K} alive_{jk}}$$

Relative survival

The two estimates, observed survival and expected survival, then enable deduction of a relative survival estimate for each interval (rsi_j) which consists in the probability of survival in the event that the cancer in question is the only possible cause of death (Ederer *et al*., 1961; Hakulinen *et al*., 1987). The relative survival is defined as the ratio between the observed survival and expected survival:

$$rsi_j = \frac{osi_j}{esi_j}$$

Cumulative survival

Using the annual probabilities from the date of diagnosis until the end of follow-up, the cumulative survivals at *J* years are defined as the product of the survivals by 1-year interval from the first to the *Jth* year. The cumulative observed survival (osc_J), cumulative expected survival (esc_J) and cumulative relative survival (rsc_J) are defined as follows:

$$osc_J = \prod_{j=1}^{J} osi_j \qquad esc_J = \prod_{j=1}^{J} esi_j \qquad rsc_J = \prod_{j=1}^{J} rsi_j$$

Excess mortality

The complement to 1 of the relative survival probability is the probability of dying of cancer and reflects the excess risk of dying relative to a subject not having presented with cancer. That probability, termed excess mortality (mri_j), is given for each interval *j* by:

$$mri_j = 1 - rsi_j$$

That indicator is appropriate to the objective of this expert report.

Standard deviations

The standard deviations of the observed and relative survivals by interval and cumulative relative and observed survivals were calculated using Greenwood's method (1926) as follows:

- **osei**: standard deviation of the observed survival by interval

$$osei_j = osi_j \times \left(\frac{dead_j}{arisk_j (arisk_j - dead_j)} \right)^{\frac{1}{2}}$$

- **osec**: standard deviation of the cumulative observed survival (until the end of interval *J*)

$$osec_J = osc_J \times \left[\sum_{j=i}^{J} \frac{dead_j}{arisk_j (arisk_j - dead_j)} \right]^{\frac{1}{2}}$$

- **rsei**: standard deviation of the relative survival by interval and of the excess mortality

$$rsei_j = \frac{osei_j}{esi_j}$$

- **rsec**: standard deviation of the cumulative relative survival (until the end of interval *J*)

$$rsec_J = \frac{osec_J}{esc_J}$$

Estimation of the standard deviation of the survivals by interval involves the number of deaths occurring during the interval. If no death is reported (i.e. the observed survival for the interval is 100%), the standard deviation of the observed and relative survivals by interval will be nil. In that case, the standard deviation obtained for the preceding interval is retained.

Confidence interval

The 95% confidence interval of the excess mortality for each interval *j* was constructed symmetrically as follows:

$$IC_{95\%}(mri_j) = mri_j \pm 1{,}96 \times rsei_j$$

Result presentation

For the pooled data for the eight countries (including France) and for each disease site selected, all the estimates were calculated for the following pools:

- both genders, any age and any cohort;
- by gender: any age and any cohort;
- by age group: any gender and any cohort;
- by diagnostic cohort: any gender and any age.

Excess mortalities are shown as graphs with their 95% confidence intervals. In order to render the excess mortality estimates comparable between sites, the scale was restricted to: -5 to +15%. Values greater than 15% are therefore not shown on the graphs but indicated in the corresponding tables. On the graphs, the points situated in the center of each interval estimate the mean annual excess mortality. Those points have been connected to show the time course of excess mortality. The size of a confidence interval depends on the population at the start of the interval and thus varies markedly between disease sites. The annual excess mortality estimates are shown in the corresponding tables. The tables also indicate the number of cases diagnosed in each group.

For certain disease sites, very long-term survival data (10, 15 and 20 years) were retrieved from the literature. Those data are then presented in addition to the data generated by the Eurocare analysis. In that case, the remote excess mortality associated with the diagnosis was calculated by considering the annual rates as constants over each 5-year interval. Those annual rates then enabled calculation of the relative survivals by 1-year interval and deduction of the annual excess mortality. That calculation, although an approximation, enabled confirmation, in the majority of cases, of the time course of remote annual excess mortality demonstrated by the analysis of the Eurocare 10-year data. When the data were derived from calculations using the period analysis method, the results were expected to be similar to those of the cohort studies.

When relative survival or annual excess mortality data (e.g. SEER data) were available, they were presented by histology, stage, grade or treatment.

The clinical stage was defined using the cTNM classification of the International Union Against Cancer[3]. The TNM system consists in describing the tumor using 3 dimensions: its size (T), the presence of lymph node invasion (N) and the existence of metastases (M). For those three components, a number indicating the extent of the cancer (from 0 to 4 for T, 0 to 2 for N and 0 or 1 for M) is associated. A given tumor may have a dual classification: first, clinical, the cTNM, and, secondly, pathologic or post-surgical and referred to as pTNM. The cTNM information is derived from the clinical and other investigations of the initial workup and orients the therapeutic strategy. The pTNM information is derived from the surgical specimens. That information yields prognostic indications and thus orients adjuvant therapy. The use of the TNM system enables a precise but condensed description of tumor stage. While that presentation is perfectly suitable for the description of a case in a clinical file, it is too detailed to describe or analyze the time course of groups of patients. For a given type of tumor, the four T scores, three N scores and two M scores, give rise to 24 potential TNM categories. In order to enable use of the TNM system for the description of results for cohorts of medium size, the TNM categories (or pTNM) may be grouped into stages (from I to IV). The definition of the stages is determined by prognostic considerations. It varies as a function of disease site and time course. Cancer registries frequently use an even more simplified description consisting of 3 levels: localized disease (tumor with no spread to lymph nodes or metastases), regional disease (lymph node involvement without metastases) and metastatic disease (disease with distant metastasis).

In addition, histologic study of the surgical specimen also enables determination of the histologic and prognostic grade of the tumor. The grade ranges from grade I (well differentiated tumor with few mitoses) to grade III (highly proliferative tumor with numerous atypical cells).

Progress in therapeutic management, the development of new prognostic markers and early screening are also factors liable to markedly reduce the annual excess mortality for certain disease sites in coming years.

In conclusion, annual excess mortalities were estimated for each of the disease sites studied, all stages taken together using the Eurocare data available. The annual diagnosis-remote excess mortality estimates may be considered fully pertinent insofar as it is observed that the annual diagnosis-remote excess mortality is little influenced by tumor stage at time of diagnosis. In contrast, the annual excess mortality estimates in the temporal proximity of the diagnosis are markedly dependent on tumor stage at the time of diagnosis. The data available by stage or for localized disease can thus enable more precise annual excess mortality estimates in the first years post-diagnosis for certain disease sites.

The studies conducted on hospital series may shed light on certain factors influencing survival (new treatments, impact of surgery, etc.).

Lastly, it is to be noted that the estimates presented herein are not exclusively based on French data. They are derived from European data (including French data) or American data and must thus be interpreted with a degree of caution.

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I

Adulthood cancers

3

All cancers

In 2000, in France, the number of new cases of cancer was estimated to be about 280,000. Men accounted for 58%. The number of deaths was about 150,000, of which men accounted for 61%. In terms of incidence, 4 disease sites each accounted for over 25,000 cases: cancer of the breast (almost 42,000 cases), prostatic cancer (about 40,000 cases), colorectal cancer (36,000 cases) and lung cancer (almost 28,000 cases). The incidence was greater than 10,000 cases for cancer of the lips, mouth and pharynx (15,000 cases) and cancer of the bladder (11,000 cases). The incidences for the other disease sites were less than 10,000 cases (Remontet *et al*., 2003).

In terms of mortality, 4 sites account for over 10,000 deaths per year: lung cancer (27,000), colorectal cancer (16,000), breast cancer (12,000) and prostate cancer (10,000).

In men, the most frequent forms of cancer were cancer of the prostate followed by lung cancer, colorectal cancer and cancer of the lips, mouth and pharynx. Lung cancer gives rise to the highest mortality.

In women, the five most frequent forms of cancer were breast cancer followed by colorectal cancer, *corpus uteri* cancer, lung cancer and ovarian cancer. In terms of mortality, breast and lung cancer take the first and second place. The incidence and mortality data for France are shown in table 3.I.

Table 3.I: Age-standardized incidence and mortality rates per 100,000 person-years in France (world standard population) (Remontet *et al.*, 2003)

	Incidence rate				Mortality rate			
	2000		Time course*		2000		Time course	
Type of cancer	Men	Women	Men	Women	Men	Women	Men	Women
Breast	-	88.9	-	+2.42	-	19.7	-	+0.42
Prostate	75.3	-	+5.33	-	15.9	-	+0.17	-
Lung	52.2	8.6	+0.58	+4.36	48.9	7.5	+0.67	+2.86
Colorectal	39.1	24.6	0.99	+0.83	15.8	8.9	-0.76	-1.07
Lips-mouth-pharynx	32.2	4.7	-1.00	+1.73	10.4	1.3	-2.14	-0.04
Bladder	18.3	2.3	+1.14	-0.50	6.3	1.1	-0.18	-0.12
Non-Hodgkin's malignant lymphoma	13.3	7.8	+3.82	3.46	5.3	3.4	+3.87	+5.06
Kidney	12.2	5.7	+2.70	+3.74	4.6	1.7	+1.08	+0.63
Liver	11.0	1.5	4.84	+3.38	12.8	2.0	+3.48	+0.44
Esophagus	9.3	1.5	-2.13	+2.35	8.3	1.0	-2.39	-0.56
Larynx	9.3	0.7	-1.66	0.00	4.5	0.3	-4.37	-1.48
Corpus uteri	-	9.2	-	+0.25	-	2.4	-	-0.84
Ovary	-	9.0	-	+0.55	-	5.4	-	+0.93
Stomach	9.0	3.4	-2.01	-2.52	5.9	2.2	-3.67	-4.41
Leukemia	8.9	5.5	+0.04	0.00	5.1	3.0	-1.00	-0.82
Cervix	-	8.0	-	-2.88	-	1.9	-	-4.44
Skin melanoma	7.6	9.5	+5.93	+4.33	1.6	1.1	+2.86	+2.19
Central nervous system	7.4	6.4	+2.25	+3.01	4.2	2.9	+1.95	+2.90
Pancreas	5.8	3.2	1.27	+2.07	7.6	4.4	+0.41	+1.52
Acute leukemia	4.3	3.2	+1.48	+0.92	2.6	1.7	-0.61	-0.17
Multiple myeloma and immuno-proliferative diseases	4.0	2.5	+2.65	+1.96	2.1	1.4	+0.85	+0.80
Chronic lymphoid leukemia	2.4	1.6	-1.52	-0.02	1.1	0.5	+0.66	+0.99
Thyroid	2.2	7.5	+2.89	+4.80	0.3	0.3	-1.37	-1.87
Hodgkin's disease	2.2	2.0	-1.37	-0.50	0.3	0.2	-5.08	-4.66
Mesothelioma	1.4	0.4	+4.76	+6.83	1.7	0.4	+2.84	+1.00
All forms of cancer**	349.4	226.3	+1.31	+1.36	187.4	83.1	-0.34	-0.46

* Percent mean annual time course from 1980 to 2000; ** Skin tumors other than melanoma have been excluded

Relative 5-year survival

Considering all types of cancer (all disease sites available), the Eurocare study for the eight countries selected (735,358 patients), showed a relative 5-year survival for the last diagnostic cohort (1992-1994) of 55.13%.

The relative 5-year survival estimates for diagnostic cohort 1992-1994 are shown, for each disease site studied in this expert report, in table 3.II. This is the most recent estimate available with respect to the Eurocare 3 study data.

Table 3.II: Relative 5-year survivals (%) for diagnostic cohort 1992-1994 for the eight Eurocare 3 study countries

Site	Relative survival (%)
All forms of cancer	55.13
Testes	95.12
Thyroid	90.12
Melanoma	86.63
Corpus uteri	84.54
Breast	83.92
Hodgkin's disease	83.67
Cervix	73.04
Chronic lymphocytic leukemia	72.71
Prostate	70.17
Larynx	68.11
Kidney	59.65
Non-Hodgkin's lymphoma	58.09
Colon	56.08
Rectum	57.51
Nasopharynx	49.42
Ovary	44.87
Chronic myeloid leukemia	43.88
Oropharynx	40.27
Acute lymphoblastic leukemia	31.26
Acute myeloid leukemia	29.61
Hypopharynx	25.37
Lung	12.13

Annual excess mortality

The overall annual excess mortality estimates (with their 95% confidence intervals) are presented globally in table 3.III. The estimates were obtained by taking into account all the patients in diagnostic cohorts 1983-1994 of the Eurocare study, all disease sites and the eight countries selected for this expert report. The table shows that annual excess mortality decreased over time. It ranged from more than 27% 0-1 year post-diagnosis to less than 2% 11-12 years post-diagnosis. Figure 3.1 shows the decline. Since the populations are very

large, the 95% confidence intervals are of very small amplitude and little visible on figure 3.1. The annual excess mortality was less than 15% as of year 2 post-diagnosis, then less than 5% as of year 5 post-diagnosis, falling to about 2% for year 12.

Table 3.IV shows the annual excess mortality estimates (with their 95% confidence intervals) as a function of gender. The annual excess mortality was lower in women than in men. It ranged from about 20% for 0-1 year post-diagnosis to less than 2% for 11-12 years post-diagnosis for women. For men, the annual excess mortality ranged from about 33% for 0-1 year to a little more than 2% for 11-12 years post-diagnosis. Figure 3.2 shows that the difference between men and women was more marked in the first years post-diagnosis.

Table 3.V shows the annual excess mortality for the following age groups: 15-44 years, 45-54 years, 55-64 years and 65-74 years. The annual excess mortality increased from age group 15-44 years to age group 65-74 years (for all years post-diagnosis). For age group 15-44 years, the annual excess mortality ranged from 12% for 0-1 year post-diagnosis to a little more than 1% for 11-12 years post-diagnosis. For age group 65-74 years, the annual excess mortality ranged from more than 33% for 0-1 year post-diagnosis to more than 3% for 11-12 years post-diagnosis. Figure 3.3 shows that the annual excess mortality was highest for age group 65-74 years. For that age group, the annual excess mortality was 5% after year 6 while, for age group 15-44 years, it was less than 5% after year 4.

Table 3.VI shows the annual excess mortality data for each of the four diagnostic cohorts: 1983-1985, 1986-1988, 1989-1991, 1992-1994. The data show that the annual excess mortality decreased from the oldest to the most recent cohort. Figure 3.4 illustrates the phenomenon, which was most patent in the first years post-diagnosis.

Lastly, for each disease site, recent data generally enable evaluation of survival as per various prognostic factors over the first years post-diagnosis. In fact, the annual excess mortality during the first years post-diagnosis is more strongly influenced by the various characteristics of the disease (histologic type, stage, etc.), the age at diagnosis and treatment modalities.

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Excess mortality data from the Eurocare study

Table 3.III: Annual excess mortality: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Overall (N = 735,358)
0-1	27.33 [27.23-27.44]
1-2	13.53 [13.44 -13.63]
2-3	8.25 [8.16 -8.34]
3-4	5.93 [5.84 -6.01]
4-5	4.70 [4.61 -4.78]
5-6	3.83 [3.74 -3.91]
6-7	3.30 [3.21 -3.39]
7-8	2.86 [2.76 -2.95]
8-9	2.51 [2.41 -2.62]
9-10	2.27 [2.14 -2.39]
10-11	2.16 [2.02 -2.29]
11-12	1.99 [1.84 -2.14]

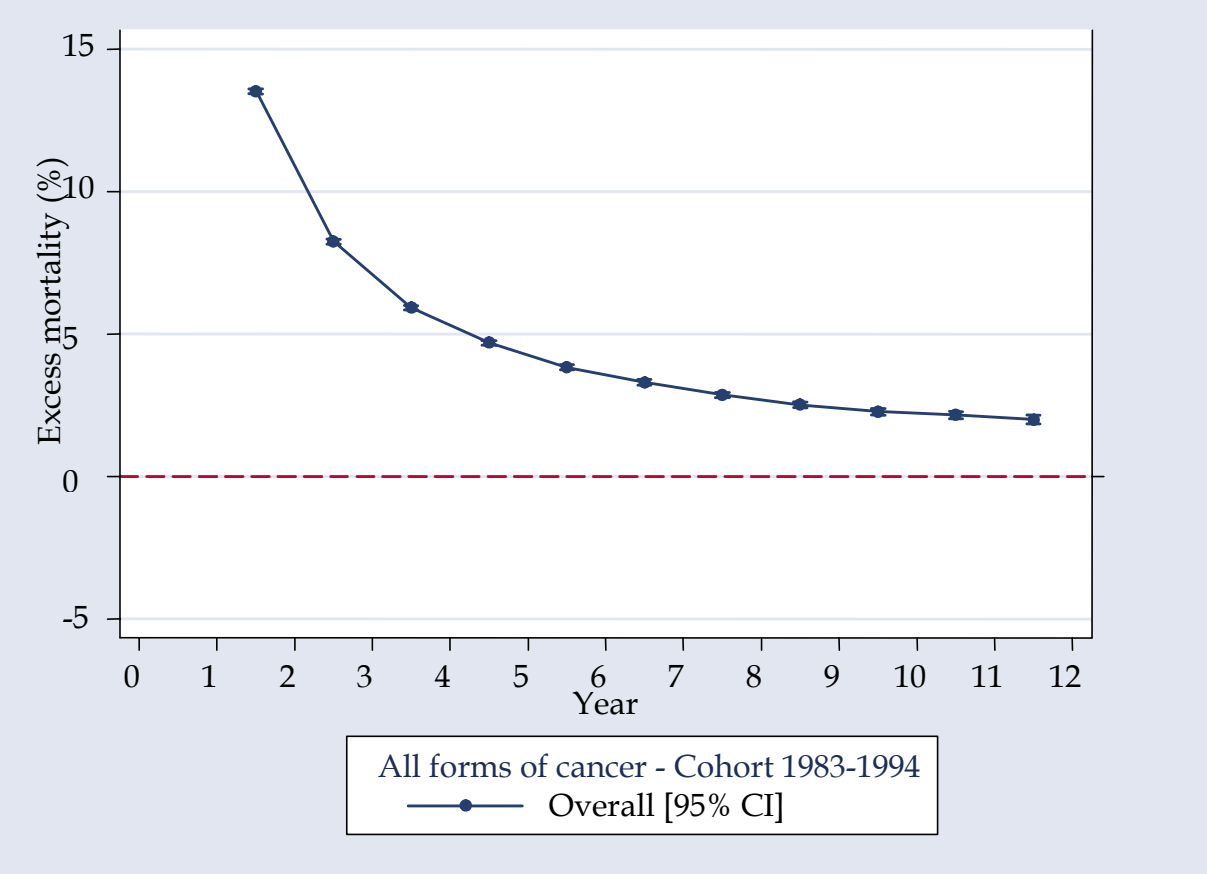

Figure 3.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 3.IV: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (% annual) Women (N = 357,616)	Men (N = 377,742)
0-1	20.69 [20.55-20.83]	33.71 [33.55-33.86]
1-2	10.42 [10.30-10.54]	17.23 [17.07-17.39]
2-3	6.86 [6.75-6.96]	10.15 [10.00-10.30]
3-4	4.98 [4.88-5.08]	7.35 [7.21-7.49]
4-5	3.98 [3.88-4.07]	5.88 [5.74-6.03]
5-6	3.24 [3.14-3.33]	4.91 [4.76-5.06]
6-7	2.76 [2.65-2.86]	4.39 [4.22-4.56]
7-8	2.45 [2.34-2.56]	3.79 [3.61-3.97]
8-9	2.16 [2.04-2.28]	3.42 [3.22-3.62]
9-10	1.95 [1.82-2.08]	3.18 [2.94-3.41]
10-11	1.84 [1.70-1.99]	3.11 [2.86-3.37]
11-12	1.79 [1.62-1.95]	2.83 [2.53-3.12]

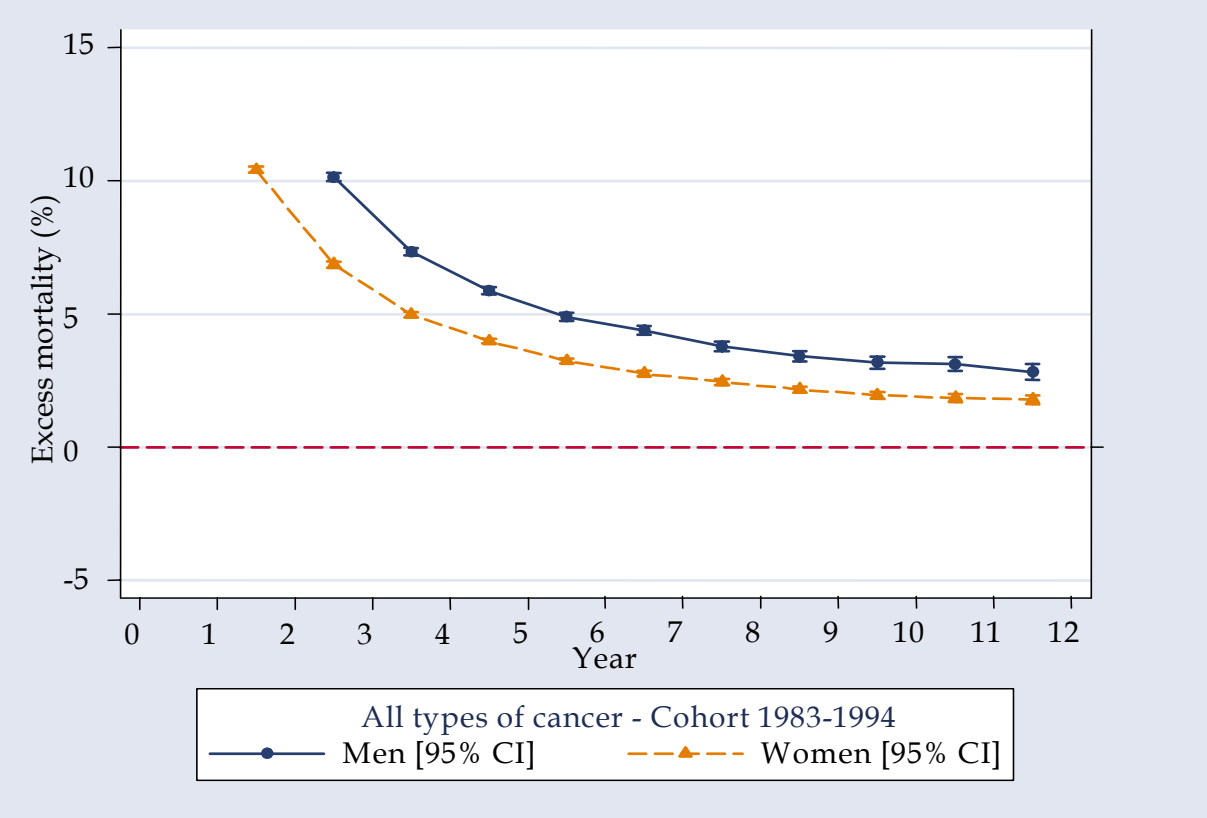

Figure 3.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 3.V: Annual excess mortality by age group: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (% annual) 15-44 years (N = 89,022)	45-54 years (N = 114 ,701)	55-64 years (N = 215,240)	65-74 years (N = 316,395)
0-1	11.97 [11.75-12.18]	20.44 [20.20-20.67]	28.73 [28.53-28.92]	33.36 [33.19-33.53]
1-2	8.06 [7.87-8.25]	11.92 [11.70-12.13]	15.01 [14.82-15.20]	15.30 [15.13-15.48]
2-3	5.25 [5.09-5.42]	7.13 [6.95-7.32]	9.03 [8.87-9.20]	9.51 [9.34-9.67]
3-4	3.87 [3.72-4.02]	5.00 [4.83-5.16]	6.27 [6.11-6.42]	7.11 [6.94-7.27]
4-5	3.01 [2.87-3.15]	4.11 [3.94-4.27]	5.03 [4.87-5.18]	5.60 [5.43-5.76]
5-6	2.53 [2.39-2.67]	3.26 [3.10-3.42]	4.04 [3.88-4.19]	4.69 [4.51-4.86]
6-7	2.03 [1.89-2.17]	2.79 [2.63-2.96]	3.49 [3.32-3.66]	4.19 [3.99-4.40]
7-8	1.76 [1.63-1.90]	2.40 [2.23-2.57]	2.94 [2.77-3.11]	3.76 [3.54-3.98]
8-9	1.62 [1.48-1.77]	2.07 [1.89-2.24]	2.63 [2.44-2.82]	3.31 [3.06-3.56]
9-10	1.24 [1.09-1.38]	2.06 [1.85-2.27]	2.42 [2.21-2.64]	3.03 [2.72-3.34]
10-11	1.31 [1.15-1.47]	1.82 [1.61-2.04]	2.31 [2.08-2.55]	2.95 [2.60-3.29]
11-12	1.12 [0.95-1.29]	1.53 [1.29-1.77]	2.04 [1.77-2.31]	3.11 [2.68-3.54]

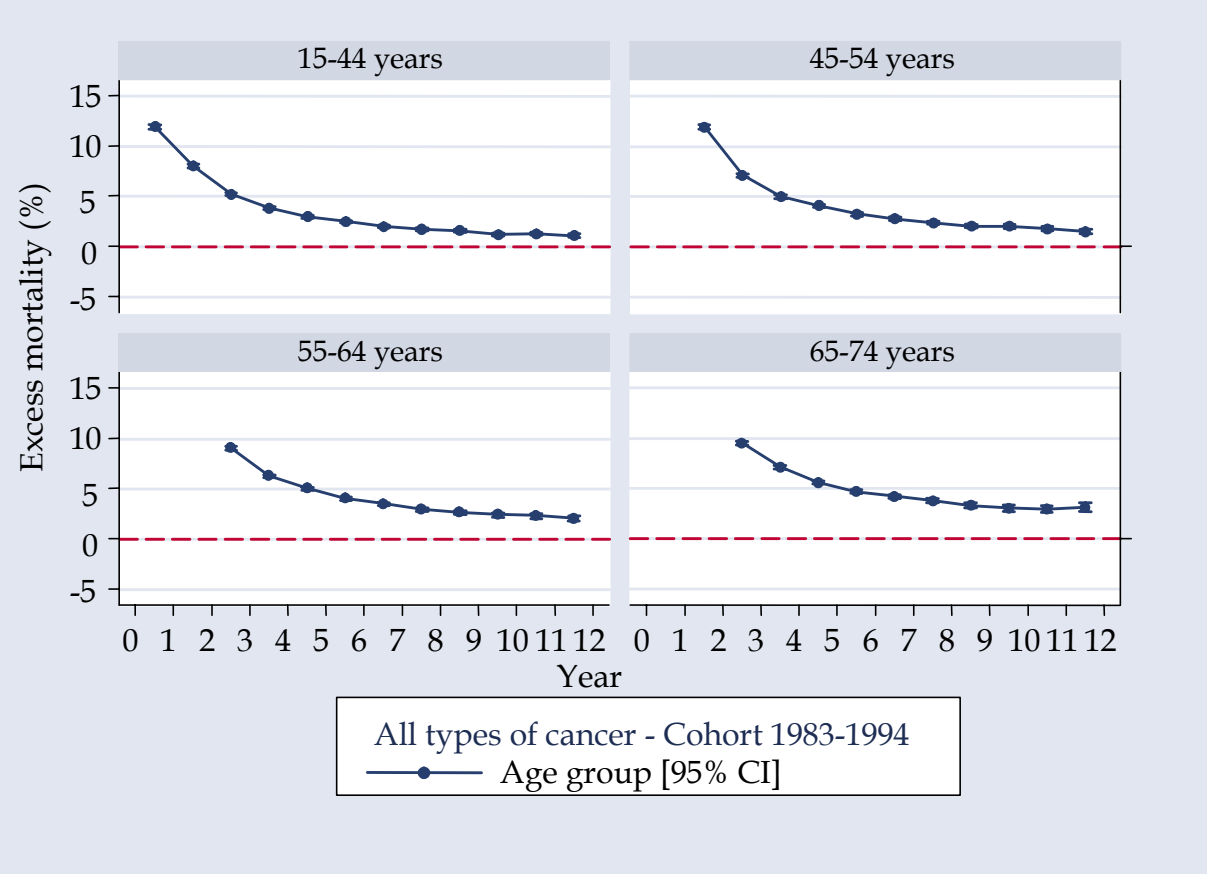

Figure 3.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 3.VI: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (% annual) Cohort 1983-1985 (N = 161,046)	Cohort 1986-1988 (N = 185,730)	Cohort 1989-1991 (N = 190,667)	Cohort 1992-1994 (N = 197,915)
0-1	29.68 [29.45-29.91]	28.64 [28.43-28.85]	26.69 [26.49-26.90]	24.82 [24.63-25.02]
1-2	15.08 [14.86-15.30]	14.05 [13.85-14.25]	13.08 [12.90-13.27]	12.33 [12.15-12.51]
2-3	9.20 [8.99-9.40]	8.61 [8.43-8.80]	7.91 [7.74-8.08]	7.57 [7.41-7.73]
3-4	6.55 [6.36-6.74]	6.15 [5.98-6.32]	5.76 [5.60-5.92]	5.44 [5.29-5.59]
4-5	5.23 [5.04-5.42]	4.94 [4.77-5.10]	4.42 [4.27-4.57]	4.28 [4.12-4.44]
5-6	4.20 [4.02-4.39]	3.93 [3.77-4.10]	3.54 [3.39-3.68]	3.62 [3.42-3.83]
6-7	3.66 [3.48-3.84]	3.35 [3.19-3.51]	2.99 [2.84-3.13]	-
7-8	2.97 [2.79-3.15]	2.91 [2.75-3.07]	2.67 [2.51-2.83]	-
8-9	2.66 [2.48-2.85]	2.40 [2.24-2.56]	2.45 [2.23-2.66]	-
9-10	2.26 [2.08-2.45]	2.27 [2.11-2.43]	-	-
10-11	2.18 [1.99-2.37]	2.11 [1.93-2.30]	-	-
11-12	2.04 [1.85-2.24]	1.88 [1.63-2.12]	-	-

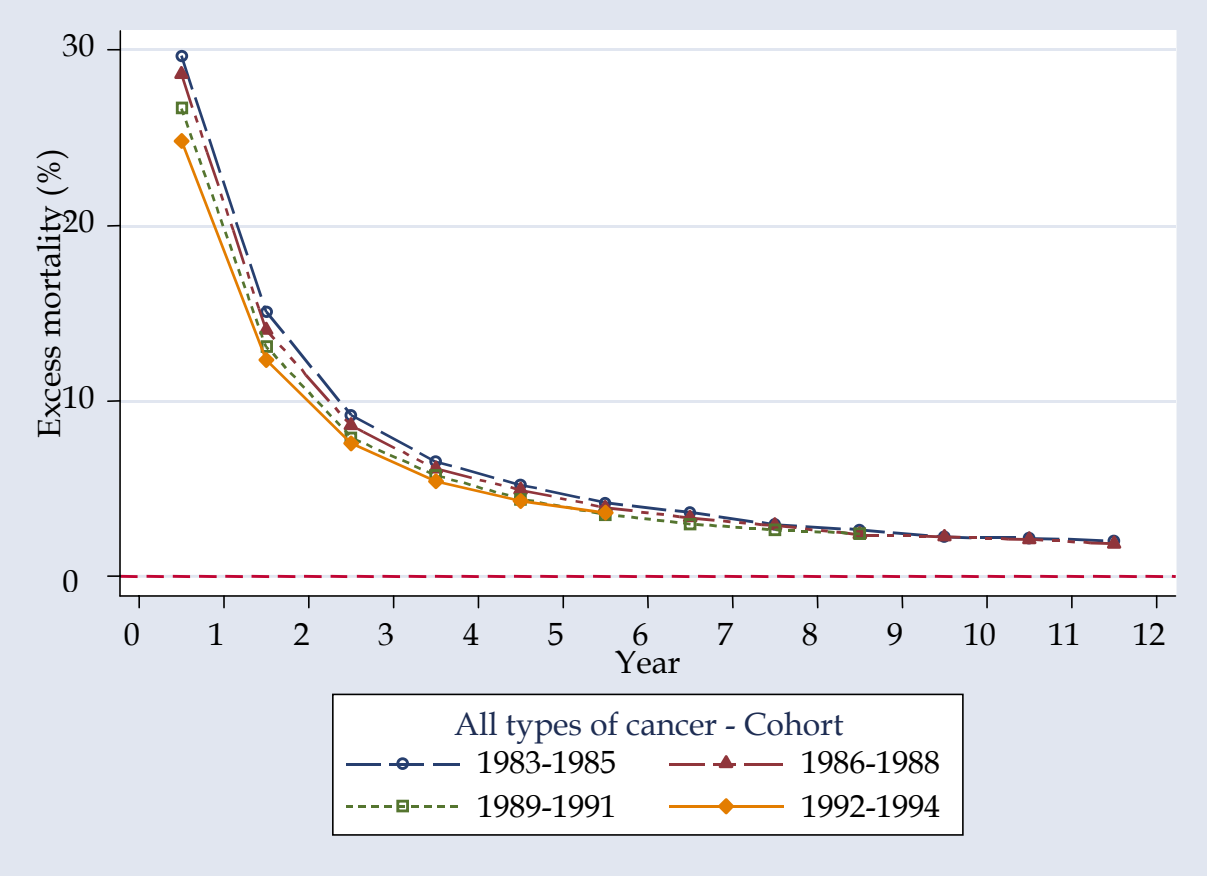

Figure 3.4: Time course of annual excess mortality by cohort

4

Breast cancer

Breast cancer is the most frequent cancer among women in Western countries. In France, 42,000 new cases occurred in 2000. In France, breast cancer accounts for 36% of female neoplastic diseases (Remontet *et al*., 2003).

The incidence of breast cancer is constantly rising. The age-standardized incidence rate (world standard) population increased from 55.5/100,000 in 1980 to 88.9/100,000 in 2000 (Remontet *et al*., 2003), i.e. an annual increase of 2.4%. The incidence increases with age: approximately 75% of incident cases of breast cancer occur after age 50 years. The median age at diagnosis is 61 years.

Despite the increased incidence and due to the progress in breast cancer treatment, the mortality rate currently appears to be stable. The mortality rate was 19.7/100,000 in 2000. Breast cancer nonetheless remains the leading cause of death due to cancer for women with 11,637 deaths reported in 2000.

On the basis of the Eurocare data, the relative 5-year survival for all stages of the disease and for the eight countries selected was 83.9% for women whose disease was diagnosed between 1992 and 1994. France is one of the countries with the highest 5-year survival rates in Europe.

Annual excess mortality (all stages considered): Eurocare data

Table 4.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates take into account all patients whose breast cancer was diagnosed between 1983 and 1994 in Europe (8 countries). The annual excess mortality peaked at 4.9% between 2 and 3 years post-diagnosis, then fell off gradually to a rate of 2.35% after 10 years (figure 4.1).

Table 4.II shows the annual excess mortality results obtained for the various age groups. The annual excess mortality rates are very similar for the 4 age groups and for the first years post-diagnosis and remotely from diagnosis. The annual excess mortality profiles (figure 4.2) confirm the similarity.

The annual excess mortality data for the four Eurocare cohorts are shown in table 4.III. The most recent cohort showed the lowest excess mortality rates for the first years post-diagnosis. The annual excess mortality rate reached 2.5% as of year 8 for women whose disease was diagnosed between 1989 and 1991. This was not statistically different from the values observed 11-12 years post-diagnosis for cohorts 1983-1985 (2.44%) and 1986-1988 (2.19%). Figure 4.3 clearly shows an improvement in survival over time for those cohorts.

Very long-term annual excess mortality (all stages considered): other studies

Among the European studies, two Scandinavian studies enable analysis of the very long-term survival. The study by Tejler *et al.* (2004) addressed the 15-year survival of 7,892 women whose breast cancer was diagnosed in Sweden between 1986 (date of mass screening introduction) and 1999. The study confirmed that the annual excess mortality 5 years post-diagnosis, for all stages of the disease, is continuing to decrease. The excess mortality was of the order of 2.5% between 5 and 10 years post-diagnosis and close to 1% between 10 and 15 years post-diagnosis.

The Finnish study (Brenner and Hakulinen, 2004) included 18,578 women less than 50 years old whose disease was diagnosed between 1953 and 1999, enabling very long-term results. This study used the period analysis method and thus takes into account the improvement in survival in the more recent periods. The study shows the marked improvement observed in the most recent decades: 10-year survival increased from 50% for diagnostic period 1953-1959 to 70% for diagnostic period 1983-1989. However, the study generated results in terms of remote excess risk that were more pejorative than those of the preceding study and, in particular, demonstrated that low-amplitude excess mortality persists beyond time point 20 years.

Long-term relative survival or annual excess mortality by stage

A European study of 4,478 patients whose disease was diagnosed in 1990-1992 (Sant *et al.*, 2003) enabled determination of the 5-year survival rate by cancer stage. The cases studied were representative samples of 17 registries in 6 European countries (Estonia, France, Italy, the Netherlands, Spain and the United Kingdom) combined with 9 regional groups with similar survivals. Table 4.IV shows the 5-year survivals by stage.

Table 4.IV: 5-year survival by stage (taken from Sant *et al.*, 2003)

Stage	5-year relative survival (%)	Stage distribution (%)
T1N0M0	98	28.9
T2-3N0M0	87	18.6
T1-3N+M0	77	31.0
T4NxM0	55	6.8
M1	18	6.2
Not determined	69	8.5

In France, data derived from the Bas-Rhin, Côte d'Or, Hérault and Isère, Tarn, Somme, Calvados and Doubs registries were analyzed. The influence of stage as an independent prognostic factor was demonstrated (relative 5-year survival greater than 93% for stage pT1 or pN0M0 tumor) (Grosclaude *et al.*, 2001).

The 5-year survival of patients treated for breast cancer in the Ile-de-France region (293 patients) and with chronic neoplastic disease treatment status (ALD 30) in one of the three main health insurance organizations in 1994 (cohort 1994-1999) was recently followed up (PETRI, *Prévention et Épidémiologie des Tumeurs en Région Ile-de-France*, 2004). The relative 5-year survival, all stages considered, was 82%. For one third of the cases, the disease was

diagnosed at an early stage (T1N0M0) and the 5-year relative survival was 98%, close to the survival for the female population with the same age structure.

The Hérault tumor registry (2005) has supplied 5-year relative survival rates for 1,707 incident cases of breast cancer for which the diagnostic period was 1995-1998. The relative 5-year survival was 89%, all stages and all ages considered. The relative 5-year survival rates were 97, 91, 82 and 29% for stages I, II, III and IV, respectively.

Two European studies (Tejler *et al*., 2004; Brenner and Hakulinen, 2004) report 5- and 10-year survival data by stage. Tejler *et al*. (2004) reported a relative survival for stage T1N0M0 of 96.3% at 5 years, 89.7% at 10 years and 89% at 15 years. The mean annual excess mortality was of the order of 1.4% after 5 years and less than 0.2% after 10 years.

The study by Brenner and Hakulinen (2004) also reported very long-term survival data, by stage, for women aged less than 50 years whose disease was diagnosed post-1953. The mean annual excess mortality rates beyond 10 years were less than 1% for localized tumors.

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has reported relative survival rates by year and by stage. The stage distribution (localized, regional and metastatic) was as follows: 62.1, 29.6 and 5.7%. An annual excess mortality can be calculated from the data. The data are presented for all ages considered at the time of diagnosis and for the diagnostic period 1988-2001 (table 4.V).

Table 4.V: Annual excess mortality by stage at diagnosis for the period 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized stage	Regional stage (N+)	Metastatic stage (M+)
0-1	0.00	1.90	33.60
1-2	0.00	5.10	27.56
2-3	0.90	5.59	23.70
3-4	0.81	5.46	20.71
4-5	1.02	5.05	17.87
5-6	0.92	4.31	15.06
6-7	0.93	4.37	12.32
7-8	0.84	3.19	9.55
8-9	0.95	3.43	9.32
9-10	0.75	2.96	10.27

The results for the population of US women show an annual excess mortality 9-10 years post-diagnosis of 0.75% for localized disease (T1N0M0). The annual excess mortality rate for that stage is close to or less than 1% irrespective of the time since diagnosis. The results are similar to those of the two European studies cited above.

Influence of screening programs on survival

Two factors seem to have contributed to the consistent improvement in survival rates over the last 20 years: screening by mammography and the progress in treatment with, in particular, the development of increasingly effective adjuvant treatments and intended to a more significant number of women.

The efficacy of mammographic screening programs was demonstrated in the 1970s by large-scale randomized studies conducted in the United States and Sweden. The studies showed a 30% reduction in breast cancer mortality in the screened population aged over 50 years. The efficacy of screening before age 50 years has yet to be demonstrated.

In France, breast cancer screening was initially implemented on an individual basis but access was expanded towards the middle of the 1980s. Only in 1989-1991 were the first departmental screening programs organized. Only very recently, were the screening programs generalized to cover the whole country, in 2003.

Influence of other prognostic factors and treatments on survival

In addition to clinical staging, pathologic staging (pTNM) is implemented post-operatively. The latter determines the macroscopic size of the tumor and histologic invasion of the lymph nodes removed during curettage. Invasion of the axillary lymph nodes is one of the major parameters conditioning the indication for adjuvant treatment.

Histologic study of the surgical specimen enables determination of the pathologic and prognostic stage of the tumor—as per Scarff, Bloom and Richardson (SBR), or more recently as per Ellis and Elston (1991)—and the presence of hormone receptors. The grade ranges from grade I, well differentiated tumor with few mitoses, to grade III, highly proliferative tumor with numerous atypical cells. Treatment is based on the pathologic and clinical prognosis of the disease.

The presence of hormone receptors determines the sensitivity to hormonal treatments. In the context of breast cancer, numerous other prognostic markers have been studied but have yet to be validated for use in clinical practice.

While local/regional treatment, which combines surgery and radiotherapy, has advanced toward increasingly less radical treatments, the progress mainly derives from early control of metastatic disease spread using adjuvant treatments.

The concept of adjuvant chemotherapy, which emerged in the 1980s, has been assessed by numerous phase III clinical trials and has been the subject of several meta-analyses. Adjuvant chemotherapy progressed with the emergence of new cytotoxic agents, the anthracyclines, in the 1980s, then, more recently, with the advent of the taxanes, which were recently authorized for adjuvant treatment indications. Adjuvant hormone therapy, which was long restricted to tamoxifen or castration, is currently progressing with the advent of new-generation aromatase inhibitors which block endogenous estrogen production and which prolonged used beyond 4 years has been validated. Other recent therapeutics as the use of anti-HER2 antibodies will also contribute to improve the prognosis in adjuvant condition for some populations.

Special cases of familial forms

About 5% of cancer are reported to consist in forms involving genetic predisposition (Eisinger and Lefranc, 2005), i.e. about 2,000 new cases per year. The frequency of subjects presenting with a BRCA1 or BRCA2 mutation ranges from 1/200 to 1/900. Women carrying the BRCA mutation have a 40 to 80% risk of developing breast cancer at age 70 years, while the risk is 10% for the overall population. The risk of contralateral cancer in the 10 years following diagnosis appears to be 2-fold greater relative to sporadic breast cancer.

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Excess mortality data from the Eurocare study

Table 4.I: Annual excess mortality for women: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (% annual)
Interval (years)	Women (N = 117,051)
0-1	3.20 [3.08-3.31]
1-2	4.45 [4.32 -4.58]
2-3	4.91 [4.77 -5.05]
3-4	4.40 [4.26 -4.54]
4-5	3.88 [3.74 -4.02]
5-6	3.65 [3.50 -3.81]
6-7	2.98 [2.82 -3.14]
7-8	3.03 [2.85 -3.20]
8-9	2.76 [2.57 -2.95]
9-10	2.57 [2.35 -2.80]
10-11	2.37 [2.13 -2.61]
11-12	2.35 [2.07 -2.63]

Figure 4.1: Annual excess mortality for women: diagnostic cohort 1983-1994

Table 4.II: Annual excess mortality for women by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (% annual)			
Interval (years)	15-44 years (N = 19,469)	45-54 years (N = 30,427)	55-64 years (N = 32,749)	65-74 years (N = 34,406)
0-1	2.05 [1.84-2.25]	2.13 [1.96-2.31]	3.36 [3.15-3.57]	4.65 [4.39-4.91]
1-2	4.48 [4.18-4.78]	4.15 [3.91-4.38]	4.56 [4.31-4.81]	4.60 [4.33-4.87]
2-3	5.87 [5.52-6.21]	4.39 [4.14-4.63]	5.02 [4.76-5.29]	4.71 [4.43-5.00]
3-4	5.42 [5.07-5.76]	4.00 [3.75-4.24]	4.50 [4.23-4.76]	4.05 [3.77-4.34]
4-5	4.76 [4.42-5.10]	3.46 [3.22-3.70]	3.87 [3.61-4.13]	3.77 [3.46-4.07]
5-6	4.34 [3.99-4.70]	3.25 [2.99-3.50]	3.53 [3.25-3.80]	3.69 [3.32-4.05]
6-7	3.29 [2.94-3.64]	2.61 [2.35-2.88]	3.00 [2.70-3.29]	3.12 [2.75-3.50]
7-8	3.22 [2.86-3.59]	2.57 [2.29-2.85]	2.93 [2.62-3.25]	3.46 [3.04-3.88]
8-9	2.98 [2.59-3.37]	2.20 [1.91-2.49]	2.67 [2.33-3.01]	3.29 [2.81-3.76]
9-10	1.95 [1.58-2.32]	2.33 [1.98-2.68]	2.79 [2.38-3.21]	3.06 [2.47-3.65]
10-11	2.40 [1.96-2.83]	2.02 [1.66-2.38]	2.54 [2.10-2.98]	2.56 [1.92-3.21]
11-12	2.05 [1.59-2.51]	1.79 [1.39-2.19]	2.45 [1.93-2.96]	3.19 [2.37-4.01]

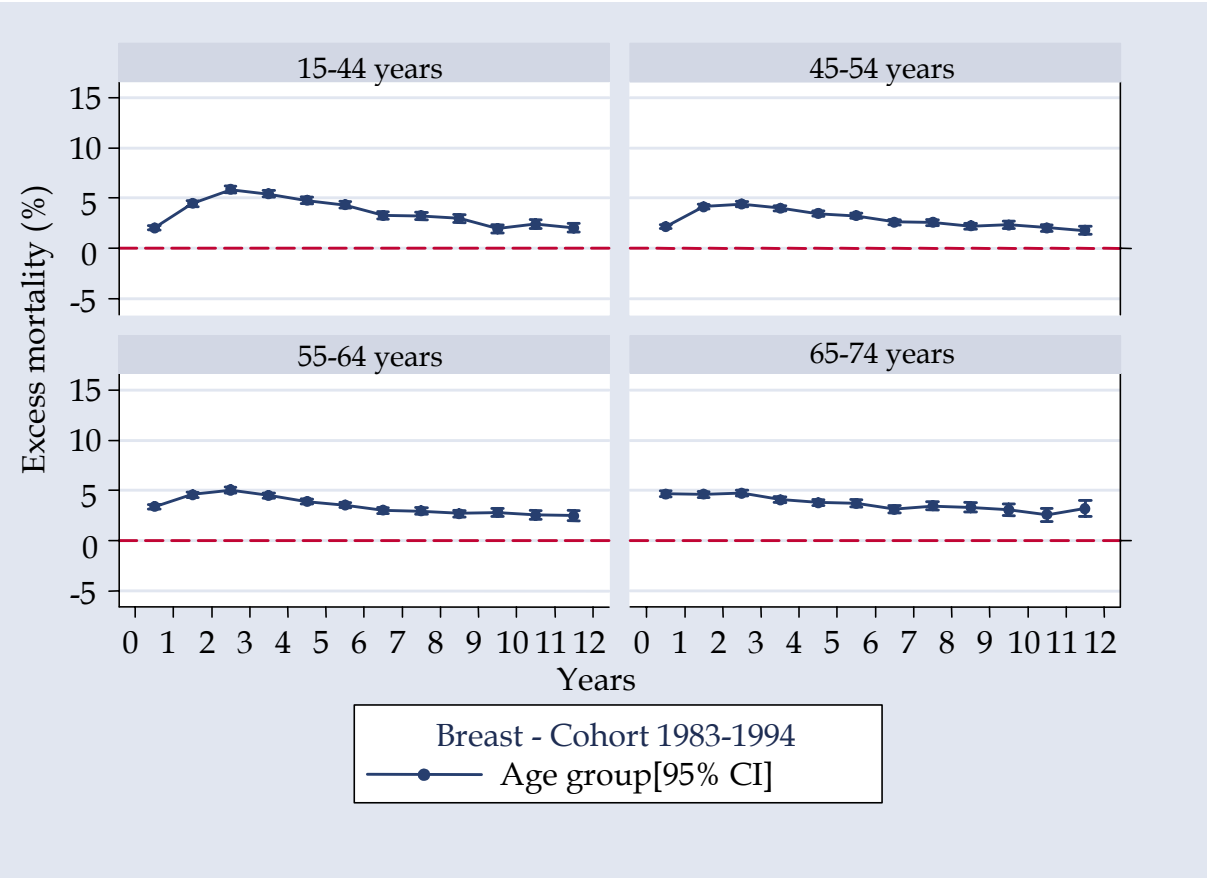

Figure 4.2: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 4.III: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (% annual)			
Interval (years)	Cohort 1983-1985 (N = 23,633)	Cohort 1986-1988 (N = 28,816)	Cohort 1989-1991 (N = 32,077)	Cohort 1992-1994 (N = 32,525)
0-1	4.08 [3.80-4.36]	3.67 [3.43-3.91]	2.90 [2.70-3.11]	2.43 [2.24-2.62]
1-2	5.55 [5.22-5.87]	4.88 [4.60-5.15]	3.97 [3.74-4.21]	3.75 [3.52-3.98]
2-3	6.06 [5.71-6.40]	5.32 [5.02-5.62]	4.47 [4.21-4.72]	4.19 [3.95-4.44]
3-4	5.50 [5.15-5.85]	4.68 [4.38-4.97]	4.20 [3.94-4.46]	3.59 [3.35-3.83]
4-5	4.67 [4.33-5.02]	4.19 [3.90-4.48]	3.60 [3.34-3.85]	3.25 [2.99-3.51]
5-6	4.25 [3.90-4.59]	3.79 [3.50-4.08]	3.23 [2.97-3.48]	3.24 [2.85-3.62]
6-7	3.66 [3.32-4.00]	3.03 [2.75-3.31]	2.48 [2.24-2.71]	-
7-8	3.09 [2.76-3.43]	3.42 [3.11-3.72]	2.56 [2.28-2.83]	-
8-9	3.33 [2.97-3.68]	2.44 [2.16-2.72]	2.49 [2.12-2.87]	-
9-10	2.81 [2.46-3.16]	2.39 [2.10-2.68]	-	-
10-11	2.67 [2.31-3.03]	2.08 [1.76-2.40]	-	-
11-12	2.44 [2.08-2.80]	2.19 [1.75-2.64]	-	-

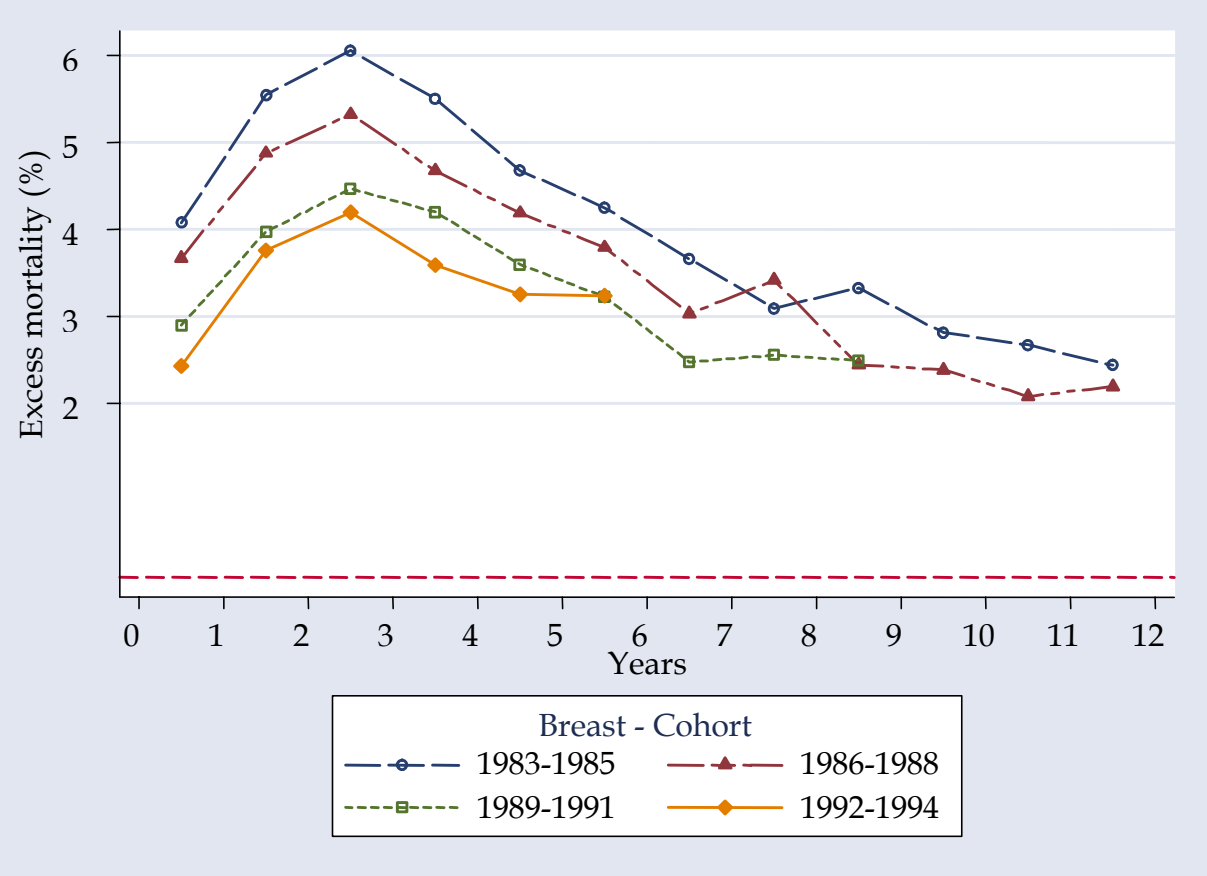

Figure 4.3: Time course of annual excess mortality by cohort

5

Ovarian cancer

With an estimated 4,500 new cases in France in 2000, ovarian cancer ranks 5th among female cancers. The age-standardized incidence rate (world population) was estimated to be 9/100,000 (Remontet *et al*., 2003).

The incidence is lower in the cohorts of women born after 1930. However, the incidence rate has slightly increased over the last two decades: the mean annual growth rate is +0.55%.

The median age at diagnosis is 65 years and the incidence peaks at about 75 years. In addition, the annual mortality rate has slightly increased over the last 20 years: the mean annual growth rate is estimated to be +0.93%. In 2000, the standardized mortality rate was 5.4/100,000.

According to the Eurocare data, for women in diagnostic cohort 1992-1994, the relative 5-year survival is 44.9%, all stages considered, and the eight countries considered.

Annual excess mortality (all stages considered): Eurocare data

Table 5.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates took into account all patients whose ovarian cancer was diagnosed between 1983 and 1994 in Europe (8 countries). The annual excess mortality was less than 5% as of year 6 post-diagnosis. The annual excess mortality fell to 2% toward year 9 post-diagnosis and fell off substantially subsequently (figure 5.1).

Table 5.II shows the annual excess mortality results for the various age groups. The early and late annual excess mortality for women in the age group 15-44 years was markedly lower than that for women in the age group 65-74 years. For the age group 15-44 years, the annual excess mortality was close to 2% as of year 5 post-diagnosis. The age at diagnosis more strongly influenced early annual excess mortality than late annual excess mortality (figure 5.2).

The annual excess mortality data for the 4 cohorts are shown in table 5.III. The annual excess mortality rates fall slightly in the more recent cohorts for the first 2 years post-diagnosis (figure 5.3).

Very long-term annual excess mortality (all stages considered): other studies

For the evaluation of the very long-term annual excess mortality associated with ovarian cancer, three sources of population data are available: the US data generated by the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the Finnish and Swedish national registry data.

Brenner (2002) has reported the relative 5-, 10-, 15- and 20-year survivals for patients whose ovarian cancer was diagnosed between 1973 and 1998 using the data generated by the US

SEER program. The relative survival estimates, calculated using the period analysis method (which takes into account the survival observed over the first few years post-diagnosis for the recent periods) were 55, 49.3, 49.9 and 49.6%, respectively. On the basis of those data, the mean annual excess mortality becomes nil beyond 10 years.

The Finnish study by Brenner and Hakulinen (2001) showed relative survivals (calculated using the period analysis method) at 5, 10, 15 and 20 years of 51.2, 46, 42 and 41.9%, respectively. The mean annual excess mortality for the period 10-15 years was of the order of 0.8% and subsequently became nil.

In the Swedish study by Talbäck *et al*. (2004), the relative survivals estimated by the period analysis method were 45.6, 39.1 and 39.7% at 5, 10 and 15 years, respectively. The data were comparable to the 5-, 10- and 15-year survivals observed for patients whose disease was diagnosed during the most recent period: 45.4, 35 and 39.9%. The mean annual excess mortality for the period, 10-15 years, was nil.

Long-term relative survival or excess mortality by stage

The PETRI study (Ile-de-France, 2004) reported a 5-year relative survival in France of 44% for women presenting with ovarian cancer (cohort: 1994-1999). The results are very imprecise for stages I, II and III (too few cases). For patients diagnosed at stage IV (69 cases), the relative 5-year survival was 25%.

The relative 5-year survival estimated from the Hérault tumor registry (2005) for women presenting with ovarian cancer (ovaries and adnexa) was 43% for all stages and all ages considered. For stages I, II, III and IV, the survivals were 84, 59, 35 and 22%, respectively.

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has reported relative survival data by year for three stages of ovarian cancer: local, regional and metastatic (distant metastases) and a non-determined stage (insufficient data in the base to determine the stage). The annual excess mortalities have been calculated from those data (table 5.IV). The stage distribution (localized, regional and metastatic) of the ovarian cancer cases was as follows: 19.6, 6.2 and 67.7%. The results are for women, all ages considered, whose disease was diagnosed between 1988 and 2001.

Table 5.IV: Annual excess mortality by stage at diagnosis for the period 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease (N+)	Metastatic disease (M+)
0-1	1.9	13.5	32.1
1-2	1.9	9.3	24.9
2-3	1.8	7.6	22.9
3-4	1.4	6.5	17.8
4-5	0.86	2.0	15.8
5-6	1.52	4.1	12.1
6-7	1.21	2.4	8.0
7-8	1.11	3.6	5.9
8-9	0.68	2.5	4.4
9-10	0.91	1.9	2.0

For localized ovarian cancer, the annual excess mortality decreased regularly and becomes less than 1% as of year 8.

Influence of prognostic factors on survival

Most ovarian tumors are malignant epithelial tumors: they account for about 80% of malignant ovarian tumors. There are several histologic subtypes: serous carcinoma (46%), mucinous carcinoma (36%), endometrioid carcinoma (8%) and clear-cell carcinoma (3%). The prognosis of ovarian cancer is generally pejorative since it is frequently diagnosed too late. Tumor progression remains asymptomatic for a long time with symptoms only emerging when the tumor becomes bulky or spreads. However, the prognosis for certain tumors is good even if they are locally advanced. Those tumors are tumors on the borderline of malignancy and account for 20% of common epithelial tumors.

The prognosis for ovarian tumor depends on several types of factor (Clark *et al.*, 2001): the clinical factors (staging generally as per the FIGO[4] system), residual tumor size, age and histologic factors (grade and type). Biological factors also intervene (Skirnisdottir *et al.*, 2004; Mor *et al.*, 2005). The importance of the prognostic factors varies as a function of stage. Numerous other laboratory markers have been suggested but have yet to be validated in clinical practice. Early diagnosis of ovarian cancer is imperative in order to enhance survival. Instruments such as tumor markers must therefore be developed (Mor *et al.*, 2005).

In combination with surgery, adjuvant medical treatment of ovarian cancer mainly consists in chemotherapy. Ovarian epithelial carcinomas are relatively chemotherapy-sensitive. The main drugs used in the treatment of ovarian cancer are platinum salts, anthracyclines, taxanes and alkylating agents. Hormone therapy and immunotherapy are only of marginal interest currently (FNCLCC, 2003). Positron-emission tomography (FDG-PET) is of value in the diagnosis of local recurrence or metastases (FNCLCC, 2003).

[4] International Federation of Gynecology and Obstetrics

Special case of familial forms

About 5% of cancer cases are reported to consist in forms involving genetic predisposition (Eisinger and Lefranc, 2005), i.e. about 200 new cases per year. The frequency of subjects presenting with a BRCA1 or BRCA2 mutation ranges from 1/200 to 1/900. Women carrying the BRCA mutation have a 10 to 63% risk of developing ovarian cancer at age 70 years, while the risk is 1% for the overall population. However, the risk is somewhat different depending on whether a BRCA1 or BRCA2 mutation is involved, since the risk is of the order of 20 to 60% for BRCA1 and 6 to 27% for BRCA2 in the studies conducted.

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Excess mortality data from the Eurocare study

Table 5.I: Annual excess mortality for women: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (% annual) Women (N = 21,513)
0-1	23.33 [22.76-23.91]
1-2	21.73 [21.08 -22.37]
2-3	14.85 [14.21 -15.48]
3-4	9.87 [9.28 -10.46]
4-5	6.34 [5.80 -6.87]
5-6	4.59 [4.07 -5.11]
6-7	4.15 [3.59 -4.72]
7-8	2.62 [2.11 -3.13]
8-9	2.19 [1.66 -2.72]
9-10	1.80 [1.22 -2.38]
10-11	1.77 [1.14 -2.39]
11-12	1.40 [0.72 -2.08]

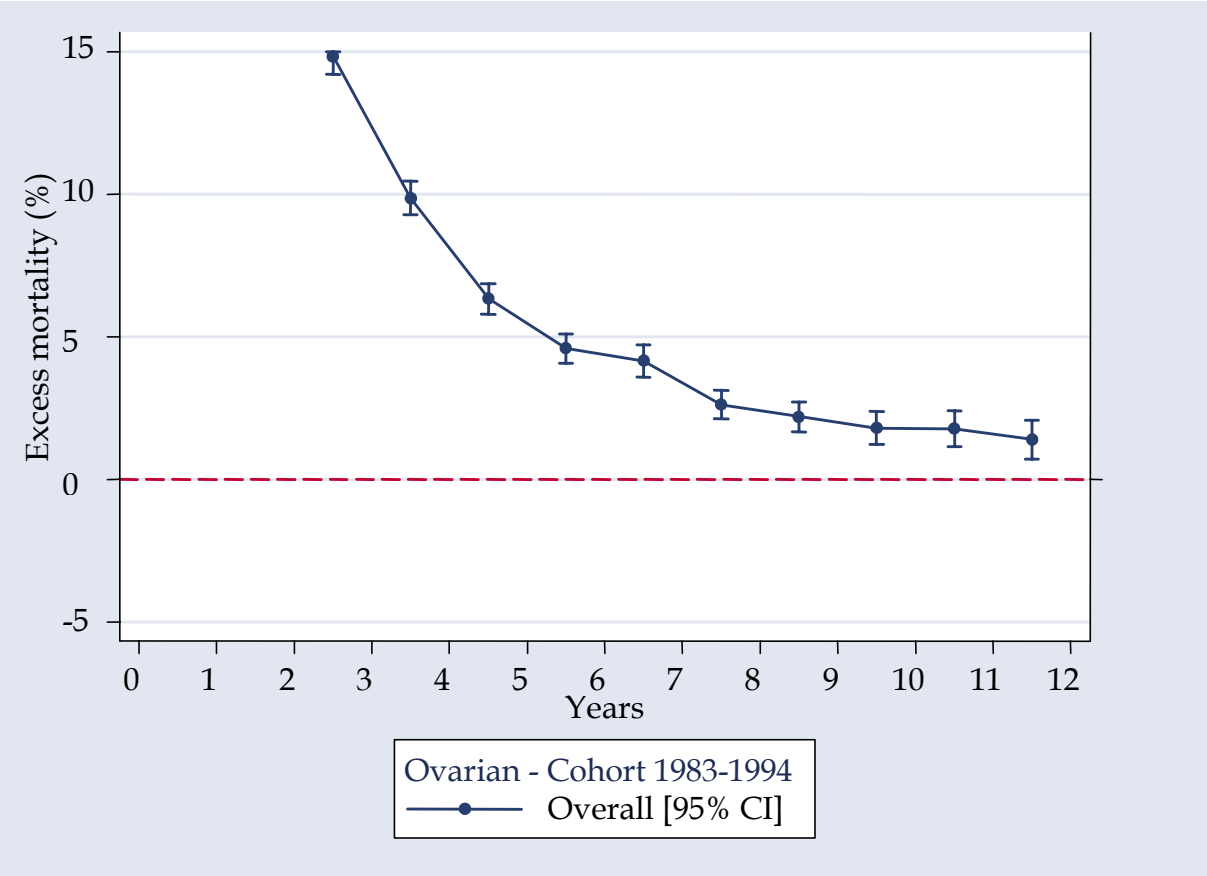

Figure 5.1: Annual excess mortality for women: diagnostic cohort 1983-1994

Table 5.II: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] % annual			
Interval (years)	15-44 years (N = 3,157)	45-54 years (N = 4,542)	55-64 years (N = 6,636)	65-74 years (N = 7,178)
0-1	10.35 [9.29-11.42]	15.70 [14.64-16.77]	22.68 [21.66-23.71]	34.63 [33.50-35.76]
1-2	9.76 [8.66-10.86]	17.96 [16.73-19.19]	25.10 [23.89-26.30]	28.56 [27.22-29.91]
2-3	7.26 [6.24-8.28]	13.43 [12.22-14.64]	17.01 [15.79-18.23]	19.73 [18.29-21.17]
3-4	4.34 [3.51-5.18]	9.91 [8.76-11.05]	11.73 [10.56-12.89]	12.73 [11.32-14.13]
4-5	2.47 [1.79-3.14]	7.38 [6.29-8.47]	7.96 [6.87-9.06]	7.14 [5.85-8.43]
5-6	2.05 [1.39-2.72]	5.17 [4.14-6.20]	5.42 [4.38-6.46]	5.75 [4.40-7.09]
6-7	2.03 [1.31-2.76]	4.34 [3.26-5.42]	5.09 [3.95-6.22]	5.29 [3.76-6.81]
7-8	1.09 [0.52-1.66]	3.09 [2.10-4.08]	3.51 [2.45-4.56]	2.82 [1.40-4.25]
8-9	1.33 [0.66-2.00]	2.69 [1.66-3.72]	2.38 [1.36-3.40]	2.50 [0.92-4.08]
9-10	1.51 [0.72-2.31]	2.23 [1.12-3.34]	1.34 [0.34-2.34]	2.39 [0.51-4.26]
10-11	0.92 [0.23-1.60]	1.75 [0.66-2.83]	1.43 [0.33-2.53]	3.68 [1.41-5.96]
11-12	0.62 [-0.04-1.28]	1.47 [0.30-2.64]	1.35 [0.10-2.60]	2.71 [0.10-5.32]

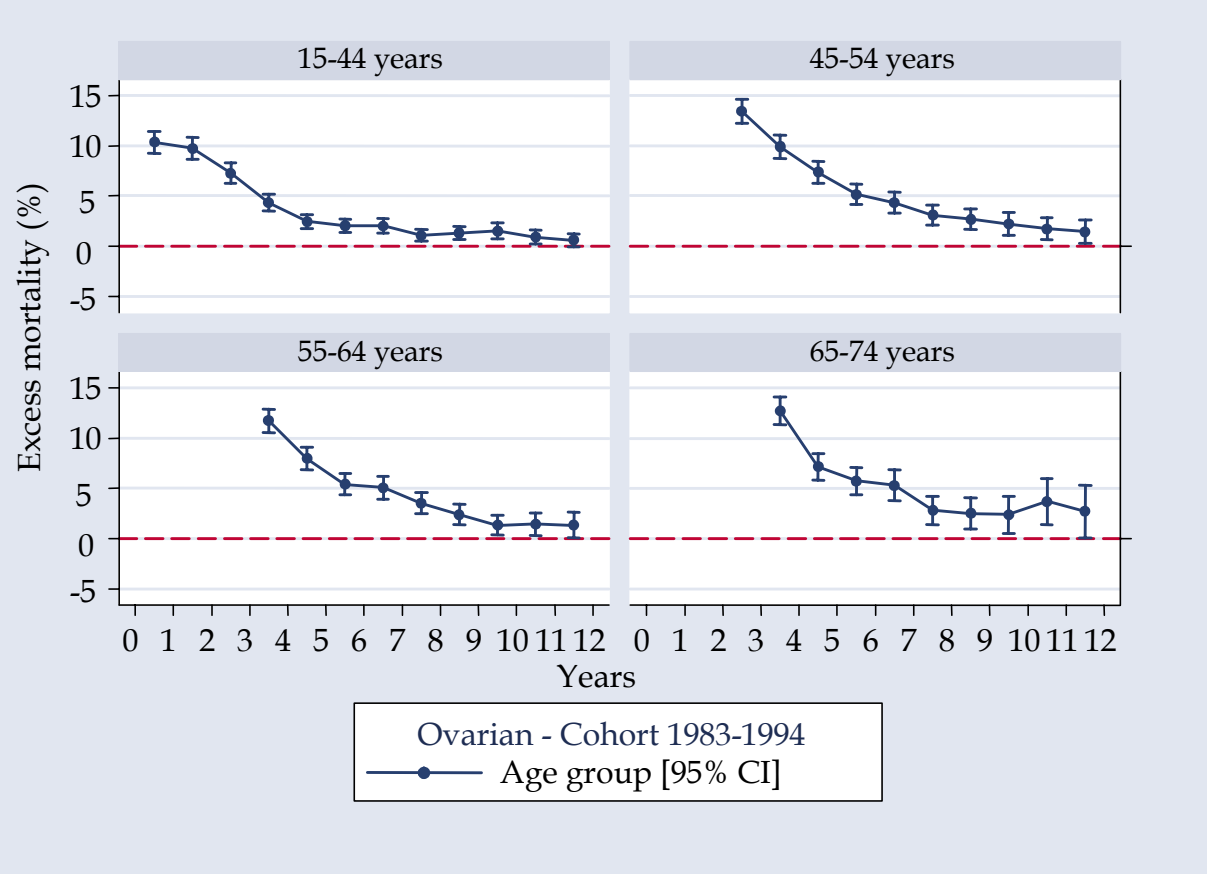

Figure 5.2: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 5.III: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (% annual)			
Interval (years)	Cohort 1983-1985 (N = 5,249)	Cohort 1986-1988 (N = 5,501)	Cohort 1989-1991 (N = 5,287)	Cohort 1992-1994 (N = 5,476)
0-1	25.91 [24.71-27.12]	25.00 [23.84-26.17]	22.78 [21.63-23.93]	19.72 [18.65-20.79]
1-2	23.11 [21.75-24.47]	22.17 [20.87-23.46]	21.93 [20.63-23.23]	19.90 [18.70-21.11]
2-3	14.03 [12.74-15.33]	14.59 [13.33-15.86]	15.17 [13.88-16.46]	15.47 [14.24-16.71]
3-4	9.08 [7.89-10.26]	9.46 [8.30-10.62]	9.96 [8.77-11.15]	10.86 [9.68-12.03]
4-5	5.63 [4.59-6.66]	5.53 [4.53-6.52]	6.88 [5.79-7.97]	7.38 [6.21-8.55]
5-6	4.10 [3.14-5.06]	4.46 [3.51-5.41]	4.44 [3.49-5.40]	6.00 [4.52-7.47]
6-7	3.51 [2.57-4.44]	4.52 [3.53-5.51]	4.40 [3.41-5.38]	-
7-8	2.19 [1.36-3.01]	2.00 [1.22-2.77]	3.88 [2.82-4.95]	-
8-9	1.77 [0.96-2.57]	2.39 [1.54-3.23]	2.60 [1.35-3.85]	-
9-10	1.65 [0.83-2.47]	1.94 [1.12-2.77]	-	-
10-11	1.77 [0.91-2.63]	1.76 [0.85-2.67]	-	-
11-12	1.43 [0.58-2.27]	1.33 [0.19-2.47]	-	-

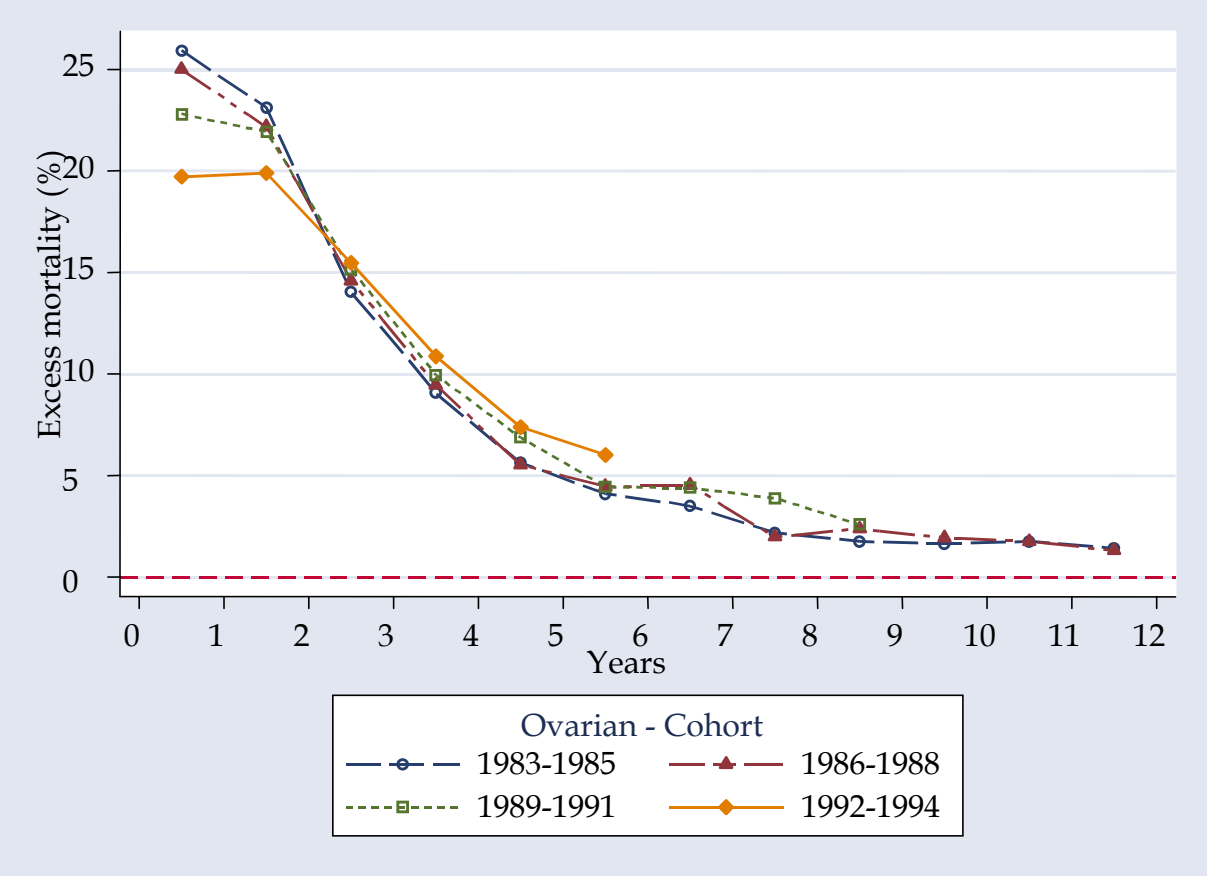

Figure 5.3: Time course of annual excess mortality by cohort

6

Cervical cancer

With almost 3,400 new cases diagnosed in France in 2000, invasive cervical cancer ranks 8th among female cancers (Remontet *et al.*, 2003). The age-standardized incidence rate (world population) was estimated to be 8/100,000 for France in 2000. The incidence has fallen for the cohorts of women born after 1930. The incidence has also decreased over the last two decades: the mean annual growth rate between 1980 and 2000 was -2.88%. More widespread screening mainly explains the change in the epidemiological profile of cervical cancer.

The median age at diagnosis is 51 years and the incidence peaks at age 40 years. The annual mortality rate is low (less than 5/100,000) for women aged less than 70 years. Overall, the annual mortality rate has also fallen over the last 20 years. The age-standardized mortality rate (world population) was estimated to be 1.9/100,000 in 2000.

On the basis of the Eurocare data, for the diagnostic cohort 1992-1994, the relative 5-year survival was 73%, all stages considered, for the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 6.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates taken into account all the patients whose cervical cancer was diagnosed in Europe (8 countries) between 1983 and 1994. The annual excess mortality was less than 5% 4 years post-diagnosis. The annual excess mortality falls to close to 2% towards year 6 post-diagnosis and continued to fall to about 1% at year 8 (figure 6.1).

Table 6.II shows the annual excess mortality results for the various age groups. Young women have an annual excess mortality rate that is markedly lower than that for elderly women. For the age group 15-44 years, the excess mortality is of the order of 1% as of year 5 and becomes negligible thereafter (figure 6.2).

The annual excess mortality data for the 4 cohorts are shown in table 6.III. The data show no noteworthy influence of diagnosis period on annual excess mortality (figure 6.3).

Very long-term annual excess mortality (all stages considered): other studies

The long-term excess mortality and survival data are rare. However, three sources of population data are available for the evaluation of the very long-term annual excess mortality associated with cervical cancer: the US data generated by the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the Finnish and Swedish national registries.

Brenner (2002) evaluated the relative 5-, 10-, 15- and 20-year survivals of the patients presenting with cervical cancer in diagnostic cohort 1973-1998 on the basis of the data generated by the US SEER program. The relative survival estimates, calculated using the period analysis method (which takes into account the survival observed over the first few

years post-diagnosis for the more recent periods) were 70.5, 64.1, 62.8 and 60.0%, respectively. The mean annual excess mortality estimate was of the order of 0.9% for the period 15-20 years.

The Finnish study by Brenner and Hakulinen (2001) reported relative survivals (calculated using the period analysis method) at 5, 10, 15 and 20 years of 70.7, 64.1, 60.5 and 60.6%, respectively. The mean annual excess mortality for the period, 10-15 years, was of the order of 1% and became nil thereafter.

The Swedish study by Talbäck *et al*. (2004) reported relative survivals estimated using the period analysis method of 70.3, 66.2 and 63.6% at 5, 10 and 15 years, respectively. Those data are compatible with the relative 5-, 10- and 15-year survivals observed for patients whose disease was diagnosed in the most recent period. Those survivals were 70.9, 67.4 and 63.1%, respectively. The mean annual excess mortality beyond 10 years is 0.8%.

Gatta *et al*. (1999) published 5-year survival results for almost 41,000 women whose cervical cancer was diagnosed in ten European countries between 1978 and 1989. In that study, the method used to estimate survival was based on the 'cure rate model'. The model yields an estimated percentage cure rate and an estimated uncured patient mortality rate. The percentage patients cured (i.e. not presenting with excess mortality relative to the overall population) was 55%. For all the patients, the life expectancy was the same as that for the overall population as of 8 years post-diagnosis.

As was the case with the Eurocare data, an effect of age at diagnosis was present with a recovery rate of 72% for women aged 25-44 years at the time of diagnosis. The authors discuss the interpretation to be given to the absence of improvement in survival in certain European countries. In countries where screening is conducted, no improvement in survival has been observed with the diagnostic period. This seems to reflect the efficacy of screening, which reduces incidence by detecting forms not qualified as malignant, leaving the more serious forms.

Long-term relative survival or excess mortality by stage

The PETRI study (Ile-de-France, 2004) showed a relative 5-year survival in France of 66% of patients presenting with cervical cancer (cohort 1994-1999). A third of the cases were at stage I at the time of diagnosis with a relative 5-year survival rate of 84%. For patients presenting with stage II, III or IV disease, the survival rates were 73, 68 and 35%, respectively.

The Hérault Tumor Registry (2005) reports relative 5-year survival data for 196 incident cases of cervical cancer diagnosed over the period 1995-1998. The 5-year survival was 72% for all stages and all ages. For stages I, II and III, the survivals were 93, 75 and 59%, respectively (no data for stage IV).

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has reported relative survival data by year for three stages of cervical cancer: local, regional and metastatic (distant metastases) and a non-determined stage (insufficient data in the base to determine the stage). The annual excess mortality has been calculated from those data (table 6.IV). The stage distribution (localized, regional and metastatic was as follows: 53.8, 32.1 and 7.7%. The results are for women of all ages considered whose disease was diagnosed between 1988 and 2001.

Table 6.IV: Annual excess mortality by stage at diagnosis for the period 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease (N+)	Metastatic disease (M+)
0-1	1.6	16.0	56.1
1-2	2.4	18.2	40.3
2-3	1.9	12.2	24.0
3-4	1.3	8.5	17.1
4-5	0.9	5.3	13.9
5-6	0.9	4.2	4.9
6-7	1.0	2.8	5.9
7-8	0.4	3.7	3.9
8-9	0.8	2.6	0.0
9-10	0.6	1.3	0.0

For localized cervical cancer, the annual excess mortality is less than or equal to 1% as of year 4.

Influence of prognostic factors on survival

There are two types of cervical cancer: squamous-cell carcinoma, which develops from the epithelium of the cervix (95% of cases) and adenocarcinoma, which develops from the glandular cells (5% of cases). Substantial progress has been achieved in the management of cervical cancer in the last decade with, in particular, an increase in survival.

The prognosis of cervical cancer is mainly based on the following factors (FNCLCC, 2000):

- stage determined as per the FIGO[5] classification;
- tumor volume;
- lymph node involvement: number, upper level of invasion and bilateral nature of the invasion also have prognostic value. [18F]-FDG positron-emission tomography (FDG-PET) is a sensitive investigation for lymph node staging (FNCLCC, 2003).

There are other prognostic factors such as age, histologic type and biological factors.

The treatment of cervical cancer depends on disease stage. In early-stage disease and in the event of a small tumor with no lymph node involvement, treatment consists in surgery or radiotherapy or a combination of both. In advanced disease either due to lymph node involvement or local spread, external-beam radiotherapy in combination with brachytherapy plays a preponderant role (FNCLCC, 2000).

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Excess mortality data from the Eurocare study

Table 6.I: Annual excess mortality for women: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Women (N = 14,361)
0-1	10.13 [9.63-10.64]
1-2	10.76 [10.21 -11.31]
2-3	6.31 [5.85 -6.78]
3-4	4.09 [3.69 -4.50]
4-5	2.97 [2.59 -3.35]
5-6	2.28 [1.92 -2.65]
6-7	1.90 [1.51 -2.28]
7-8	1.44 [1.07 -1.81]
8-9	1.29 [0.90 -1.68]
9-10	1.13 [0.69 -1.57]
10-11	0.83 [0.39 -1.27]
11-12	1.23 [0.68 -1.77]

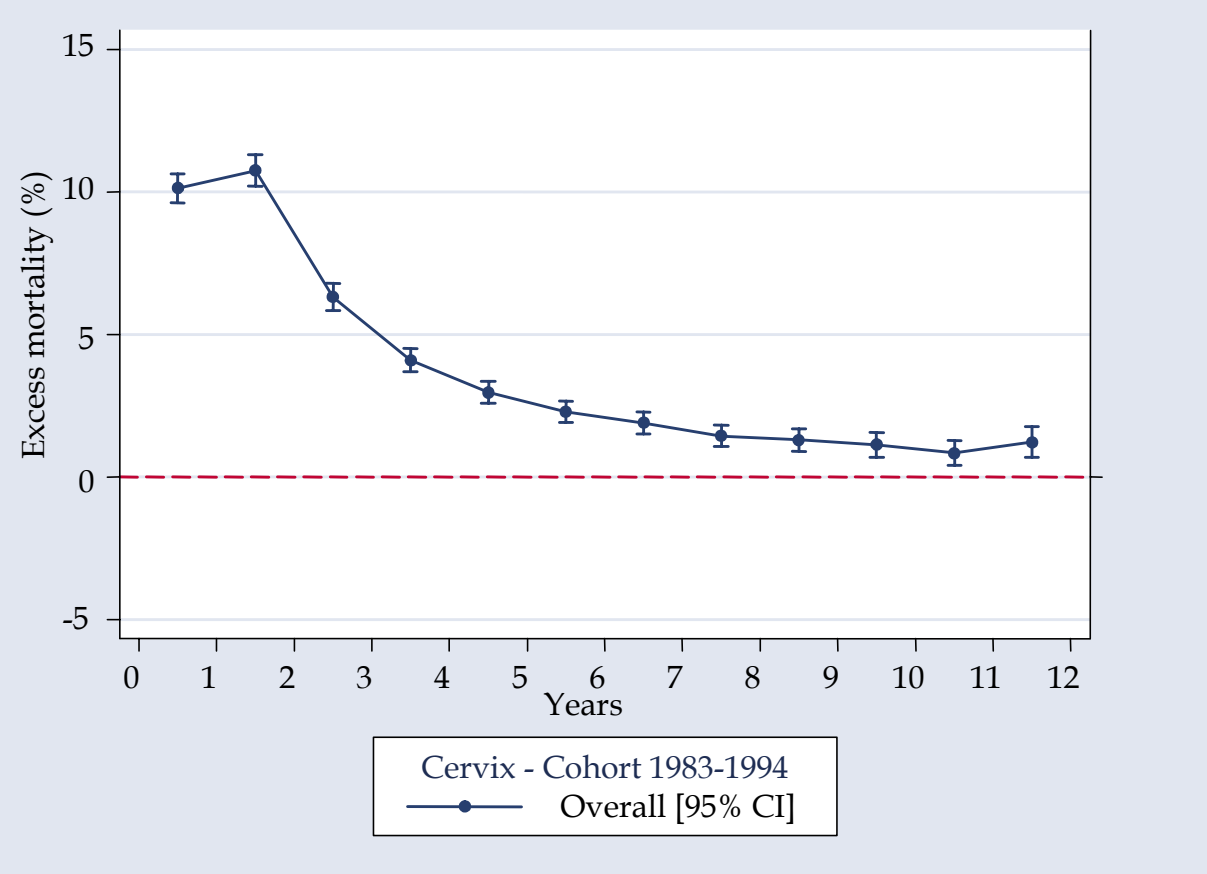

Figure 6.1: Annual excess mortality for women: diagnostic cohort 1983-1994

Table 6.II: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	15-44 years (N = 5,619)	45-54 years (N = 2,740)	55-64 years (N = 2,823)	65-74 years (N = 3,179)
0-1	4.91 [4.34-5.48]	8.94 [7.86-10.02]	12.54 [11.29-13.80]	18.39 [16.98-19.80]
1-2	7.05 [6.36-7.74]	11.05 [9.80-12.29]	12.78 [11.43-14.14]	16.40 [14.88-17.92]
2-3	3.75 [3.21-4.28]	6.61 [5.54-7.67]	7.54 [6.36-8.72]	10.92 [9.47-12.38]
3-4	2.27 [1.84-2.71]	3.71 [2.86-4.57]	5.44 [4.36-6.52]	7.89 [6.49-9.30]
4-5	1.42 [1.06-1.79]	3.27 [2.42-4.12]	3.97 [2.96-4.97]	5.88 [4.49-7.26]
5-6	1.01 [0.68-1.35]	2.19 [1.42-2.96]	3.73 [2.68-4.79]	4.48 [3.06-5.90]
6-7	0.82 [0.49-1.16]	2.29 [1.41-3.17]	2.29 [1.31-3.27]	4.29 [2.69-5.89]
7-8	0.52 [0.23-0.81]	0.77 [0.15-1.39]	2.76 [1.66-3.87]	3.64 [1.96-5.31]
8-9	0.46 [0.16-0.76]	1.13 [0.36-1.90]	2.41 [1.25-3.57]	2.92 [1.11-4.73]
9-10	0.32 [0.02-0.62]	0.80 [-0.00-1.60]	2.25 [0.94-3.55]	2.98 [0.82-5.15]
10-11	0.25 [-0.04-0.55]	2.08 [0.89-3.27]	1.42 [0.17-2.67]	0.41 [-1.59-2.41]
11-12	0.14 [-0.15-0.42]	0.53 [-0.36-1.42]	2.95 [1.24-4.67]	3.83 [0.91-6.75]

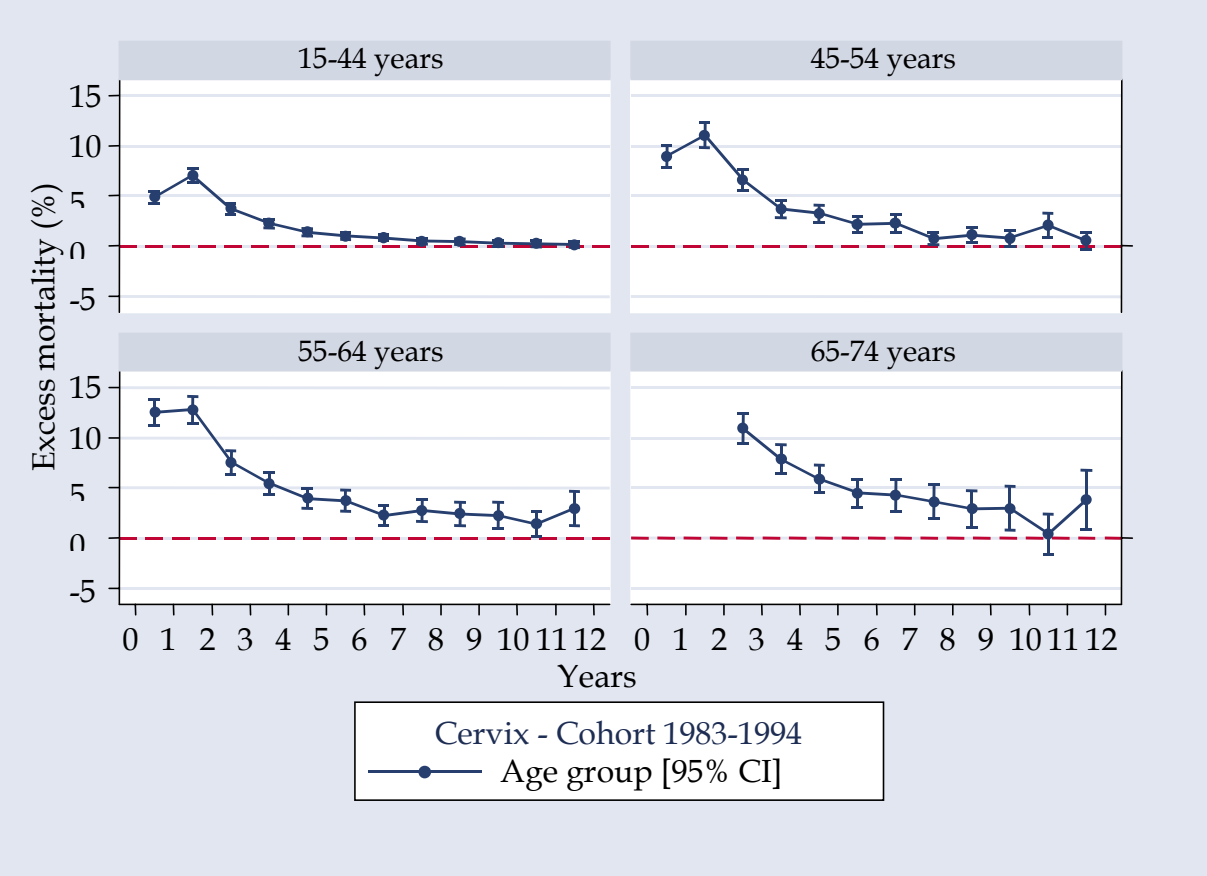

Figure 6.2: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 6.III: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (% annual)			
Interval (years)	Cohort 1983-1985 (N = 3,649)	Cohort 1986-1988 (N = 3,664)	Cohort 1989-1991 (N = 3,565)	Cohort 1992-1994 (N = 3,483)
0-1	10.45 [9.43-11.47]	12.13 [11.05-13.22]	9.14 [8.17-10.11]	8.72 [7.75-9.68]
1-2	11.02 [9.91-12.13]	11.80 [10.65-12.95]	11.23 [10.11-12.35]	8.96 [7.94-9.99]
2-3	7.12 [6.13-8.11]	7.00 [6.01-7.99]	5.57 [4.68-6.46]	5.58 [4.70-6.46]
3-4	4.05 [3.23-4.87]	4.46 [3.60-5.32]	4.01 [3.21-4.81]	3.86 [3.08-4.64]
4-5	2.84 [2.11-3.58]	3.26 [2.48-4.04]	2.63 [1.93-3.32]	3.17 [2.36-3.98]
5-6	2.43 [1.72-3.14]	2.14 [1.46-2.82]	2.05 [1.40-2.69]	2.70 [1.69-3.70]
6-7	2.06 [1.37-2.75]	1.61 [0.97-2.24]	2.01 [1.35-2.67]	-
7-8	1.38 [0.75-2.00]	1.54 [0.89-2.18]	1.38 [0.73-2.03]	-
8-9	1.37 [0.73-2.01]	1.13 [0.53-1.73]	1.40 [0.53-2.27]	-
9-10	0.99 [0.39-1.60]	1.28 [0.64-1.91]	-	-
10-11	1.07 [0.44-1.71]	0.52 [-0.07-1.11]	-	-
11-12	1.06 [0.40-1.71]	1.55 [0.55-2.55]	-	-

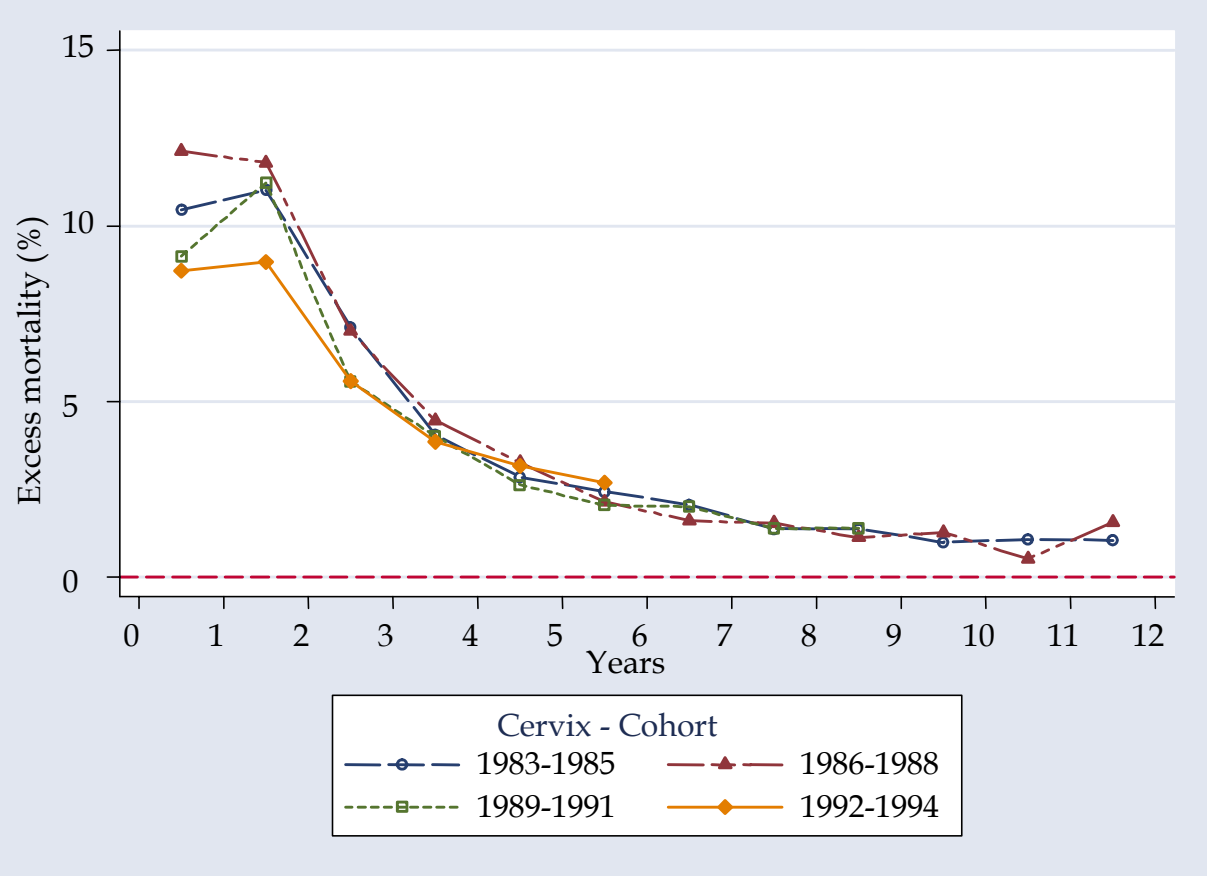

Figure 6.3: Time course of annual excess mortality by cohort

7

Corpus uteri cancer

With almost 5,000 new cases in France in 2000, *corpus uteri* cancer ranks 3rd among female cancers. The age-standardized incidence rate (world population) was estimated to be 9.2/100,000 (Remontet *et al*., 2003). The incidence decreased in recent cohorts. However, the incidence rate has remained stable over the last two decades.

The median age at diagnosis is 69 years and the incidence peaks at about 75 years. The annual mortality rate for women aged less than 50 years is very low (less than 2/100,000). The mortality rate subsequently increases regularly with age. Overall, the annual mortality rate has slightly decreased over the last 20 years (-0.84% per year). The age-standardized mortality rate (world population) was estimated to be 2.4/100,000 in 2000.

According to the Eurocare data on the 1992-1994 diagnostic cohort, the relative 5-year survival was 84.5%, all stages considered, and for the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 7.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates are based on all patients whose *corpus uteri* cancer was diagnosed between 1983 and 1994 in Europe (8 countries). The annual excess mortality, close to 6% for the first year post-diagnosis, falls regularly to 1% as of year 6 and the rate is close to zero for subsequent years (figure 7.1).

Table 7.II shows the annual excess mortality results for the various age groups. The annual excess mortality falls to below 2% as of year 3 and is negligible after year 8 for the age group, 15-44 years. The age at diagnosis influences the early annual excess mortality and very weakly influences the late annual excess mortality (figure 7.2).

The annual excess mortality data for the 4 cohorts are shown in table 7.III. The diagnosis period does not influence the annual excess mortality rate (figure 7.3).

Very long-term annual excess mortality (all stages considered): other data

Three sources of population data are available for evaluation of the very long-term annual excess mortality associated with *corpus uteri* cancer: the US data generated by the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the Finnish and Swedish national registry data.

For patients presenting with *corpus uteri* cancer diagnosed between 1973 and 1998, Brenner (2002) evaluated the relative 5-, 10-, 15- and 20-year survivals from the data generated by the US SEER program. The relative survival estimates, calculated using the period analysis method (which takes into account the survival observed over the first years post-diagnosis

for the more recent periods) were 84.3, 83.2, 80.8 and 79.2%, respectively. The estimated mean annual excess mortality was less than 0.5% as of year 5.

The Finnish study by Brenner and Hakulinen (2001) reported relative survivals (calculated using the period analysis method) at 5, 10, 15 and 20 years of 82.4, 80.4, 77.4 and 73.9%, respectively. The mean annual excess mortality after 10 years was of the order of 0.7%.

In the Swedish study by Talbäck *et al*. (2004), the relative survivals estimated using the period analysis method were 82.3, 79.1 and 77.0% at 5, 10 and 15 years, respectively. Those data are similar to the relative 5-, 10- and 15-year survivals observed for the patients whose disease was diagnosed in the most recent period. The survivals were 83.4, 75.9 and 77.7%, respectively. The mean annual excess mortality after 10 years was 0.6%.

Long-term relative survival or excess mortality by stage

In the PETRI study (Ile-de-France, 2004), the 5-year relative survival in France was 76% for patients presenting with *corpus uteri* cancer (cohort 1994-1999). For patients presenting with stage I *corpus uteri* cancer, the 5-year survival rate was 99%. For stages II and III, the survivals were 82 and 67%, respectively. For stage IV, the survival rate fell to 42%.

The Hérault tumor registry (2005) has supplied data on the relative 5-year survivals of 228 incident cases of *corpus uteri* cancer diagnosed over the period 1995-1998. The 5-year survival was 77% for all stages and all ages taken together. The data by stage were 95, 60, 47 and 11% for stages I, II, III and IV, respectively.

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated relative survival data by year using three levels of *corpus uteri* cancer progression—localized, regional and metastatic (distant metastases)—and a non-determined stage (information insufficient to determine the stage). On the basis of those data, annual excess mortality rates have been calculated (table 7.IV). The distribution of *corpus uteri* cancer cases by stage (localized, regional and metastatic) was as follows: 72.4, 14.7 and 8.5%. The data presented concern the women, all ages considered, whose disease was diagnosed between 1988 and 2001.

Table 7.IV: Annual excess mortality by stage at diagnosis for cohort 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease (N+)	Metastatic disease (M+)
0-1	0.8	12.1	43.8
1-2	1.2	11.1	29.2
2-3	1.0	7.9	20.1
3-4	0.6	5.6	12.3
4-5	0.5	3.5	7.2
5-6	0.5	4.1	4.2
6-7	0.2	1.6	2.0
7-8	0.7	1.5	4.5
8-9	0.0	1.1	0.0
9-10	0.7	0.3	0.0

For localized *corpus uteri* cancer, the annual excess mortality was of the order of 0.5% as of year 4 post-diagnosis.

Influence of prognostic factors on survival

Corpus uteri carcinoma is most frequently observed (about 80% of cases). The variants of the carcinoma are secretory forms and clear-cell forms.

The prognosis of *corpus uteri* cancer is based on the following factors (FNCLCC, 2001): stage, determined as per the FIGO[6] classification, grade and histologic differentiation, involvement or non-involvement of the cervix, myometrial lesion depth, pelvic lymph node involvement, etc.

The good prognostic factors mainly consist in low grade and limited myometrial invasion, while the poor prognostic factors consist in myometrial invasion greater than 2/3 (FNCLCC, 2001).

The management of *corpus uteri* cancer in most cases consists in surgery, which constitutes both a treatment and a means of staging (Narducci *et al.*, 2003). Depending on certain prognostic factors, surgery may be followed by radiotherapy.

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Excess mortality data from the Eurocare study

Table 7.I: Annual excess mortality for women: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Women (N = 23,897)
0-1	6.10 [5.77-6.43]
1-2	5.26 [4.94 -5.58]
2-3	3.32 [3.04 -3.60]
3-4	2.04 [1.79 -2.28]
4-5	1.58 [1.34 -1.82]
5-6	1.33 [1.08 -1.58]
6-7	0.89 [0.62 -1.15]
7-8	0.98 [0.69 -1.27]
8-9	0.53 [0.24 -0.82]
9-10	0.28 [-0.04 -0.61]
10-11	0.93 [0.52 -1.33]
11-12	0.51 [0.07 -0.95]

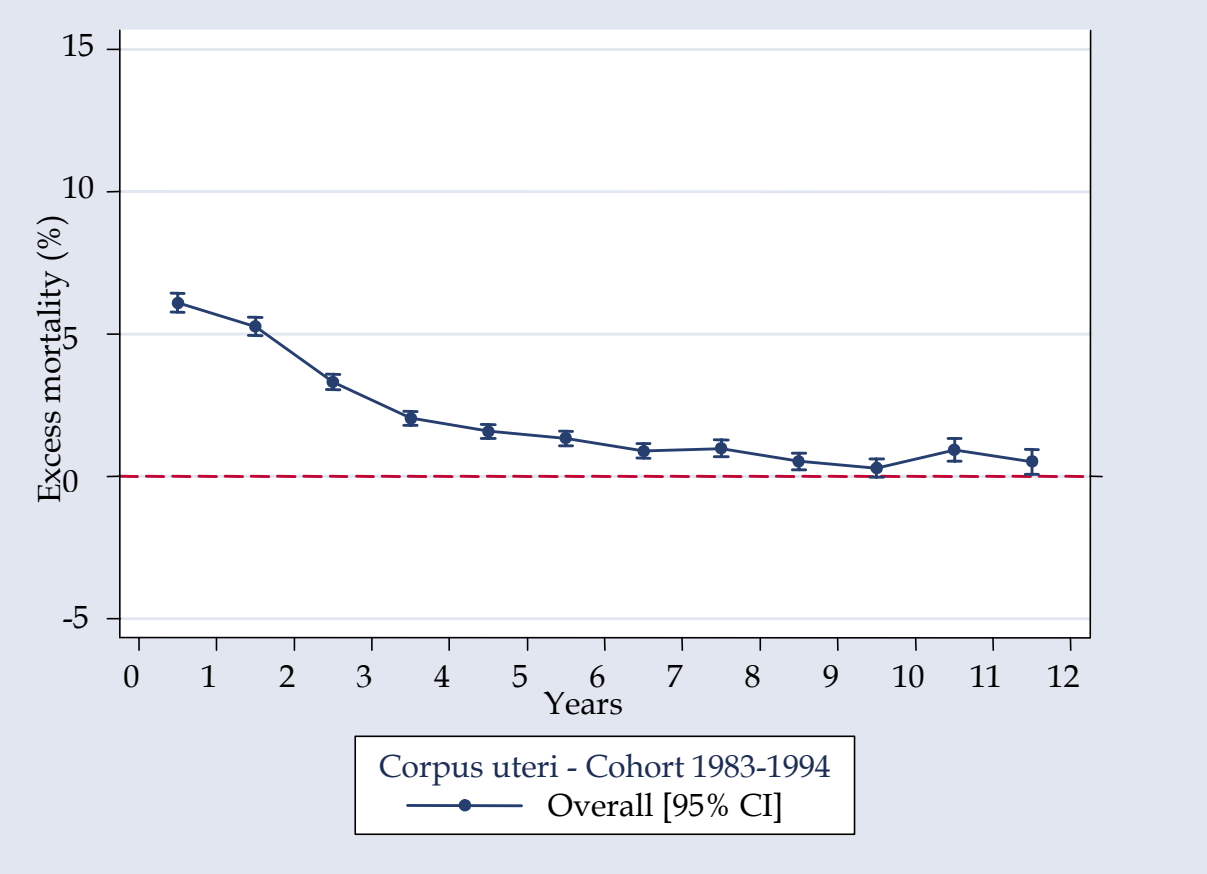

Figure 7.1: Annual excess mortality for women: diagnostic cohort 1983-1994

Table 7.II: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	15-44 years (N = 1,018)	45-54 years (N = 4,489)	55-64 years (N = 9,140)	65-74 years (N = 9,250)
0-1	3.24 [2.13-4.35]	2.99 [2.47-3.51]	5.00 [4.52-5.47]	9.05 [8.41-9.68]
1-2	2.23 [1.28-3.18]	2.73 [2.22-3.24]	5.13 [4.64-5.63]	7.11 [6.49-7.73]
2-3	1.23 [0.50-1.97]	2.07 [1.61-2.53]	2.99 [2.57-3.40]	4.66 [4.09-5.23]
3-4	1.99 [1.07-2.91]	1.05 [0.69-1.41]	1.59 [1.25-1.93]	3.13 [2.60-3.66]
4-5	0.53 [-0.01-1.07]	0.80 [0.46-1.14]	1.53 [1.17-1.88]	2.29 [1.76-2.82]
5-6	1.07 [0.31-1.83]	0.67 [0.32-1.01]	1.06 [0.72-1.40]	2.16 [1.58-2.74]
6-7	0.55 [-0.09-1.20]	0.62 [0.25-0.99]	1.01 [0.63-1.40]	0.97 [0.36-1.57]
7-8	0.28 [-0.26-0.82]	0.53 [0.15-0.90]	1.27 [0.85-1.70]	1.05 [0.38-1.72]
8-9	0.70 [-0.10-1.49]	0.04 [-0.25-0.34]	0.61 [0.20-1.01]	0.79 [0.04-1.54]
9-10	-0.01 [-0.44-0.43]	0.19 [-0.20-0.57]	0.23 [-0.20-0.67]	0.51 [-0.39-1.41]
10-11	-0.00 [-0.48-0.48]	0.76 [0.21-1.30]	0.79 [0.25-1.33]	1.53 [0.42-2.63]
11-12	0.33 [-0.50-1.16]	0.66 [0.05-1.26]	0.22 [-0.33-0.77]	0.98 [-0.31-2.28]

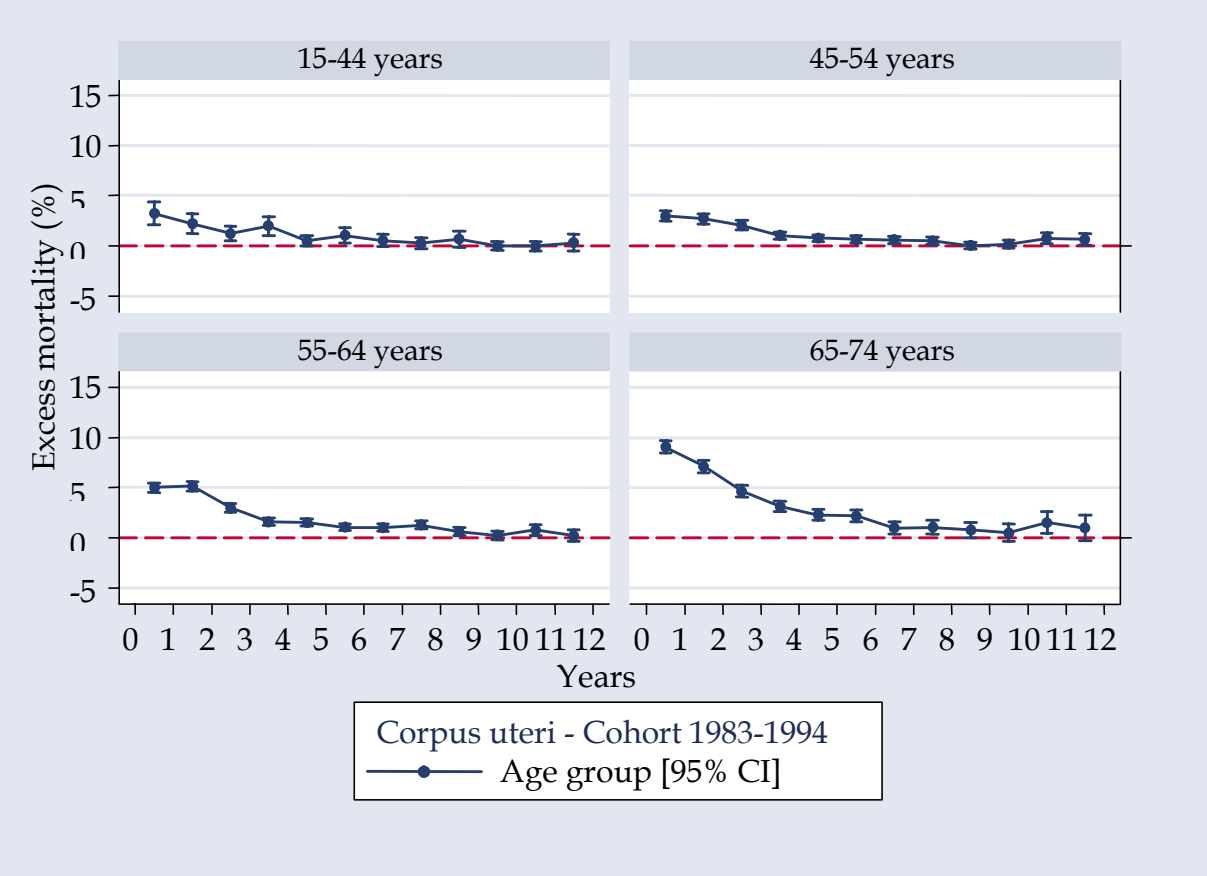

Figure 7.2: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 7.III: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 1983-1985 (N = 5,431)	Cohort 1986-1988 (N = 6,011)	Cohort 1989-1991 (N = 6,121)	Cohort 1992-1994 (N = 6,334)
0-1	7.05 [6.33-7.78]	6.92 [6.23-7.60]	5.48 [4.86-6.09]	5.11 [4.52-5.70]
1-2	5.41 [4.72-6.09]	5.47 [4.82-6.12]	5.37 [4.74-6.01]	4.84 [4.24-5.44]
2-3	3.00 [2.43-3.58]	3.60 [3.02-4.18]	3.68 [3.11-4.26]	2.97 [2.45-3.48]
3-4	2.03 [1.51-2.55]	2.03 [1.54-2.53]	2.32 [1.81-2.82]	1.78 [1.33-2.23]
4-5	1.93 [1.40-2.46]	1.21 [0.76-1.65]	1.47 [1.01-1.93]	1.76 [1.25-2.27]
5-6	1.23 [0.74-1.72]	1.56 [1.07-2.05]	1.39 [0.92-1.86]	0.98 [0.39-1.57]
6-7	0.74 [0.28-1.20]	1.24 [0.76-1.71]	0.68 [0.26-1.10]	-
7-8	1.08 [0.57-1.59]	0.66 [0.21-1.11]	1.24 [0.70-1.77]	-
8-9	0.68 [0.18-1.17]	0.37 [-0.07-0.80]	0.57 [-0.07-1.21]	-
9-10	0.28 [-0.20-0.75]	0.29 [-0.16-0.74]	-	-
10-11	0.72 [0.18-1.26]	1.15 [0.55-1.75]	-	-
11-12	0.35 [-0.18-0.87]	0.81 [0.03-1.58]	-	-

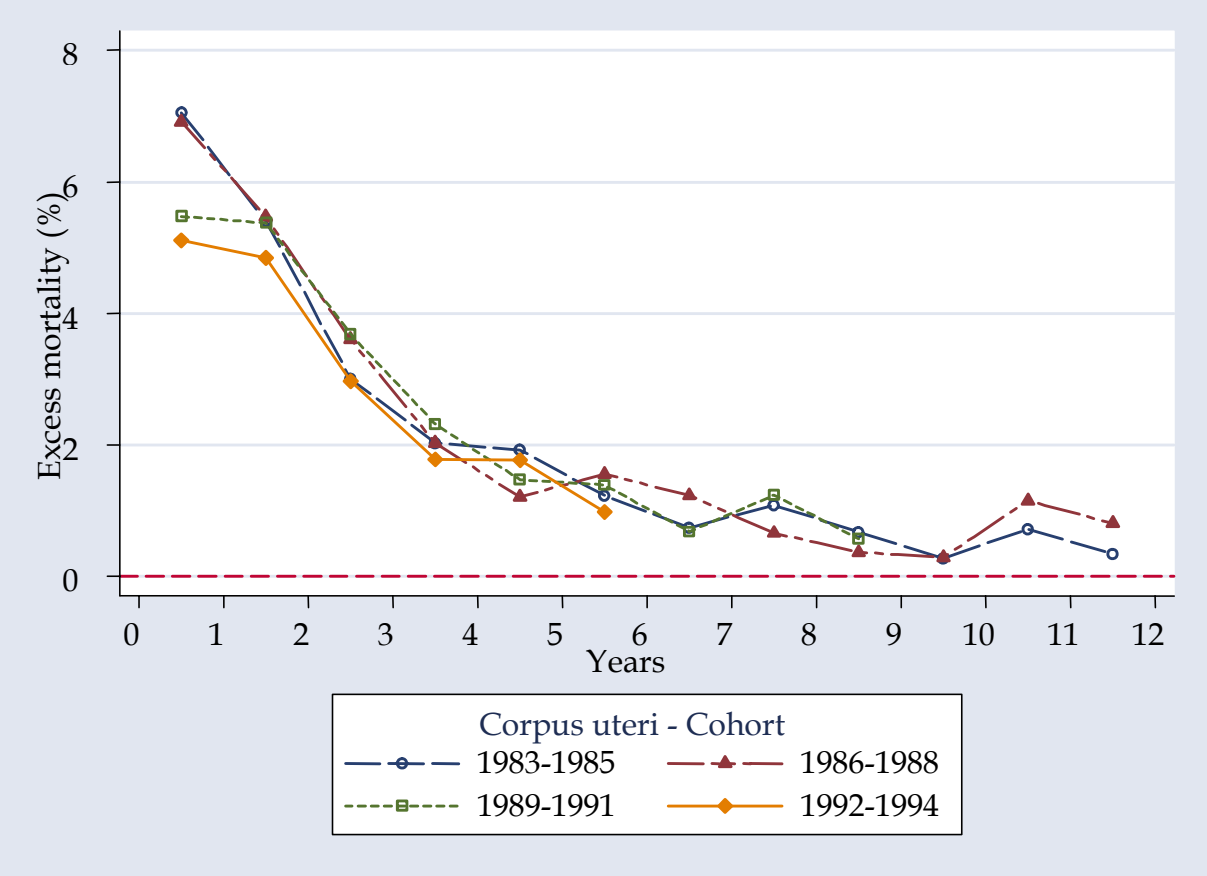

Figure 7.3: Time course of annual excess mortality by cohort

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Prostatic cancer

Prostatic cancer has, in recent years, become the most frequent form of cancer in men aged over 50 years. Prostatic cancer constitutes the second cause of death (after lung cancer) in men aged over 50 years in Europe and the United States. The incidence of prostatic cancer has increased very markedly over the last two decades. In France, the number of new cases diagnosed in 2000 was estimated to be 40,000. The age-standardized incidence rate (world population) was 75.3/100,000 in 2000. The median age at diagnosis was 74 years.

In 2000, the mortality rate was greater than 10,000 deaths, equivalent to 11% of all cancer deaths. The age-standardized mortality rate (world population) was 15.9/100,000 in 2000. In the last 10 years, the mortality rate in France appears to have markedly decreased (Remontet *et al*., 2003).

The 5-year relative survival estimated from the Eurocare data on the most recent cohort (1992-1994), for the eight countries selected, was 70.2%.

Annual excess mortality (all stages considered): Eurocare data

Table 8.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates take into account all the patients aged less than 84 years whose prostatic cancer was diagnosed between 1983 and 1994 in the eight European countries selected. The annual excess mortality peaked at 10% between 1 and 2 years post-diagnosis, then decreased, reaching a plateau at about 6% from year 8 (figure 8.1).

Table 8.II shows the annual excess mortality results for the various age groups. Prostatic cancer is a disease that emerges late in life. Because of that characteristic, the following age groups were defined: 15-54 years, 55-64 years, 65-74 years and 75-84 years. A maximum annual excess mortality of 16% was observed for age group 15-54 years during the second year post-diagnosis, while rates of 6-7% were observed as of year 5 post-diagnosis for all age groups. For all age groups, the annual excess mortality profiles are similar from year 5 post-diagnosis (figure 8.2).

The annual excess mortality data for the 4 age groups are shown in table 8.III. The data show a decrease in annual excess mortality rate for the most recent cohort (1992-1994). In the first interval, the annual excess mortality rate for the oldest cohort was 10.01% vs. 6.15% for the most recent cohort. Figure 8.3 illustrates the marked cohort effect, which shows an improvement in survival over the first years post-diagnosis.

Very long-term annual excess mortality (all stages considered): other studies

Using the Swedish national cancer registry data, Sandblom *et al*. (2000) reported long-term survival data on patients in diagnostic cohort 1974-1986. For all patients, all ages and all treatments, the relative survivals specific to prostatic cancer were 68.9, 53.7, 44.8 and 34.2% at

5, 10, 15 and 20 years, respectively. The mean annual excess mortality was of the order of 5% between 15 and 20 years post-diagnosis.

Long-term relative survival or excess mortality by stage

Sandblom *et al*. (2000) investigated the long-term relative survival of a cohort of Swedish patients presenting with prostatic cancer. For the localized tumors, the relative survivals were 92, 81.7, 73.4 and 62.2% at 5, 10, 15 and 20 years, respectively. The mean annual excess mortality was of the order of 3% between 15 and 20 years post-diagnosis. For patients aged less than 70 years, the 5-, 10-, 15- and 20-year relative survivals were slightly greater.

Sandblom *et al*. (2000) also estimated the 10-year relative survival by tumor grade for patients presenting with localized tumors. For localized tumors of grade 1, the 10-year relative survival was 90% vs. 74% for grade 2 tumors and 59% for grade 3 tumors. Tumor grade thus appears to be an important prognostic factor influencing 10-year survival.

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated relative survival data per year using two levels of prostatic cancer progression—localized and metastatic (distant metastases)—and a non-determined stage. Annual excess mortality rates have been calculated from those data (table 8.IV). The distribution of prostatic cancer cases by stage (localized and metastatic) was as follows: 84.3 and 7.2%. The data presented are for men, all ages considered, for diagnostic period 1988-2001.

Table 8.IV: Annual excess mortality by stage at diagnosis for the period 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)	
Interval (years)	Localized disease	Metastatic disease (M+)
0-1	0	20.00
1-2	0	24.78
2-3	0	20.97
3-4	0	16.63
4-5	0	15.66
5-6	0	14.97
6-7	0	11.97
7-8	0	12.00
8-9	0.7	10.00
9-10	1.41	11.11

The results show that the annual excess mortality for localized disease over the 8 years post-diagnosis was nil. An annual excess mortality of less than 1.5% was observed after 10 years.

Influence of screening programs on survival

The increase in incidence is linked to the progress in diagnostic methods and the use of prostate-specific antigen (PSA) for screening. The countries in which mass screening is recommended showed a marked increase in incidence in the years following program setup

(United States, Canada). Screening underlies the diagnosis of little-advanced cases suitable for treatment or simple monitoring. This is to be taken into account in the interpretation of the survival curves. This improvement of average survival must with 3 phenomenons more or less associated: a diagnosis more and more precocious that extent the duration between diagnostic and death, a better efficacy of management of these cases and over-representation of cases weakly progressive among the new diagnosed cases.

If screening is generalized in France, the recent nature of the diagnosis will be conducive to a lower annual excess mortality.

Influence of prognostic factors on survival

Currently, only the localized stages of the disease can be cured. Treatment is determined by the extent of the disease at the time of diagnosis. For intraprostatic tumors, the reference treatments are surgical (total prostatectomy), external-beam radiotherapy and brachytherapy. For tumors that have spread beyond the prostatic capsule, combined external-beam radiotherapy and hormone therapy constitute the optimal therapeutic strategy. If the tumor is metastatic, hormone therapy constitutes the basis of treatment.

The three principal prognostic factors determined by multifactorial analyses and liable to predict, pre-treatment, the risk of tumor recurrence and overall patient survival are:

- serum prostate-specific antigen (PSA) level (Zagars *et al*., 1994; Hanks *et al*., 1995; Pound *et al*., 1997);
- tumor stage (Ohori *et al*., 1994; Zagars *et al*., 1994; Gerber *et al*., 1996);
- the degree of differentiation of the tumor as determined by Gleason's histologic grading (Albertsen *et al*., 1995; Hanks *et al*., 1995).

The analyses of the prognostic factors were implemented at the start of the 1990s after the advent of serum PSA assays. More recently, several studies have attempted to define the practical conditions for use of those prognostic factors to orient everyday patient management.

An initial approach was based on determining prognostic groups enabling, as a function of the prognostic factors, prediction of the biological recurrence-free (PSA assay) survival and overall survival.

In a population of 2,117 men having undergone prostatectomy, 3 groups of patients were distinguished in terms of prognosis (good, intermediate and poor). The 3 groups had 10-year laboratory recurrence-free (PSA assay) survivals of 83, 46 and 29%, respectively (D'amico *et al*., 2001). The clinical and laboratory characteristics defining the 3 groups are indicated in table 8.V.

Table 8.V: 10-year recurrence-free survival of the 3 prognostic groups defined by D'amico *et al.*, 2001

Group	TNM stage (1992 classification)	Gleason score	PSA (ng/mL)	10-year survival (%)
Low	T1c, T2a	≤ 6	≤ 10	83
Intermediate	T2b	7	10-20	46
High	≥ T2c	≥ 8	> 20	29

These results were subsequently validated with respect to specific overall survival in a cohort of 7,316 patients treated by prostatectomy or radiotherapy. The relative risks increased 5- and 14-fold, respectively, for the intermediate or poor prognosis groups vs. the good prognosis group (table 8.VI).

Table 8.VI: Relative risk of mortality for the prognostic groups defined by D'amico *et al.*, 2003

Group	Specific mortality (RR) post-surgery	Specific mortality (RR) post-radiotherapy
Low	1.1	1.0
Intermediate	4.9	5.6
High	14.2	14.3

A second approach consisted in drawing up nomograms with the objective of predicting laboratory recurrence-free survival. The approach takes into account the weight of each prognostic factor and considers each prognostic factor in its continuity. A point score is thus allocated to each patient. The point score matches a recurrence-free survival probability. Nomograms for various scenarios have been published: pre-prostatectomy with the three conventional prognostic factors (Kattan *et al.*, 1998), post-prostatectomy (Kattan *et al.*, 1999), pre-conformational external-beam radiotherapy (Kattan *et al.*, 2000) and pre-brachytherapy (Kattan *et al.*, 2001).

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Excess mortality data from the Eurocare study

Table 8.I: Annual excess mortality for men: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Men (N = 100,771)
0-1	8.17 [7.95-8.39]
1-2	9.80 [9.55-10.05]
2-3	8.88 [8.62-9.15]
3-4	8.14 [7.86-8.43]
4-5	7.39 [7.08-7.70]
5-6	7.24 [6.88-7.61]
6-7	7.34 [6.90-7.79]
7-8	7.37 [6.86-7.87]
8-9	6.78 [6.19-7.37]
9-10	6.67 [5.93-7.42]
10-11	6.63 [5.77-7.49]
11-12	6.36 [5.29-7.43]

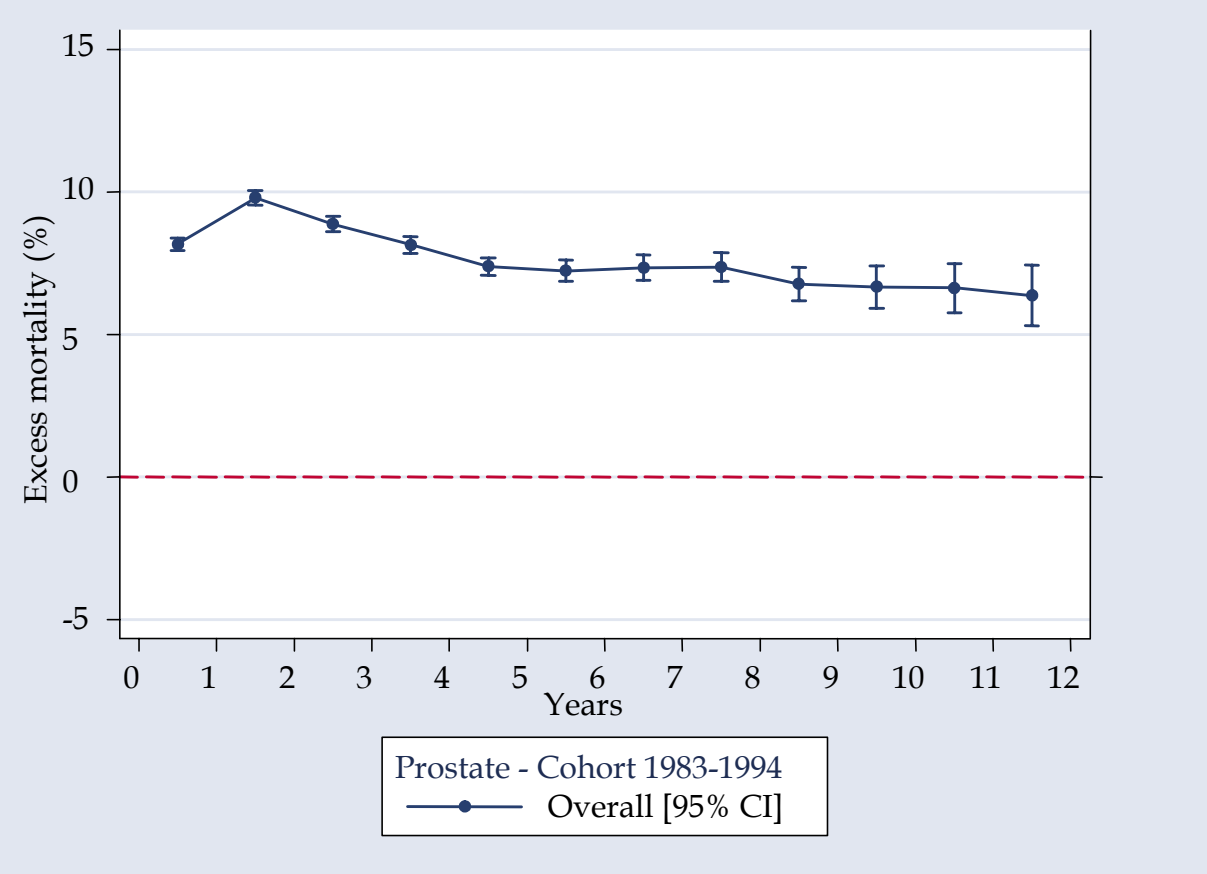

Figure 8.1: Annual excess mortality for men: diagnostic cohort 1983-1994

Table 8.II: Annual excess mortality by age group*: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) 15-54 years (N = 1,518)	55-64 years (N = 13,671)	65-74 years (N = 42,601)	75-84 years (N = 42,981)
0-1	7.64 [6.25-9.03]	5.98 [5.53-11.06]	6.62 [6.32-6.91]	10.57 [10.17-10.96]
1-2	15.93 [13.97-17.89]	10.49 [9.91-11.06]	9.19 [8.84-9.54]	9.97 [9.53-10.41]
2-3	14.93 [12.83-17.02]	9.55 [8.96-10.15]	8.44 [8.08-8.81]	8.87 [8.39-9.36]
3-4	11.51 [9.45-13.57]	8.10 [7.50-8.70]	7.79 [7.40-8.17]	8.48 [7.94-9.02]
4-5	9.65 [7.52-11.79]	7.51 [6.87-8.15]	6.83 [6.42-7.25]	7.96 [7.33-8.58]
5-6	6.51 [4.42-8.60]	6.84 [6.14-7.54]	6.97 [6.48-7.45]	7.88 [7.13-8.63]
6-7	8.82 [6.11-11.53]	6.41 [5.61-7.22]	7.37 [6.76-7.97]	7.80 [6.83-8.76]
7-8	5.32 [2.87-7.76]	6.16 [5.29-7.03]	7.28 [6.60-7.96]	8.52 [7.36-9.67]
8-9	5.68 [2.82-8.54]	5.98 [4.98-6.97]	6.76 [5.97-7.55]	7.57 [6.13-9.00]
9-10	5.79 [2.26-9.32]	5.54 [4.36-6.73]	6.48 [5.49-7.47]	8.32 [6.38-10.25]
10-11	7.20 [2.94-11.46]	5.16 [3.86-6.46]	6.99 [5.83-8.16]	7.29 [4.92-9.65]
11-12	6.79 [1.66-11.91]	4.64 [3.12-6.16]	6.94 [5.47-8.41]	7.24 [4.07-10.42]

* Since prostatic cancer emerges late in life, the age groups have been modified accordingly

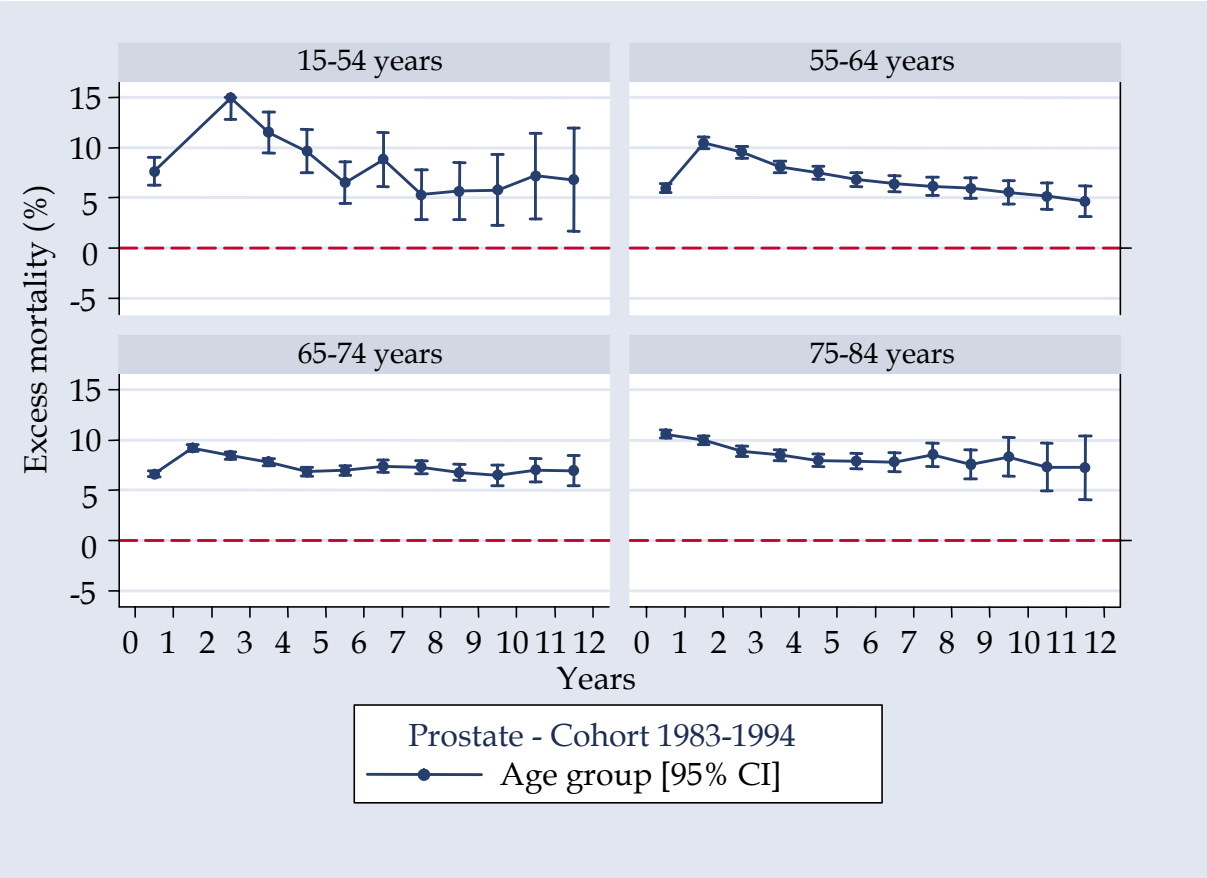

Figure 8.2: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 8.III: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 1983-1985 (N = 20,370)	Cohort 1986-1988 (N = 23,990)	Cohort 1989-1991 (N = 25,821)	Cohort 1992-1994 (N = 30,590)
0-1	10.01 [9.49-10.53]	9.16 [8.70-9.63]	8.22 [7.79-8.66]	6.15 [5.78-6.51]
1-2	12.02 [11.42-12.62]	10.16 [9.64-10.68]	9.77 [9.28-10.26]	8.16 [7.74-8.58]
2-3	11.11 [10.46-11.76]	9.85 [9.28-10.41]	8.77 [8.24-9.29]	6.93 [6.49-7.37]
3-4	9.16 [8.47-9.85]	9.33 [8.72-9.95]	7.99 [7.43-8.55]	6.85 [6.37-7.32]
4-5	8.59 [7.84-9.33]	7.85 [7.20-8.50]	7.44 [6.84-8.04]	6.10 [5.55-6.65]
5-6	8.21 [7.39-9.02]	6.90 [6.21-7.60]	7.42 [6.76-8.07]	6.26 [5.47-7.05]
6-7	8.00 [7.11-8.88]	6.97 [6.21-7.72]	7.22 [6.51-7.93]	-
7-8	8.37 [7.38-9.35]	7.34 [6.50-8.17]	6.52 [5.68-7.35]	-
8-9	7.09 [6.04-8.15]	6.50 [5.61-7.39]	6.78 [5.58-7.98]	-
9-10	6.99 [5.83-8.14]	6.44 [5.46-7.41]	-	-
10-11	6.50 [5.25-7.76]	6.72 [5.54-7.90]	-	-
11-12	6.49 [5.12-7.87]	6.13 [4.43-7.83]	-	-

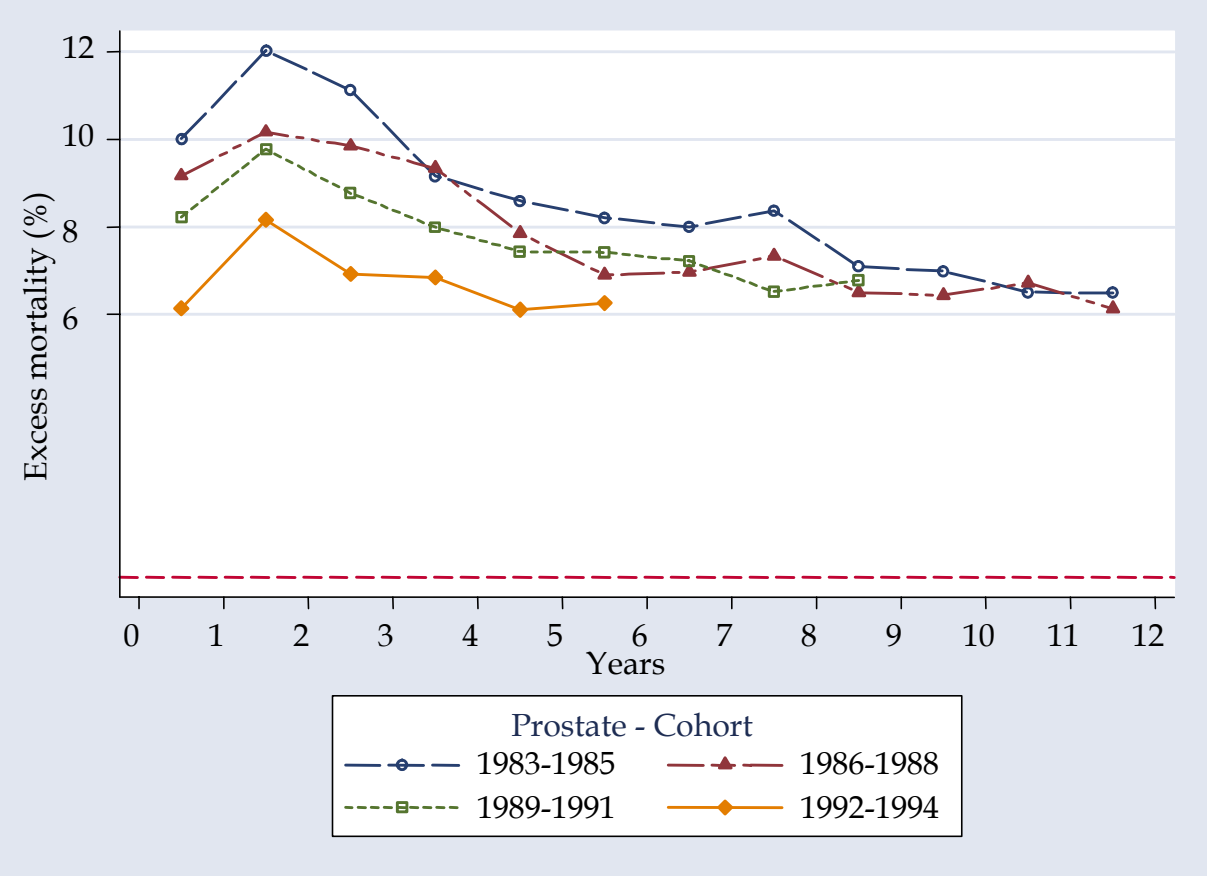

Figure 8.3: Time course of annual excess mortality by cohort

9

Testicular germ-cell tumors

Testicular germ-cell tumors account for 1 to 2% of male neoplastic diseases and 95% of malignant testicular tumors. In France, the age-standardized incidence rate (world population) is estimated 2.42/100 000 for seminomatous testicular germ-cell tumors and 1.95/100 000 for non-seminomatous testicular gem-cell tumors (Hedelin et Remontet, 2002). The tumor is most frequent in men aged 20 to 35 years. The incidence is regularly increasing: the incidence has increased 3- to 4-fold over the last 50 years (Liu *et al.*, 2000). The major therapeutic progress in the last 30 years has enabled a considerable reduction in mortality; the rate of mortality (world population standardized) decreased from 0.75 to 0.25/100 000 between 1975 and 2000 in France (Hedelin et Remontet, 2002).

Peak incidence occurs between age 25 and 35 years. The age of onset varies, however, as a function of tumor histology. Non-seminomatous testicular germ-cell tumors are practically always tumors that occur in young adults while seminomatous testicular germ-cell tumors are also observed after age 50.

The Eurocare study reported a 5-year relative survival for the patients in the most recent cohort (1992-1994) of 95.12% for the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 9.I shows the annual excess mortality estimates with their 95% confidence intervals. The data take into account all patients whose testicular germ-cell cancer was diagnosed between 1983 and 1994 in Europe (eight countries). The excess mortality was less than 0.5% and equal to zero as of the third year post-diagnosis (figure 9.1).

Table 9.II shows the annual excess mortality results for the various age groups. On average, the annual excess mortality was higher for the age group 65-74 years, particularly during the first 3 years post-diagnosis. However, an increase in the confidence intervals was observed for the oldest age groups, the number of patients in those age groups being smaller than the number in the younger age groups (figure 9.2).

The annual excess mortality data for the 4 cohorts are shown in table 9.III. The annual excess mortality was lower for the first 3 years post-diagnosis for the most recent cohort (1992-1994). For all 4 cohorts, the annual excess mortality plots converged as of year 4 and reached a plateau of close to 0% subsequently (figure 9.3).

Long-term relative survival or annual excess mortality by stage

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has reported relative survival data by year using three cancer stages (localized, regional, metastatic) and a non-determined stage (insufficient information in the database to determine the stage). Annual excess mortality rates have been calculated

from those data (table 9.IV). The distribution of the cases of testicular germ-cell tumors by stage (localized, regional and metastatic) was as follows 69.1, 18.7 and 10.7%. The data are shown for all ages taken together at diagnosis and for diagnostic period 1988-2001.

Table 9.IV: Annual excess mortality by stage for diagnostic cohort 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, *2004*)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease (N+)	Metastatic disease(M+)
0-1	0.20	1.30	15.10
1-2	0.40	1.22	9.54
2-3	0.20	0.92	4.30
3-4	0.00	0.00	0.82
4-5	0.00	0.10	0.27
5-6	0.00	0.10	0.28
6-7	0.00	0.31	1.52
7-8	0.30	0.62	1.54
8-9	0.10	0.00	0.57
9-10	0.00	0.73	0.00

The results confirm that, 3 years post-diagnosis, the annual excess mortality is nil or less than 1% irrespective of the disease stage at diagnosis. For localized disease, the annual excess mortality was equal to zero or close to zero as of the first year post-diagnosis.

Numerous studies have confirmed that the prognosis of localized seminomatous or non-seminomatous tumors is excellent: the cure rates reported in the literature are of the order of 99% (Warde *et al*., 2002; Culine, 2004; Jones *et al*., 2005).

Localized disease is taken to mean the absence of detectable gross metastases on CT scan and the normality (or normalization subsequent to orchidectomy) of the serum tumor markers. The metastatic stage is defined by detecting gross metastases by CT-scan and/or the persistence of elevated serum tumor markers post-orchidectomy.

For metastatic tumors, an international prognostic classification has been compiled (International germ cell cancer collaborative group, 1997). The classification enables estimation of the expected 5-year survival post-appropriate treatment on the basis of two principal prognostic factors: the presence or absence of non-pulmonary visceral metastases (liver, bone or brain) and the degree of elevation of serum tumor markers (table 9.V).

Table 9.V: Expected 5-year survival by prognostic group (International prognostic classification of metastatic stages of testicular germ-cell tumors, by IGCCCG, 1997)

Prognostic group	Non-seminomatous TGT	Seminomatous TGT	5-year survival (%)
Good	AFP < 1,000 ng/mL and hCG < 5,000 IU/mL and LDH < 1.5*ULN and no non-pulmonary visceral metastases	No non-pulmonary visceral metastases	90
Intermediate	1000 < AFP < 10,000 ng/mL and 5000 < hCG < 50,000 IU/mL and 1.5N < LDH < 10N and no non-pulmonary visceral metastases	Presence of non-pulmonary visceral metastases	75
Poor	AFP > 10,000 ng/mL or hCG > 50,000 IU/mL or LDH > 10*ULN or Presence of non-pulmonary visceral metastases	No poor prognosis form	50

TGT: testicular germ-cell tumor, AFP: alpha-fetoprotein, hCG: human chorionic gonadotropin; LDH: lactate dehydrogenase; ULN: upper limit of normal range

Influence of treatment on survival

According to the management principles reported by Mottet *et al*. (2004), orchidectomy is the reference treatment. The procedure enables excision of the primary tumor and histologic typing. The complementary treatments depend on the results of CT-scan staging and the assays of serum tumor markers (alpha-fetoprotein and human chorionic gonadotropin).

For localized seminomatous tumors, the reference complementary treatment remains prophylactic radiotherapy of the lumbo-aortic lymph node areas and possibly ipsilateral iliac areas. For localized non-seminomatous tumors, three approaches have been proposed: simple monitoring, lumbo-aortic lymph node curettage and adjuvant chemotherapy. The decision is made on the basis of the histologic characteristics of the primary tumor and the patient's preferences.

For metastatic tumors, the complementary treatments consist in either radiotherapy of the lumbo-aortic lymph node areas and ipsilateral iliac areas in the event of low-bulk seminomatous tumors, or chemotherapy. The total number of chemotherapy courses necessary is determined by the sites of the metastases and the degree of elevation of the serum tumor markers.

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Excess mortality data from the Eurocare study

Table 9.I: Annual excess mortality for men: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Men (N = 6,905)
0-1	2.80 [2.39-3.21]
1-2	1.78 [1.44-2.12]
2-3	0.63 [0.39-0.86]
3-4	0.33 [0.13-0.53]
4-5	0.33 [0.12-0.54]
5-6	0.03 [-0.14-0.21]
6-7	0.23 [-0.00-0.47]
7-8	0.32 [0.05-0.58]
8-9	0.09 [-0.15-0.34]
9-10	0.03 [-0.24-0.31]
10-11	-0.18 [-0.41-0.05]
11-12	0.09 [-0.27-0.45]

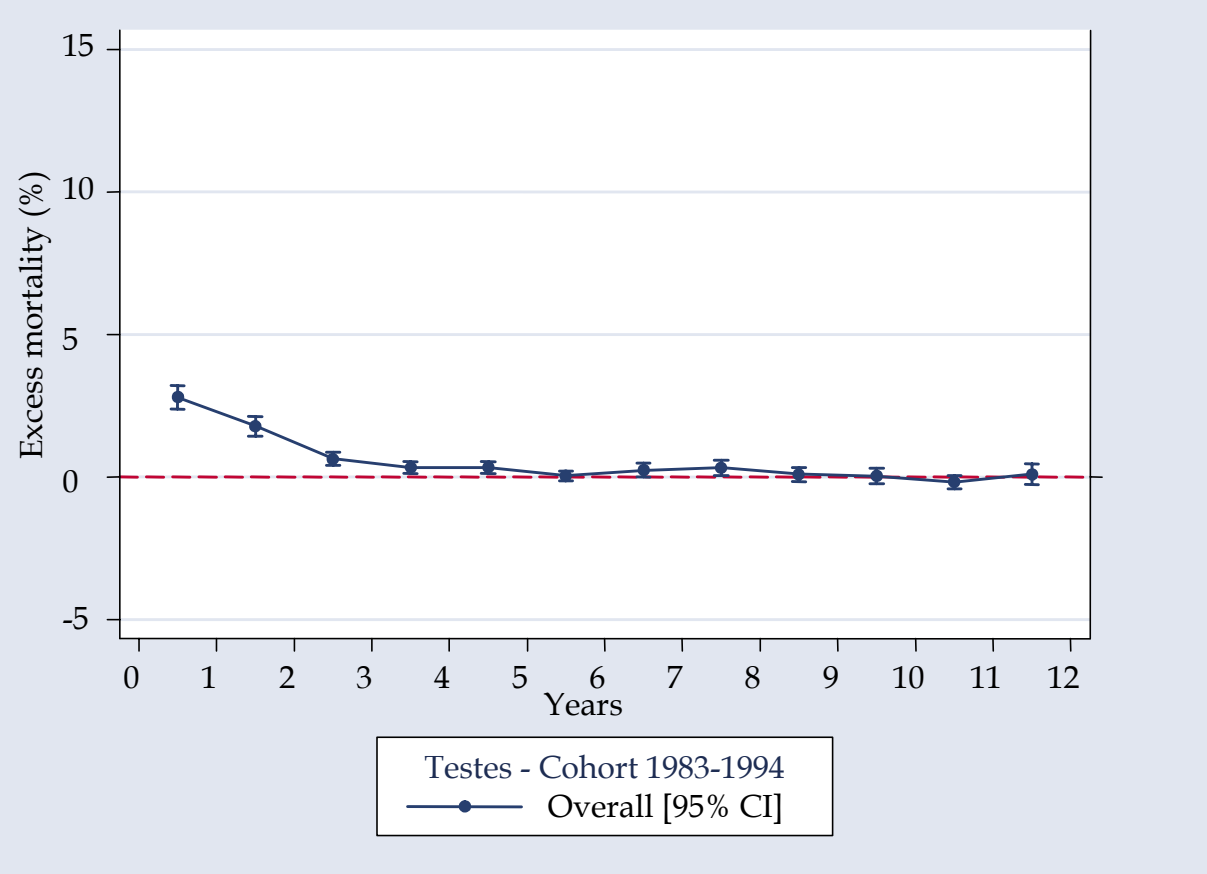

Figure 9.1: Overall annual excess mortality: diagnostic cohort 1983-1994

Table 9. II: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	15-44 years (N = 5,629)	45-54 years (N = 733)	55-64 years (N = 370)	65-74 years (N = 173)
0-1	2.02 [1.64-2.40]	4.19 [2.66-5.72]	5.02 [2.53-7.52]	18.10 [11.85-24.36]
1-2	1.81 [1.45-2.18]	1.23 [0.26-2.19]	1.84 [-0.02-3.71]	3.20 [-1.10-7.49]
2-3	0.58 [0.35-0.81]	0.64 [-0.17-1.44]	0.95 [-0.71-2.60]	1.78 [-2.32-5.87]
3-4	0.37 [0.18-0.57]	0.46 [-0.30-1.23]	-0.34 [-1.55-0.88]	-0.72 [-4.10-2.65]
4-5	0.28 [0.09-0.46]	0.16 [-0.52-0.84]	1.26 [-0.66-3.17]	1.06 [-3.32-5.44]
5-6	0.01 [-0.12-0.13]	0.02 [-0.65-0.69]	0.73 [-1.17-2.63]	-0.63 [-4.85-3.59]
6-7	0.03 [-0.12-0.18]	0.72 [-0.35-1.80]	0.70 [-1.46-2.86]	5.73 [-1.64-13.10]
7-8	0.28 [0.05-0.51]	-0.10 [-0.88-0.69]	0.76 [-1.58-3.10]	4.29 [-3.64-12.23]
8-9	0.07 [-0.12-0.27]	0.53 [-0.69-1.75]	-0.64 [-2.60-1.32]	0.30 [-7.49-8.08]
9-10	0.05 [-0.16-0.27]	0.48 [-0.93-1.90]	0.41 [-2.50-3.32]	-7.80 [-15.66-0.05]
10-11	-0.08 [-0.25-0.09]	-1.04 [-2.46-0.37]	-0.24 [-3.15-2.67]	-0.05 [-11.15-11.05]
11-12	0.32 [-0.05-0.69]	-0.62 [-1.66-0.42]	-1.94 [-4.10-0.22]	-3.30 [-13.69-7.08]

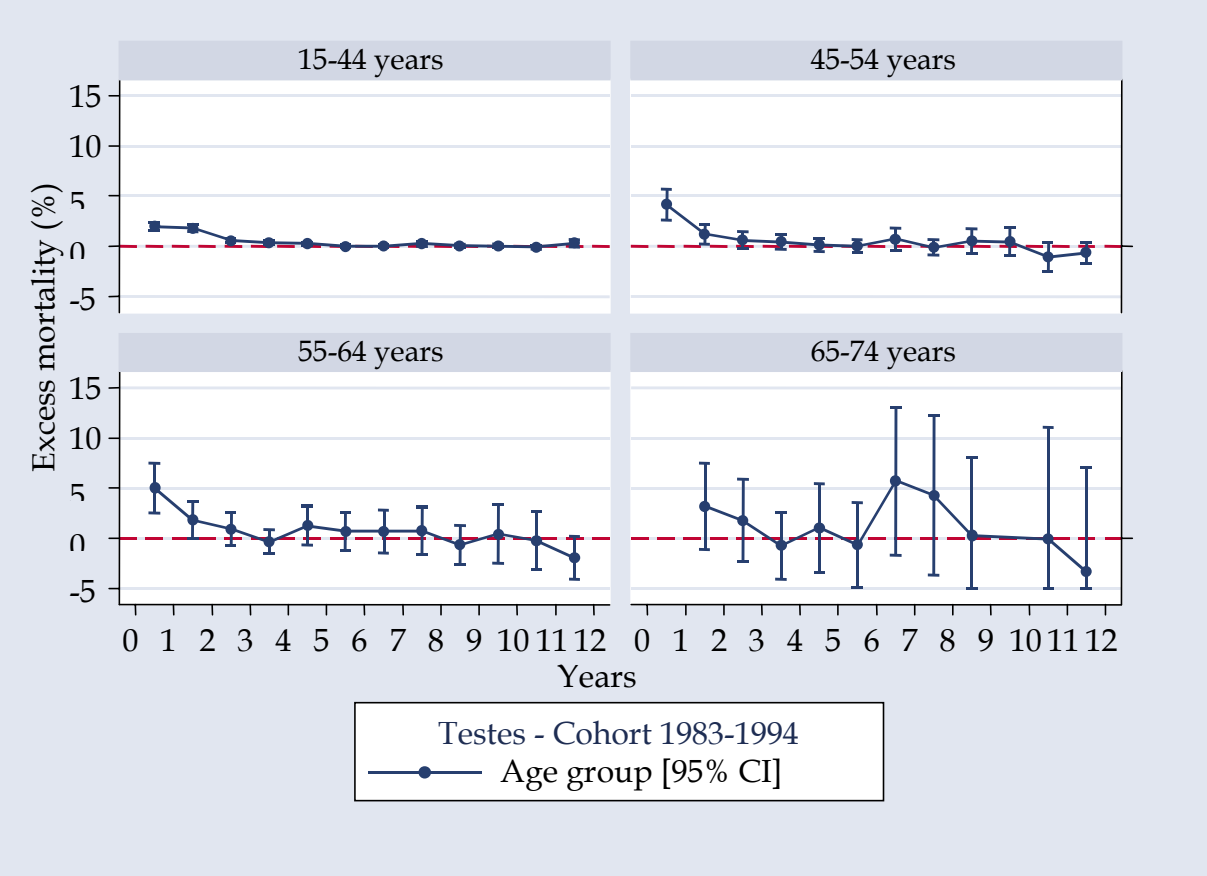

Figure 9.2: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 9.III: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 1983-1985 (N = 1,401)	Cohort 1986-1988 (N = 1,681)	Cohort 1989-1991 (N = 1,887)	Cohort 1992-1994 (N = 1,936)
0-1	4.16 [3.07-5.26]	3.20 [2.32-4.09]	1.94 [1.27-2.61]	2.30 [1.60-3.01]
1-2	3.12 [2.13-4.10]	2.04 [1.30-2.78]	1.39 [0.80-1.98]	0.99 [0.48-1.50]
2-3	0.88 [0.27-1.49]	0.62 [0.14-1.10]	0.52 [0.09-0.94]	0.57 [0.15-0.99]
3-4	0.64 [0.08-1.20]	0.22 [-0.16-0.60]	0.23 [-0.12-0.58]	0.29 [-0.06-0.65]
4-5	0.14 [-0.28-0.56]	0.54 [0.06-1.02]	-0.12 [-0.34-0.10]	0.80 [0.27-1.33]
5-6	0.04 [-0.35-0.43]	0.07 [-0.27-0.41]	0.08 [-0.23-0.40]	-0.14 [-0.44-0.16]
6-7	0.18 [-0.27-0.63]	0.32 [-0.11-0.75]	0.19 [-0.17-0.55]	-
7-8	0.33 [-0.18-0.84]	0.58 [0.08-1.09]	0.02 [-0.32-0.36]	-
8-9	-0.02 [-0.42-0.38]	0.04 [-0.31-0.39]	0.33 [-0.26-0.93]	-
9-10	-0.04 [-0.44-0.36]	0.09 [-0.29-0.47]	-	-
10-11	-0.24 [-0.57-0.09]	-0.13 [-0.46-0.20]	-	-
11-12	-0.16 [-0.53-0.21]	0.50 [-0.23-1.24]	-	-

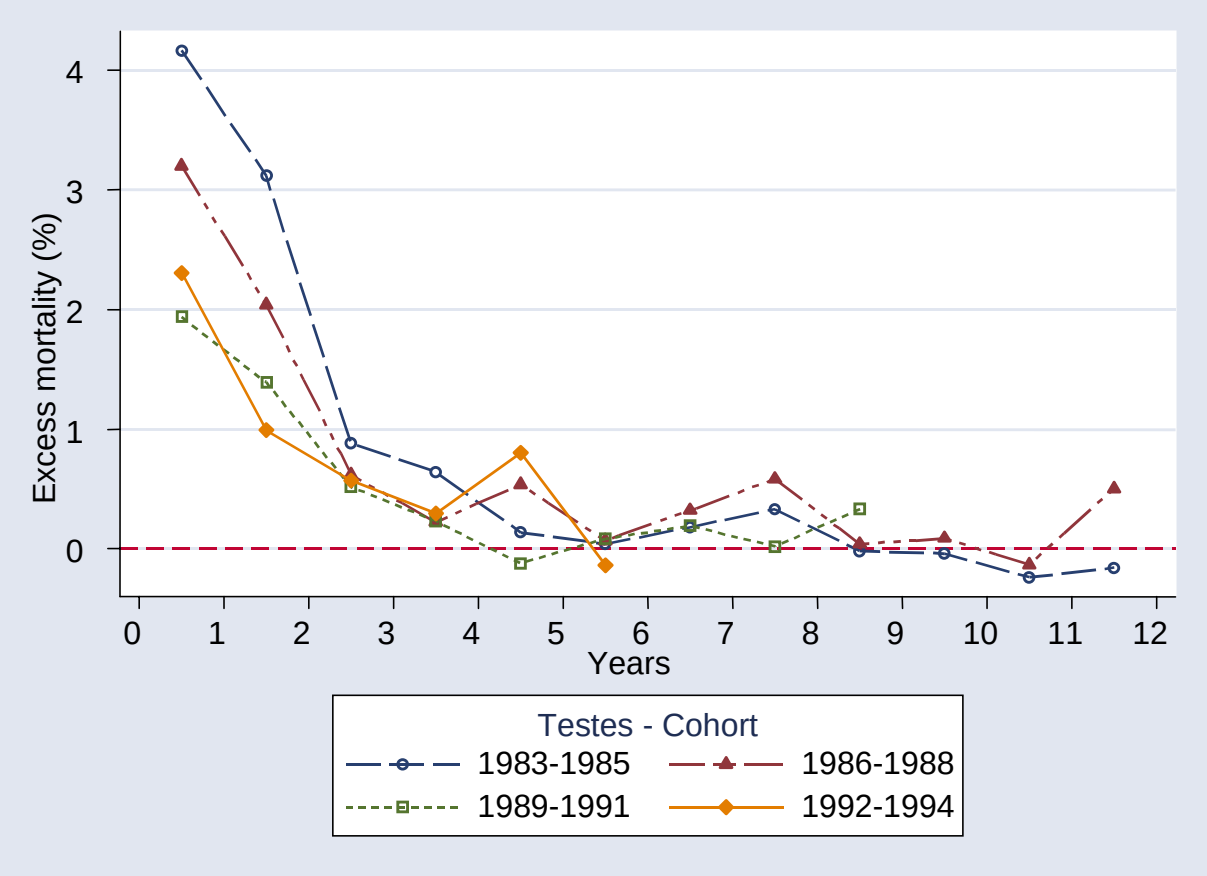

Figure 9.3: Time course of annual excess mortality by cohort

10

Kidney cancer

With an estimated number of new cases in France in 2000 of 8,300, kidney cancer accounts for 3% of all incident cancers (Remontet *et al*., 2003). The age-standardized incidence rates (world population) were 12.2/100,000 for men and 5.7/100,000 for women. The sex ratio was 2.1 (Remontet *et al*., 2003). The incidence increased from the oldest birth cohorts to the most recent birth cohorts.

Over the last two decades, the overall incidence rate has increased by 2.70% per year for men and 3.74% per year for women. The annual mortality rate has only very slightly increased over those two decades. The age-standardized mortality rates (world population) were 4.6/100,000 for men and 1.7/100,000 for women.

The median age at diagnosis was 67 years for men and 70 years for women. Incidence peaks at about age 70 years.

According to the Eurocare data, for diagnostic cohort 1992-1994, the 5-year relative survival is 59.7% for all stages taken together and the eight countries selected. In the context of the Eurocare study, the term 'kidney cancer' includes tumors of the renal parenchyma and tumors of the urinary excretory tract (except the bladder), those two tumor types accounting for 80 and 20% of the total, respectively.

Annual excess mortality (all stages considered): Eurocare data

Table 10.I shows the estimates for overall annual excess mortality with their 95% confidence intervals. The data take into account all patients whose kidney cancer was diagnosed between 1983 and 1994 in Europe (eight countries). The annual excess mortality was less than 5% as of year 5 post-diagnosis, then fell regularly to about 2% from year 10 to 12 post-diagnosis (figure 10.1).

Table 10.II shows the annual excess mortality estimates by gender. There was no difference between the early and late annual excess mortalities of men and women. The time courses of annual excess mortality were similar for the two genders (figure 10.2). For both genders, the annual excess mortality reached 2% beyond the 10th year post-diagnosis.

Table 10.III shows the annual excess mortality results for the various age groups. The age at diagnosis influenced both early and late annual excess mortality. Annual excess mortality was less than 2% as of year 7 for age group 15-44 years, while it remained greater than 2% for the other 3 age groups (figure 10.3).

Annual excess mortality data for the 4 cohorts are shown in table 10.IV. The diagnosis period influences the early annual excess mortality (figure 10.4).

Very long-term annual excess mortality (all stages considered): other studies

Three sources of population data are available for evaluation of the very long-term annual excess mortality associated with kidney cancer: the data generated by the US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the data of the Finnish and Swedish national cancer registries.

Brenner (2002) evaluated the 5-, 10-, 15- and 20-year relative survivals of patients whose kidney cancer (parenchyma and proximal excretory pathways) was diagnosed between 1973 and 1998 using the US SEER program data. The relative survival estimates, calculated using the period analysis method (which takes into account the survival observed over the first years following diagnosis for the more recent periods) were 61.8, 54.4, 49.8 and 47.3%, respectively. The mean annual excess mortality rate was estimated to be 1.7% between 10 and 15 years post-diagnosis and of the order of 1% between 15 and 20 years post-diagnosis.

Brenner and Hakulinen (2001) estimated the very long-term relative survivals of patients presenting with kidney cancer using the data from the Finnish national cancer registry. For patients diagnosed between 1985 and 1997, the 5-, 10-, 15- and 20-year relative survivals estimated using the period analysis method were 58.3, 50.3, 46.1 and 42.5%, respectively. The mean annual excess mortality was estimated to be of the order of 1.7% between 10 and 20 years post-diagnosis.

For patients presenting with kidney cancer (except renal pelvis cancer) diagnosed between 1965 and 1996, Talbäck *et al*. (2004) determined the 5-, 10- and 15-year relative survivals from the data in the Swedish national cancer registry. Using the period analysis method, the authors estimated the relative survivals to be 51.7, 40.5 and 36.0% at 5, 10 and 15 years, respectively. Those results are comparable to the 5-, 10- and 15-year relative survivals observed for patients diagnosed during the most recent period. The results were 54.1, 42.0 and 32.5%, respectively. The annual excess mortality rate was estimated to be of the order of 2.3% for the period 10-15 years post-diagnosis.

Long-term relative survival or excess mortality by stage

In the PETRI study (Ile-de-France, 2004), the 5-year relative survivals were 69% for men and 67% for women presenting with kidney cancer. For patients presenting with stage I kidney cancer, the 5-year survival rate was 100%. For patients with stage III at diagnosis, the relative survival rate was 71%. The relative survival rate fell to 17% for patients presenting with stage IV at diagnosis (no stage II in the data).

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated relative survival data by year for three disease stages—localized, regional and metastatic (distant metastases)—and a non-determined stage (insufficient information in the base to determine the stage). Annual excess mortalities by kidney cancer stage (kidney and renal pelvis) have been calculated from the relative survival data (table 10.V). The stage distribution (localized, regional and metastatic) of the cases of kidney cancer was as follows: 50.3, 21.4 and 22.4%. The results cover men and women, all ages considered, for the diagnostic period 1988-2001.

Table 10.V: Annual excess mortality by stage at diagnosis for the period 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease (N+)	Metastatic disease (M+)
0-1	2.9	16.3	67.8
1-2	2.3	12.1	44.1
2-3	1.8	7.7	26.1
3-4	2.0	5.7	19.5
4-5	1.8	5.2	10.3
5-6	1.6	4.1	11.5
6-7	1.5	4.5	7.1
7-8	1.4	2.9	3.8
8-9	1.4	3.3	2.6
9-10	2.1	4.2	5.4

For localized disease, the results show an annual excess mortality of the order of 1.5% from year 6 post-diagnosis.

Influence of other prognostic factors

Damhuis *et al*. (1998) analyzed the Eurocare data from 45 registries in 17 European countries (24,000 patients). Marked between-country differences in relative survivals were observed (differences in stage distribution were suggested but the differences were not demonstrated in the study). The authors reported an improvement in 5-year relative survival over time and a marked effect of age at diagnosis (5-year relative survival of 63% for age group 15-44 years vs. 36% for patients aged over 75 years, all stages considered, for the relatively old diagnostic period 1985-1989).

For the patients with localized disease, the three main prognostic factors identified by the multifactorial analyses and liable to predict overall survival were TNM disease stage, general condition (WHO scale) and the degree of tumor differentiation as determined by the Führman histologic score (Zisman *et al*., 2001; Frank *et al*., 2005; Patard *et al*., 2005). Those three independent prognostic factors were used to compile a nomogram taking into account the weight of each prognostic factor in its continuity (Sorbellini *et al*., 2005). A prognostic group classification compiled using the data on patients treated at the University of Los Angeles (Zisman *et al*., 2001) was also taken into account. A good prognosis was defined by a stage T1N0M0, a grade 1 or 2 and a WHO score of 0. A poor prognosis was defined as a tumor of size T4 or T3 associated with a grade > 1 and a WHO score ≥ 1. Patients not meeting either set of criteria were considered to have an intermediate prognosis (Zisman *et al*., 2001). In an independent model-validation population (3,119 patients), the relative 5-year survivals were 92, 67 and 44% for the patients with good, intermediate and poor prognoses (Patard *et al*., 2004).

Treatment is determined by disease stage at diagnosis. For localized disease, the reference treatment is surgery (radical nephrectomy or possibly partial nephrectomy as a function of tumor size and location). For already metastatic tumors, nephrectomy is considered for young patients in good general condition. In recent years, systemic treatment has mainly been based on immunotherapy (interferon α and interleukin 2). The limited efficacy and the

toxicity of that immunotherapy have led to its indications being gradually restricted to patients in good general condition presenting with a limited number of metastatic sites. The proportion of metastatic patients experiencing remission on immunotherapy is low, less than 10%. The recent development of drugs targeting neo-angiogenesis and certain intracellular molecules involved in carcinogenesis affords interesting prospects for patients who are not candidates for immunotherapy.

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Excess mortality data from the Eurocare study

Table 10.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 24,150)
0-1	26.21 [25.63-26.78]
1-2	11.98 [11.46 -12.49]
2-3	7.59 [7.12 -8.06]
3-4	5.44 [5.00 -5.88]
4-5	4.59 [4.14 -5.04]
5-6	3.44 [2.98 -3.90]
6-7	3.21 [2.69 -3.73]
7-8	3.74 [3.16 -4.33]
8-9	3.07 [2.44 -3.69]
9-10	3.13 [2.38 -3.88]
10-11	1.97 [1.21 -2.72]
11-12	2.66 [1.71 -3.60]

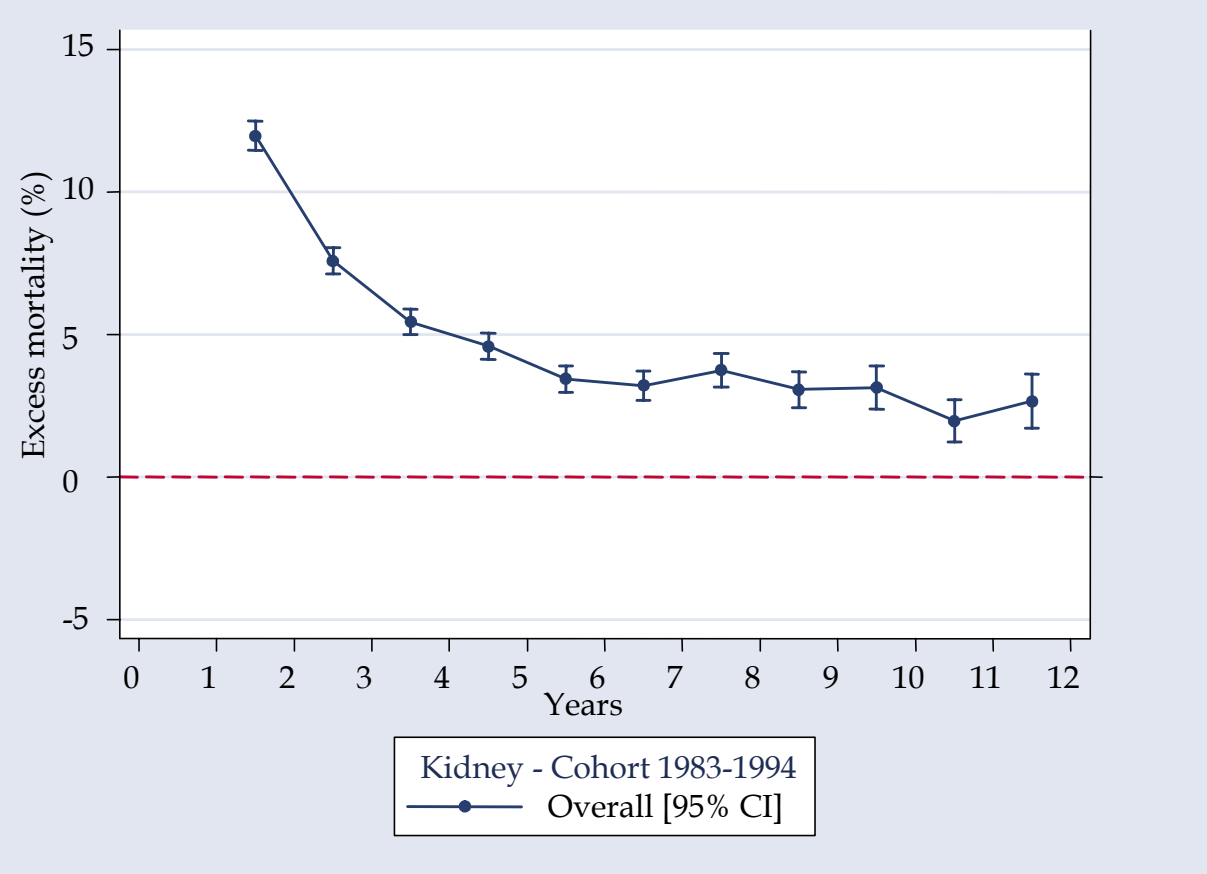

Figure 10.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 10.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 9,032)	Men (N = 15,117)
0-1	25.49 [24.58-26.41]	26.63 [25.90-27.36]
1-2	11.60 [10.79-12.41]	12.22 [11.56-12.89]
2-3	7.67 [6.94-8.41]	7.56 [6.94-8.17]
3-4	5.27 [4.59-5.94]	5.57 [4.98-6.15]
4-5	4.25 [3.59-4.92]	4.82 [4.22-5.43]
5-6	3.30 [2.63-3.98]	3.56 [2.94-4.17]
6-7	3.21 [2.44-3.98]	3.24 [2.54-3.93]
7-8	3.22 [2.39-4.05]	4.13 [3.32-4.92]
8-9	2.52 [1.64-3.39]	3.45 [2.59-4.32]
9-10	3.15 [2.04-4.25]	3.17 [2.15-4.19]
10-11	1.33 [0.31-2.34]	2.44 [1.37-3.50]
11-12	2.04 [0.76-3.33]	3.06 [1.74-4.38]

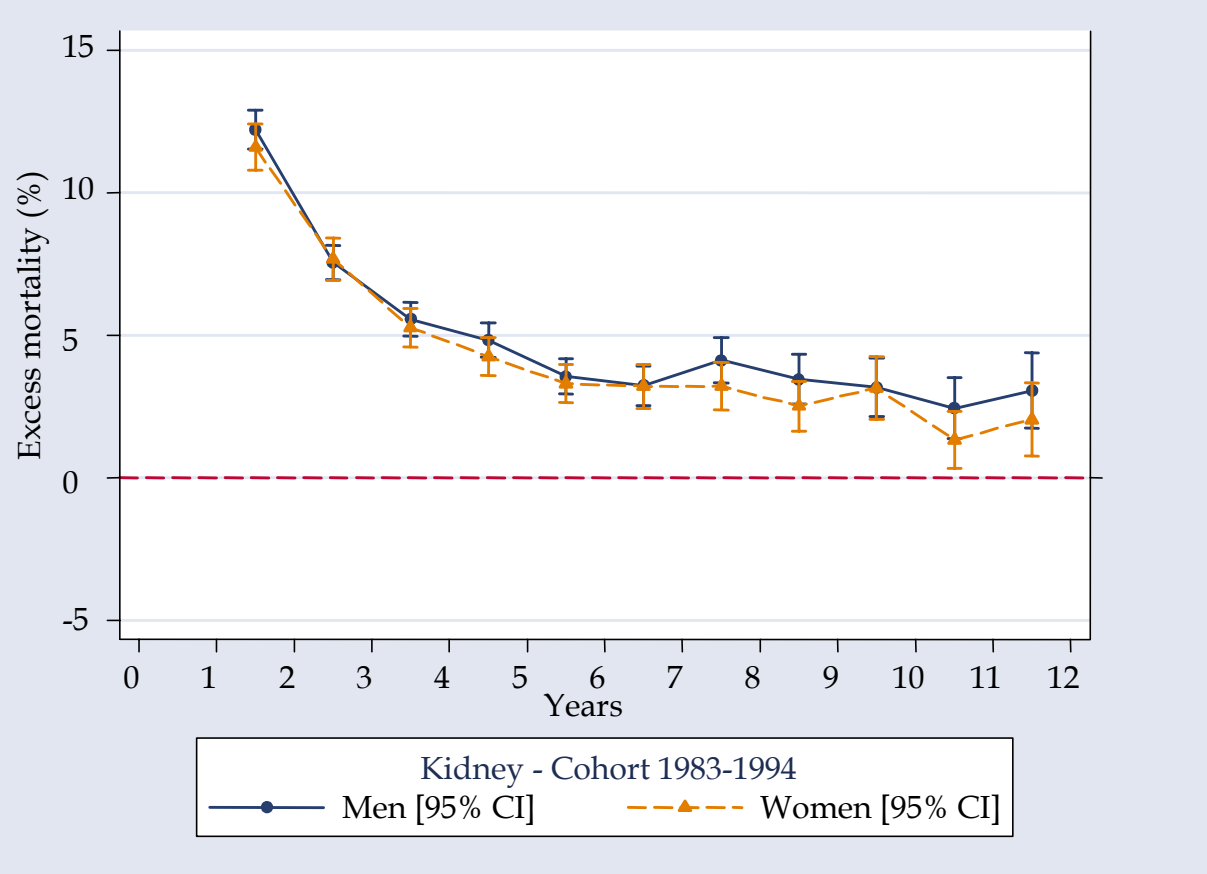

Figure 10.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 10.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) 15-44 years (N = 1,640)	45-54 years (N = 3,756)	55-64 years (N = 8,049)	65-74 years (N = 10,705)
0-1	15.53 [13.77-17.30]	20.51 [19.21-21.82]	25.64 [24.66-26.61]	30.36 [29.45-31.27]
1-2	8.38 [6.90-9.86]	10.60 [9.47-11.73]	12.10 [11.23-12.97]	13.16 [12.30-14.03]
2-3	4.49 [3.32-5.66]	6.06 [5.11-7.01]	8.18 [7.37-8.99]	8.43 [7.61-9.25]
3-4	3.38 [2.32-4.43]	3.68 [2.88-4.48]	5.61 [4.86-6.35]	6.59 [5.77-7.41]
4-5	2.59 [1.61-3.57]	4.14 [3.26-5.03]	4.54 [3.80-5.28]	5.35 [4.50-6.20]
5-6	1.83 [0.93-2.72]	2.93 [2.09-3.77]	3.55 [2.80-4.30]	4.03 [3.13-4.93]
6-7	2.26 [1.17-3.35]	3.54 [2.51-4.56]	3.26 [2.42-4.09]	3.26 [2.23-4.28]
7-8	1.79 [0.75-2.83]	3.79 [2.67-4.91]	2.76 [1.90-3.61]	5.38 [4.12-6.64]
8-9	1.34 [0.33-2.35]	2.42 [1.37-3.48]	2.77 [1.81-3.72]	4.44 [3.02-5.87]
9-10	0.98 [-0.07-2.03]	2.85 [1.54-4.16]	3.20 [2.01-4.38]	4.09 [2.33-5.84]
10-11	1.89 [0.44-3.34]	1.49 [0.34-2.63]	2.11 [0.92-3.29]	2.22 [0.38-4.05]
11-12	1.57 [0.02-3.13]	2.71 [1.11-4.31]	2.87 [1.37-4.36]	2.82 [0.50-5.13]

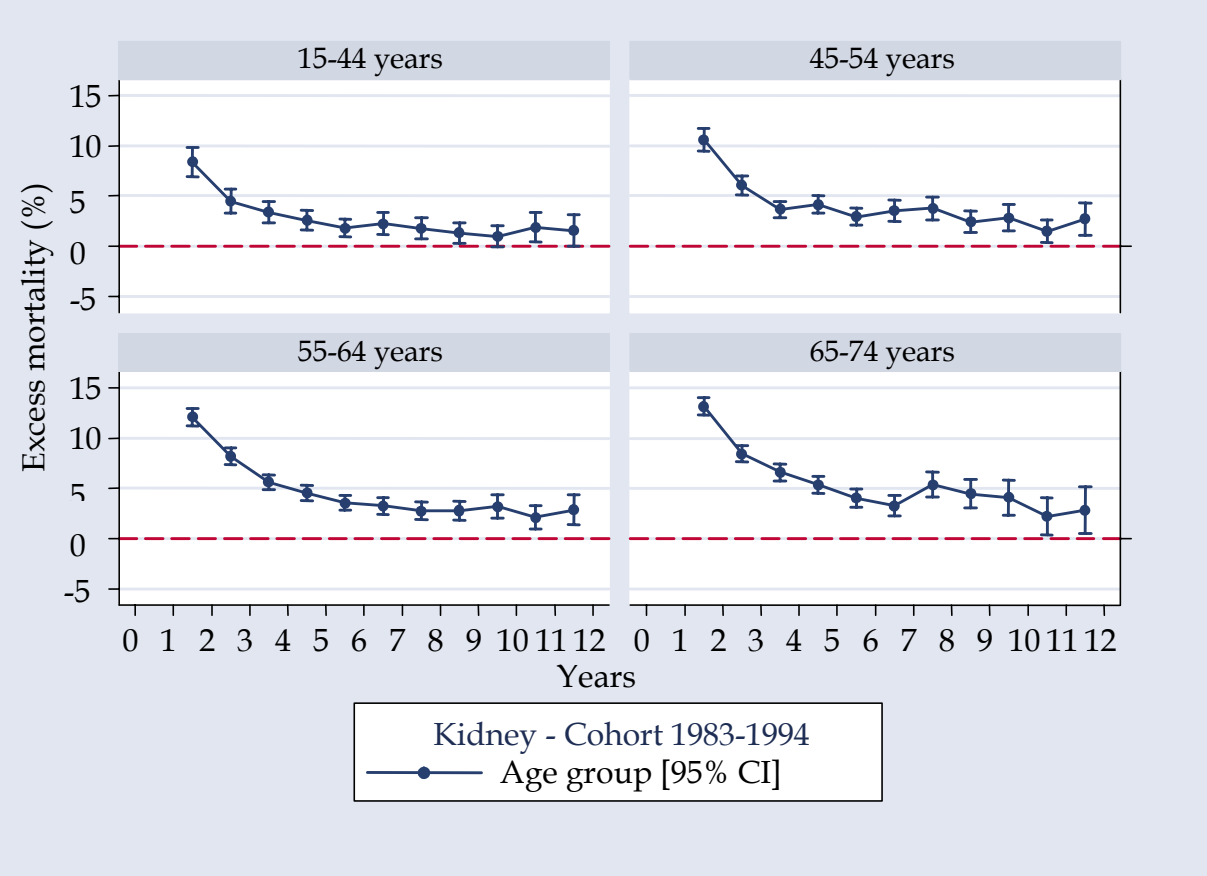

Figure 10.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 10.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (% annual) Cohort 1983-1985 (N = 5,266)	Cohort 1986-1988 (N = 6,126)	Cohort 1989-1991 (N = 6,265)	Cohort 1992-1994 (N = 6,493)
0-1	30.72 [29.44-32.01]	27.96 [26.81-29.12]	25.11 [24.00-26.22]	21.95 [20.91-23.00]
1-2	14.78 [13.55-16.01]	12.92 [11.85-13.98]	10.96 [9.99-11.94]	10.10 [9.19-11.00]
2-3	8.88 [7.75-10.01]	7.86 [6.89-8.82]	7.68 [6.76-8.59]	6.42 [5.60-7.24]
3-4	5.64 [4.61-6.67]	5.96 [5.03-6.88]	5.18 [4.34-6.03]	5.11 [4.32-5.91]
4-5	4.88 [3.86-5.91]	5.39 [4.45-6.33]	3.93 [3.12-4.74]	4.26 [3.40-5.12]
5-6	4.14 [3.12-5.17]	3.88 [2.99-4.77]	2.65 [1.90-3.41]	3.19 [2.12-4.26]
6-7	4.16 [3.09-5.23]	3.21 [2.33-4.10]	2.53 [1.75-3.31]	-
7-8	3.88 [2.77-4.98]	4.01 [3.03-4.99]	3.33 [2.37-4.29]	-
8-9	3.25 [2.14-4.36]	3.08 [2.13-4.04]	2.76 [1.51-4.01]	-
9-10	3.63 [2.44-4.81]	2.74 [1.76-3.71]	-	-
10-11	1.86 [0.78-2.94]	2.06 [1.00-3.11]	-	-
11-12	2.95 [1.71-4.19]	2.15 [0.70-3.59]	-	-

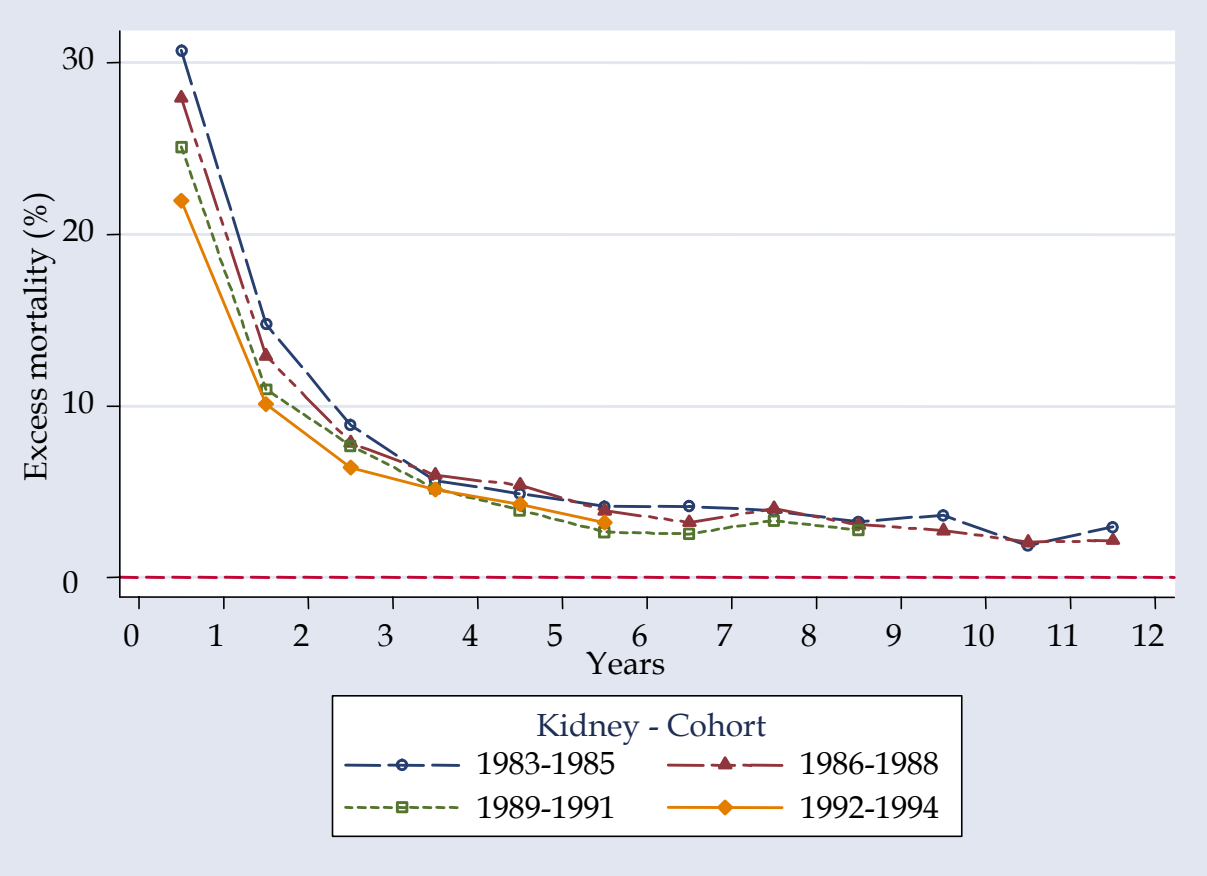

Figure 10.4: Time course of annual excess mortality by cohort

11

Colon cancer

Among the cases of colorectal cancer reported in France in 2000, 65% were sited in the colon (Remontet *et al*., 2003). Colorectal cancer, the most frequent cancer in France, accounts for almost 15% of all cancers and its frequency is continuing to rise. The incidence is estimated to be nearly 36,000 new cases per year.

Colon cancer incidence in France was estimated using registry data (Parkin *et al*., 1997; Menegoz *et al*., 1998; Benhamiche *et al*., 1999). The incidence of colon cancer in men ranges from 45.8/100,000 (Bas-Rhin, France) to 25.9/100,000 (Manche, France). In women, the incidence ranges from 28.4/100,000 (Haut-Rhin, France) to 17.4/100,000 (Somme, France). Colonic cancer predominantly affects men with a sex ratio of close to 1.5. The disease is rare before age 50 (5.9% of the cases in Côte d'Or, France). Subsequently, the incidence rises rapidly with age.

Each decade from age 40 to 70 years, the proportion of cases diagnosed doubles for both men and women. The mean age at the time of diagnosis is 69.5 years in men and 72.8 years in women. The incidence is the same for both genders until the age of 65 years, when the disease becomes predominant in males.

On the basis of the Eurocare data, for disease diagnosis between 1992 and 1994, the 5-year relative survival was 56.1% for all stages taken together and the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 11.I gives the overall annual excess mortality estimates with their 95% confidence intervals. The data are for patients whose disease was diagnosed between 1983 and 1994 in Europe (eight countries). The annual excess mortality was less than 5% as of year 4 post-diagnosis. Annual excess mortality subsequently falls rapidly becoming less than 1% between 9 and 12 years post-diagnosis (figure 11.1).

Table 11.II shows the annual excess mortality estimates by gender. The annual excess mortalities of men and women are fairly similar. The annual excess mortality plot for women is located slightly below that for men (figure 11.2). However, there is no statistically significant difference between the data for men and women. For both genders, the annual excess mortality becomes less than 1% after year 9 post-diagnosis.

Table 11.III shows the annual excess mortality results for various age groups. The age at diagnosis has little influence on early excess mortality and no influence on late annual excess mortality (figure 11.3).

The annual excess mortality data for the four Eurocare cohorts are shown in table 11.IV. The period of diagnosis influences the early annual excess mortality (figure 11.4).

Very long-term annual excess mortality (all stages considered): other studies

Three sources of population data are available for evaluation of the very long-term annual excess mortality associated with colonic cancer: the data generated by the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the data from the Finnish and Swedish national cancer registries.

Brenner (2002) evaluated the 10-, 15- and 20-year relative survivals of patients, whose colon cancer was diagnosed between 1973 and 1998, using the US SEER program data. The relative survival estimates, calculated using the period analysis method (which takes into account the observed survival during the first years post-diagnosis for the more recent periods) were 55.4, 53.9, 53.9 and 52.3%, respectively. For the period 15-20 years, the mean annual excess mortality rate was of the order of 0.6%.

Brenner and Hakulinen (2001) estimated the very long-term relative survival of patients presenting with colon cancer using the data from the Finnish national cancer registry. For diagnoses between 1985 and 1997, the 10-, 15- and 20-year relative survivals estimated using the period analysis method, were 55.6, 54.2 and 53.5%, respectively. For the period 15-20 years, the mean annual excess mortality rate was of the order of 0.3%.

Talbäck *et al*. (2004) estimated the 5-, 10- and 15-year relative survivals of patients presenting with colon cancer diagnosed between 1965 and 1996 using the Swedish national cancer registry data. Using the period analysis method, the authors' estimates of the relative survival were 56.6, 48.7 and 47.1% at 5, 10 and 15 years, respectively. The data are similar to the 5-, 10- and 15-year relative survivals observed for patients whose disease was diagnosed in the most recent period. Those survivals were 56.8, 47.7 and 44.5%. For the period, 10-15 years, the mean annual excess mortality estimate was of the order of 0.7%.

The data from the various studies show that the annual excess mortality remote from the diagnosis (period: 15-20 years) is extremely low, between 0.3 and 0.6%.

Long-term relative survival or annual excess mortality by stage

The French Côte d'Or registry includes relative survival data by stage (TNM) of colon cancer for a 10-year period. The 5-year relative survivals for patients with stage I, II, III and IV disease at the time of diagnosis were 93.9, 73.5, 47.5 and 4.4%, respectively. The 10-year relative survivals were 83.15, 66.15 and 37.8% for stages I, II and III. The results cover men and women of all ages for a diagnostic period from 1990 to 2000. The 5- and 10-year mean annual excess mortality estimates were of the order of 1% for stage I disease and 2% for stage II disease.

Influence of other prognostic factors and treatment on survival

Between 1975 and 1990, the prognosis improved with the number of recoveries increasing from 1 out of 3 to 1 out of 2. This progress is due to the development of colonoscopy. The investigation results in earlier diagnosis and an increase in the proportion of resected tumors (92% for colonic cancer in 2000 according to the French registry network covering 12 administrative departments). The progress is also a consequence of reduced operative mortality: 11% for the period 1976-1979 and 3% for the period 1996-2000 (Arveux *et al*., 1997; Faivre-Finn *et al*., 2002). Since 1990, the progress has been modest. It remains too early to evaluate the benefits related to the emergence of effective adjuvant and palliative treatments.

The risk of colorectal cancer is increased 2- or 3-fold for subjects presenting with a personal history of colorectal cancer or adenoma of dimension greater than 1 cm or in 1st degree relatives of subjects with colorectal cancer. The risk is also high in the event of ulcerative colitis or Crohn's disease that is extensive at the time of diagnosis. The risk is very high in the event of familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). In such families, almost 1 person out of 2 will present with colorectal cancer.

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Excess mortality data from the Eurocare study

Table 11.I: Annual excess mortality: diagnostic cohort 1983-1994

Interval (year)	Excess mortality [95% CI] (annual %) Overall (N = 52,720)
0-1	24.20 [23.82-24.57]
1-2	14.12 [13.76 -14.49]
2-3	9.24 [8.89 -9.58]
3-4	6.13 [5.81 -6.45]
4-5	4.44 [4.13 -4.75]
5-6	2.88 [2.57 -3.19]
6-7	2.20 [1.87 -2.53]
7-8	1.46 [1.13 -1.79]
8-9	1.16 [0.80 -1.53]
9-10	0.91 [0.49 -1.34]
10-11	1.14 [0.66 -1.62]
11-12	0.40 [-0.13 -0.93]

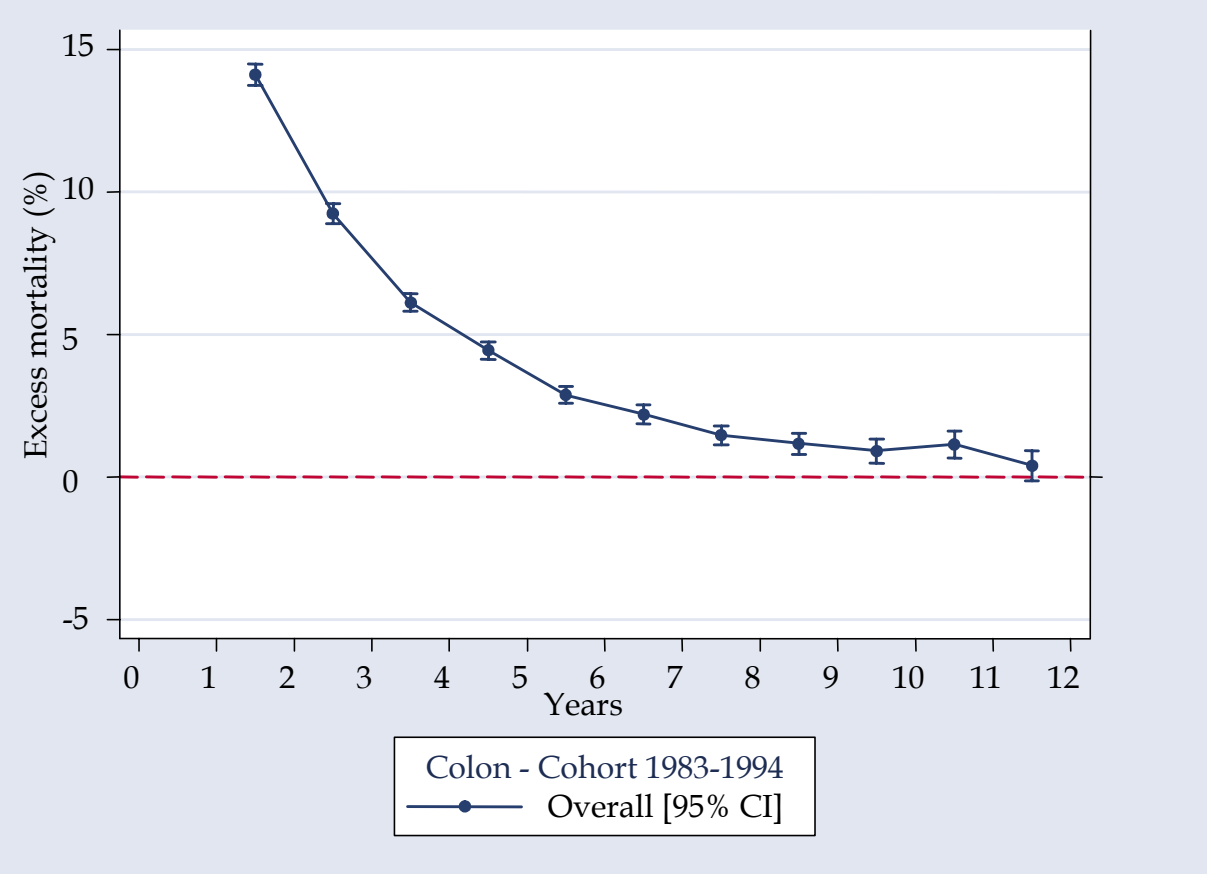

Figure 11.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 11.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 25,595)	Men (N = 27,125)
0-1	23.17 [22.64-23.70]	25.18 [24.64-25.72]
1-2	13.77 [13.27-14.28]	14.48 [13.95-15.01]
2-3	8.95 [8.48-9.41]	9.55 [9.04-10.06]
3-4	5.81 [5.39-6.23]	6.47 [5.99-6.96]
4-5	3.80 [3.41-4.19]	5.15 [4.66-5.64]
5-6	2.68 [2.30-3.07]	3.14 [2.66-3.62]
6-7	1.83 [1.43-2.24]	2.68 [2.14-3.22]
7-8	1.33 [0.92-1.73]	1.70 [1.15-2.25]
8-9	1.31 [0.86-1.77]	1.08 [0.49-1.67]
9-10	0.88 [0.36-1.40]	1.07 [0.36-1.78]
10-11	0.81 [0.24-1.38]	1.67 [0.85-2.49]
11-12	0.64 [-0.01-1.30]	0.11 [-0.75-0.98]

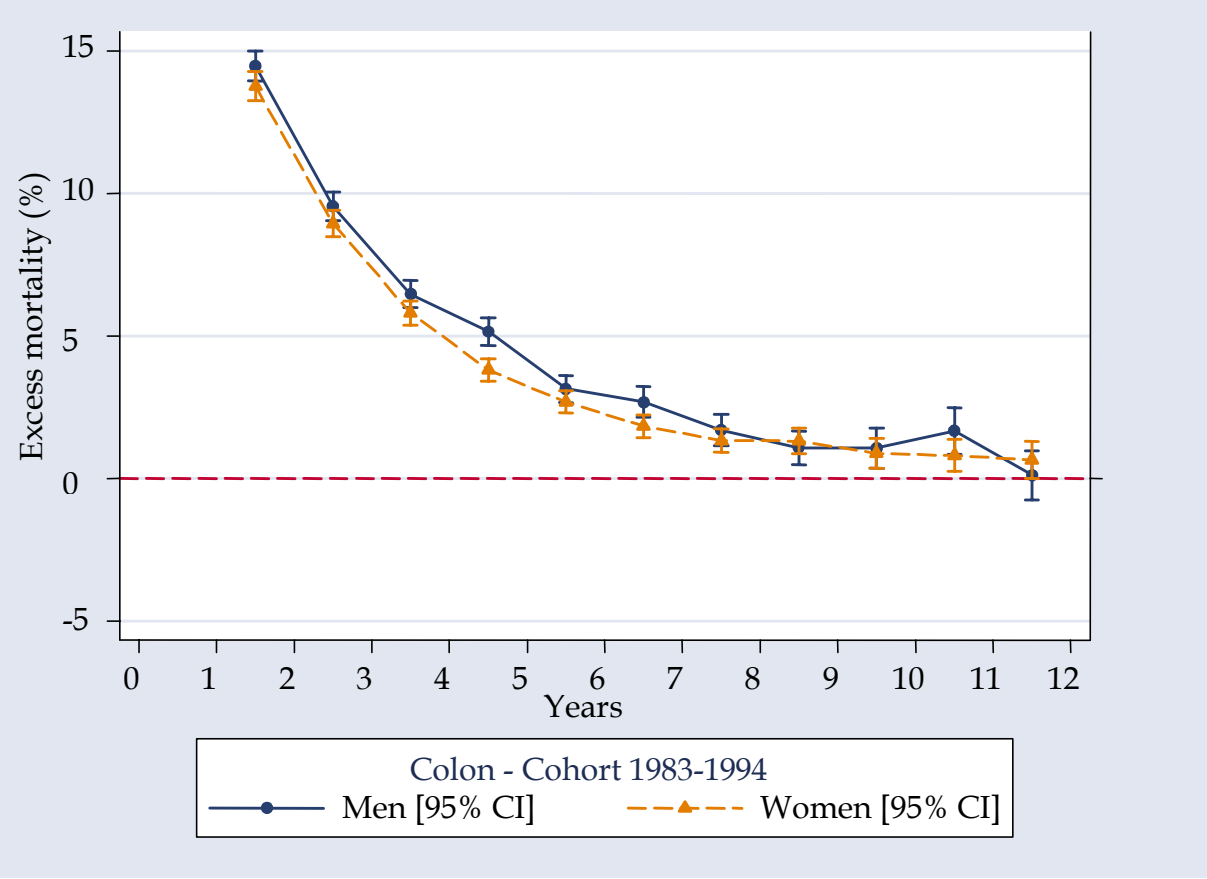

Figure 11.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 11.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	15-44 years (N = 3,116)	45-54 years (N = 6,353)	55-64 years (N = 15,715)	65-74 years (N = 27,536)
0-1	18.96 [17.58-20.34]	20.90 [19.89-21.91]	23.28 [22.60-23.95]	26.11 [25.57-26.66]
1-2	12.83 [11.52-14.15]	14.50 [13.51-15.49]	14.17 [13.52-14.82]	14.17 [13.63-14.70]
2-3	8.69 [7.50-9.88]	10.18 [9.25-11.10]	9.52 [8.92-10.13]	8.89 [8.38-9.39]
3-4	4.46 [3.53-5.39]	5.63 [4.86-6.40]	6.31 [5.76-6.87]	6.38 [5.88-6.87]
4-5	3.36 [2.51-4.22]	4.46 [3.73-5.20]	4.82 [4.28-5.36]	4.36 [3.87-4.85]
5-6	2.02 [1.29-2.76]	2.96 [2.29-3.63]	2.74 [2.25-3.24]	3.09 [2.58-3.60]
6-7	1.88 [1.09-2.66]	2.37 [1.67-3.06]	2.19 [1.66-2.71]	2.21 [1.64-2.78]
7-8	1.03 [0.39-1.67]	1.56 [0.92-2.20]	1.34 [0.84-1.84]	1.59 [0.99-2.19]
8-9	0.73 [0.12-1.34]	1.14 [0.50-1.78]	0.77 [0.25-1.28]	1.55 [0.86-2.24]
9-10	0.76 [0.03-1.48]	1.10 [0.37-1.84]	0.79 [0.18-1.40]	0.97 [0.15-1.79]
10-11	1.44 [0.46-2.41]	0.45 [-0.20-1.11]	1.93 [1.15-2.71]	0.68 [-0.23-1.59]
11-12	0.23 [-0.40-0.85]	1.49 [0.50-2.48]	0.02 [-0.68-0.73]	0.33 [-0.75-1.42]

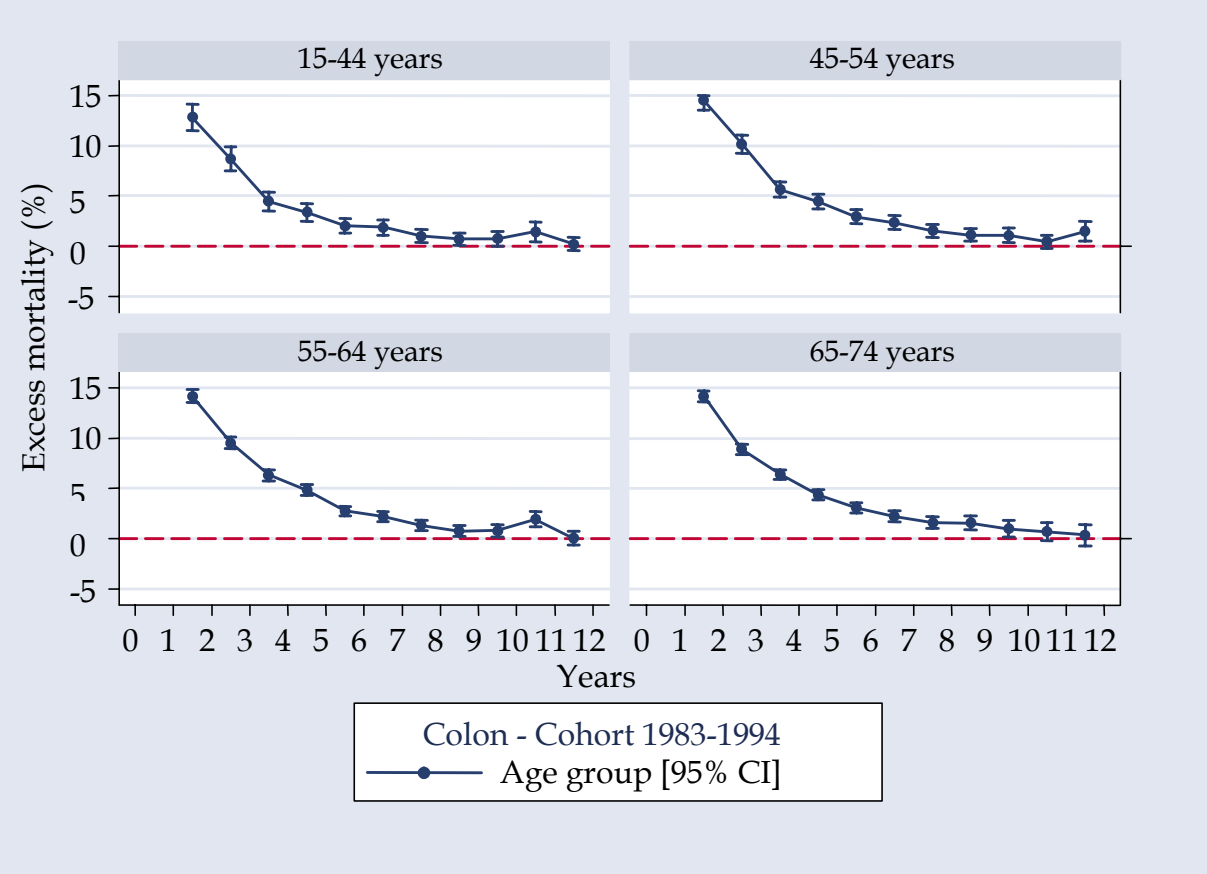

Figure 11.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 11.IV: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 1983-1985 (N = 11,327)	Cohort 1986-1988 (N = 13,364)	Cohort 1989-1991 (N = 13,528)	Cohort 1992-1994 (N = 14,501)
0-1	26.70 [25.85-27.54]	25.38 [24.61-26.14]	23.82 [23.08-24.56]	21.51 [20.81-22.20]
1-2	15.41 [14.57-16.24]	14.84 [14.09-15.58]	13.78 [13.07-14.49]	12.88 [12.22-13.54]
2-3	9.60 [8.82-10.38]	9.63 [8.92-10.33]	8.81 [8.15-9.48]	9.03 [8.40-9.66]
3-4	6.80 [6.06-7.55]	5.63 [5.00-6.26]	6.52 [5.88-7.15]	5.72 [5.15-6.30]
4-5	4.25 [3.57-4.93]	5.01 [4.38-5.65]	4.10 [3.52-4.68]	4.36 [3.75-4.96]
5-6	2.42 [1.79-3.04]	3.41 [2.81-4.01]	2.51 [1.98-3.03]	3.26 [2.50-4.02]
6-7	2.11 [1.48-2.74]	2.37 [1.80-2.94]	2.11 [1.58-2.64]	-
7-8	1.62 [0.98-2.25]	1.33 [0.79-1.87]	1.43 [0.86-2.00]	-
8-9	1.15 [0.52-1.79]	1.26 [0.70-1.83]	0.93 [0.19-1.67]	-
9-10	0.86 [0.22-1.51]	0.96 [0.38-1.53]	-	-
10-11	1.18 [0.48-1.88]	1.08 [0.41-1.74]	-	-
11-12	0.38 [-0.30-1.07]	0.38 [-0.47-1.22]	-	-

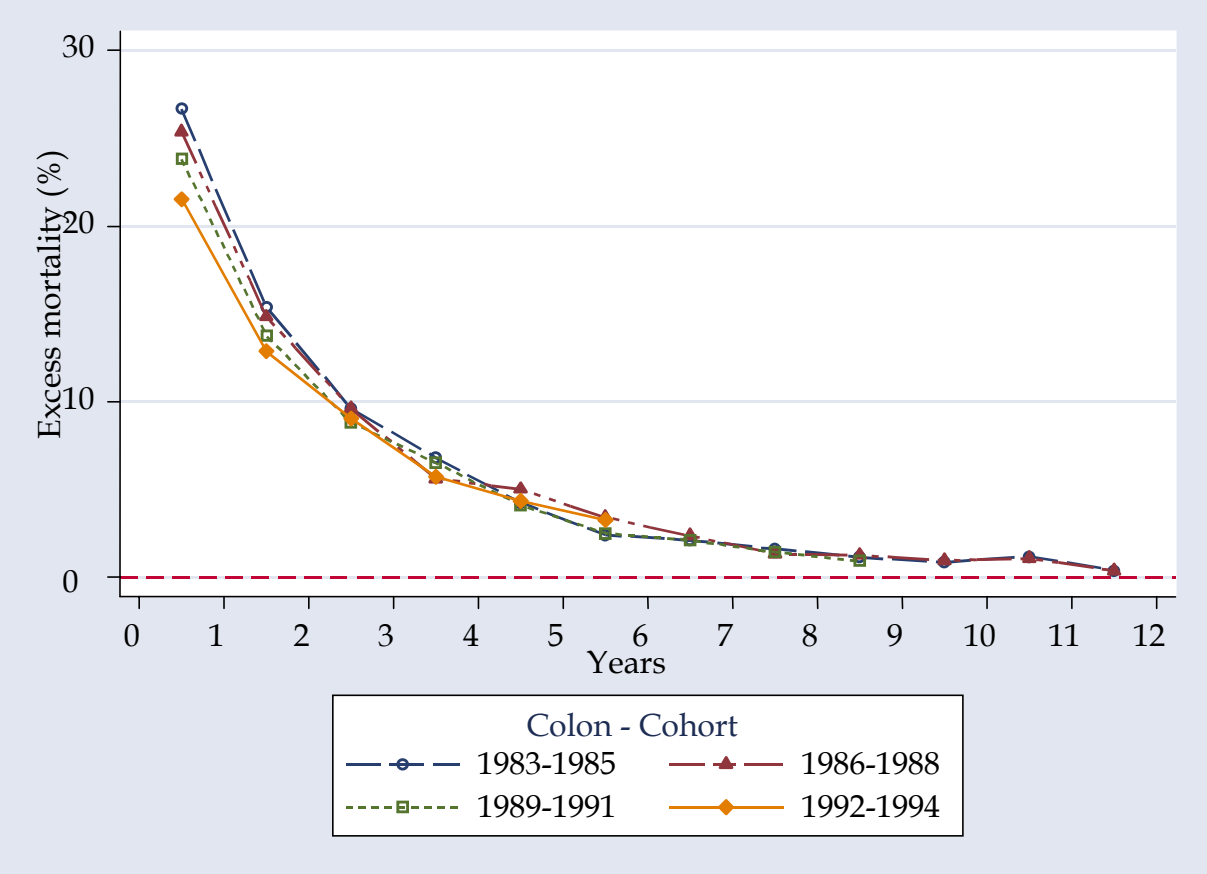

Figure 11.4: Time course of annual excess mortality by cohort

12

Rectal cancer

In all, 25% of the colorectal cancers reported in France in 2000 were located in the rectum (Remontet *et al*., 2003).

Rectal cancer incidence in France was estimated from the registry data (Parkin *et al*., 1997; Menegoz *et al*., 1998; Benhamiche *et al*., 1999). For men, the incidence rates ranged between 29.3/100,000 (Bas-Rhin) and 19.4/100,000 (Hérault) and, for women, between 15.5/100,000 (Calvados) and 10.3/100,000 (Loire-Atlantique).

The Eurocare data on patients whose rectal cancer was diagnosed between 1992 and 1994 showed a 5-year relative survival of 57.5% for all stages taken together and the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 12.I shows the overall annual excess mortality estimates with their 95% confidence intervals. The data covers patients whose rectal cancer was diagnosed between 1983 and 1994 in Europe (eight countries). The annual excess mortality was less than 5% as of year 6 post-diagnosis, then fell regularly to less than 2% between 9 and 12 years post-diagnosis (figure 12.1).

Table 12.II shows the annual excess mortality estimates as a function of gender. The time course of annual excess mortality was similar for men and women. The annual excess mortality plot for women was slightly lower than that for men (figure 12.2). There was no significant difference between men and women except between year 3 and year 6 post-diagnosis. For women, the annual excess mortality was less than 2% after year 8 post-diagnosis.

Table 12.III shows the annual excess mortality results for the various age groups. Age at diagnosis had little influence on early or late annual excess mortality (figure 12.3).

The annual excess mortality data for the 4 cohorts are shown in table 12.IV. The period of diagnosis influenced early annual excess mortality (figure 12.4).

Very long-term annual excess mortality (all stages considered): other studies

Three sources of population data are available for the evaluation of the very long-term annual excess mortality associated with rectal cancer: the data of the US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the data from the Finnish and Swedish national cancer registries.

Brenner (2002) reported 10-, 15- and 20-year relative survivals for patients whose rectal cancer was diagnosed between 1973 and 1998, using the US SEER program data. The relative survival estimates calculated using the period analysis method (which takes into account the

survival observed over the first years post-diagnosis for the more recent periods) were 55.2, 51.8 and 49.2%, respectively. The mean annual excess mortality estimate for the period 15-20 years was of the order of 1.0%.

Brenner and Hakulinen (2001) estimated the very long-term relative survivals of patients presenting with rectal cancer using the Finnish national cancer registry data. For patients diagnosed between 1985 and 1997, the 10-, 15- and 20-year relative survivals estimated using the period analysis method were 48.1, 48.2 and 47.9%, respectively. The mean annual excess mortality estimate was of the order of 0.1% for the period, 15-20 years. As of year 10 post-diagnosis, the mean annual excess mortality rate was almost nil.

Talbäck *et al*. (2004) evaluated the 5-, 10- and 15-year relative survivals for patients presenting with rectal cancer diagnosed between 1965 and 1996 using the data from the Swedish national cancer registry. Using the period analysis method, the authors estimated the 5-, 10- and 15-year relative survivals to be 55.1, 42.9 and 40.0%, respectively. Those data are similar to the 5-, 10- and 15-year relative survivals observed for patients whose disease was diagnosed during the most recent period: 56.7, 43.7 and 39.9%. The mean annual excess mortality estimate for the period 10-15 years was of the order of 1.4%.

The results of the various studies show that the annual excess mortality remote from diagnosis (period: 15-20 years) is extremely low, of the order of 1%.

Long-term relative survival or excess mortality by stage

The French Côte d'Or registry has generated data on relative survival by stage (TNM) of rectal cancer for a 10-year period. The 5-year relative survivals of patients with a diagnosis of stage I, II, III and IV disease were 86.7, 61.1, 36.0 and 5.6%, respectively. The 10-year relative survivals were 76.3 and 40.9% for disease stages I and II, respectively. The results cover men and women of all ages for a diagnostic period from 1990 to 2000. The 5- and 10-year mean annual excess mortality estimates were 2.5% for stage I and 7.7% for stage II.

Influence of other prognostic factors and treatment on survival

The marked progress between 1975 and 1990 was due to the development of colonoscopy. The investigation results in earlier diagnosis and management and in an increase in the proportion of resected tumors (85% for rectal cancer in 2000 as reported by the French registry network covering 12 administrative departments) and due to a decrease in operative mortality (11% for the period 1976-1979, 3% for the period 1996-2000) (Arveux *et al*., 1997; Faivre-Finn *et al*., 2002).

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Excess mortality data from the Eurocare study

Table 12.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 34,990)
0-1	18.13 [17.71-18.56]
1-2	14.16 [13.72 -14.59]
2-3	11.60 [11.16 -12.04]
3-4	8.47 [8.04 -8.90]
4-5	6.44 [6.02 -6.87]
5-6	5.01 [4.56 -5.45]
6-7	3.46 [3.00 -3.93]
7-8	2.20 [1.74 -2.65]
8-9	2.11 [1.60 -2.62]
9-10	1.44 [0.87 -2.02]
10-11	1.89 [1.24 -2.55]
11-12	1.00 [0.28 -1.71]

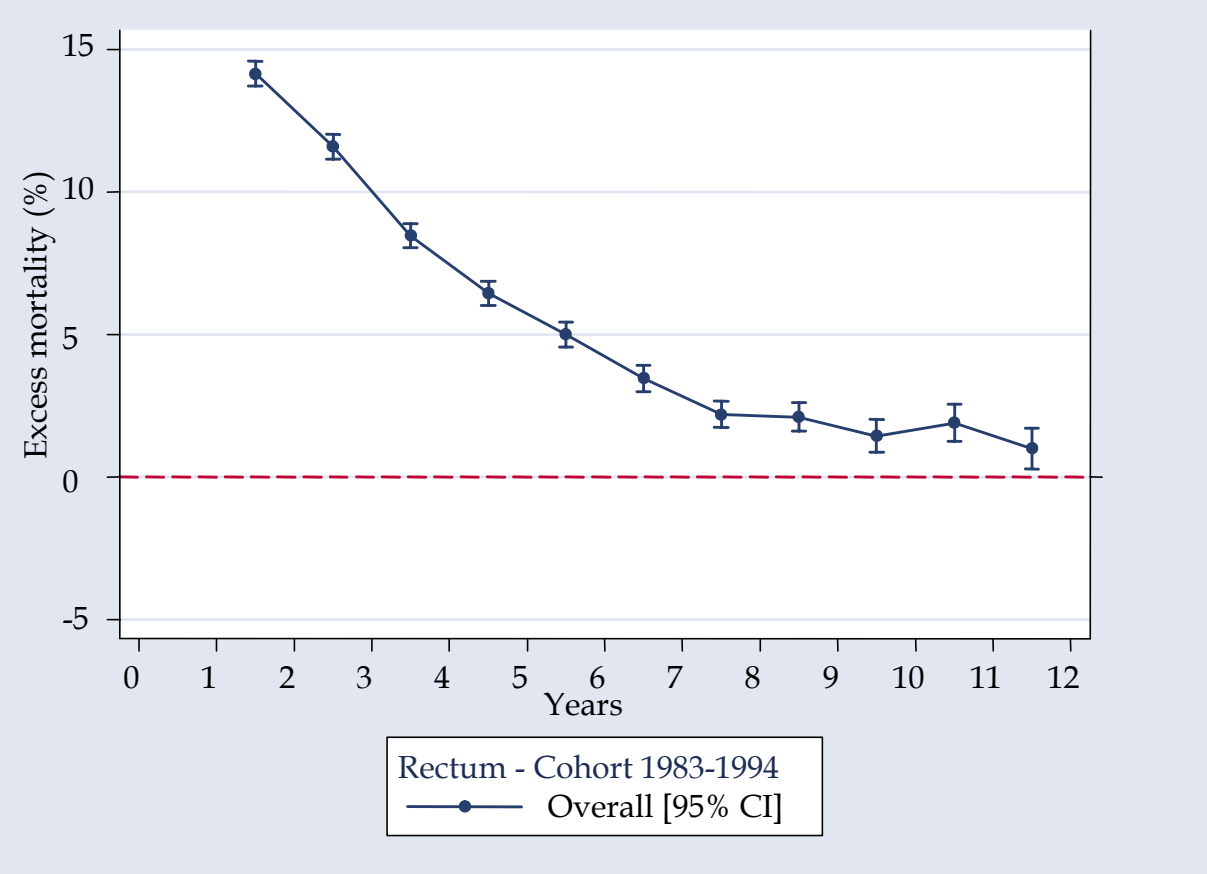

Figure 12.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 12.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 14,635)	Men (N = 20,355)
0-1	17.25 [16.62-17.89]	18.77 [18.21-19.34]
1-2	13.16 [12.53-13.80]	14.91 [14.31-15.50]
2-3	10.97 [10.33-11.60]	12.11 [11.50-12.72]
3-4	7.71 [7.11-8.31]	9.10 [8.50-9.71]
4-5	5.56 [4.98-6.13]	7.20 [6.59-7.82]
5-6	4.27 [3.69-4.85]	5.68 [5.03-6.33]
6-7	3.01 [2.41-3.61]	3.93 [3.24-4.62]
7-8	2.11 [1.53-2.70]	2.34 [1.66-3.02]
8-9	1.70 [1.07-2.33]	2.56 [1.77-3.34]
9-10	1.08 [0.38-1.77]	1.87 [0.97-2.77]
10-11	1.34 [0.55-2.13]	2.53 [1.49-3.58]
11-12	1.19 [0.28-2.10]	0.92 [-0.18-2.03]

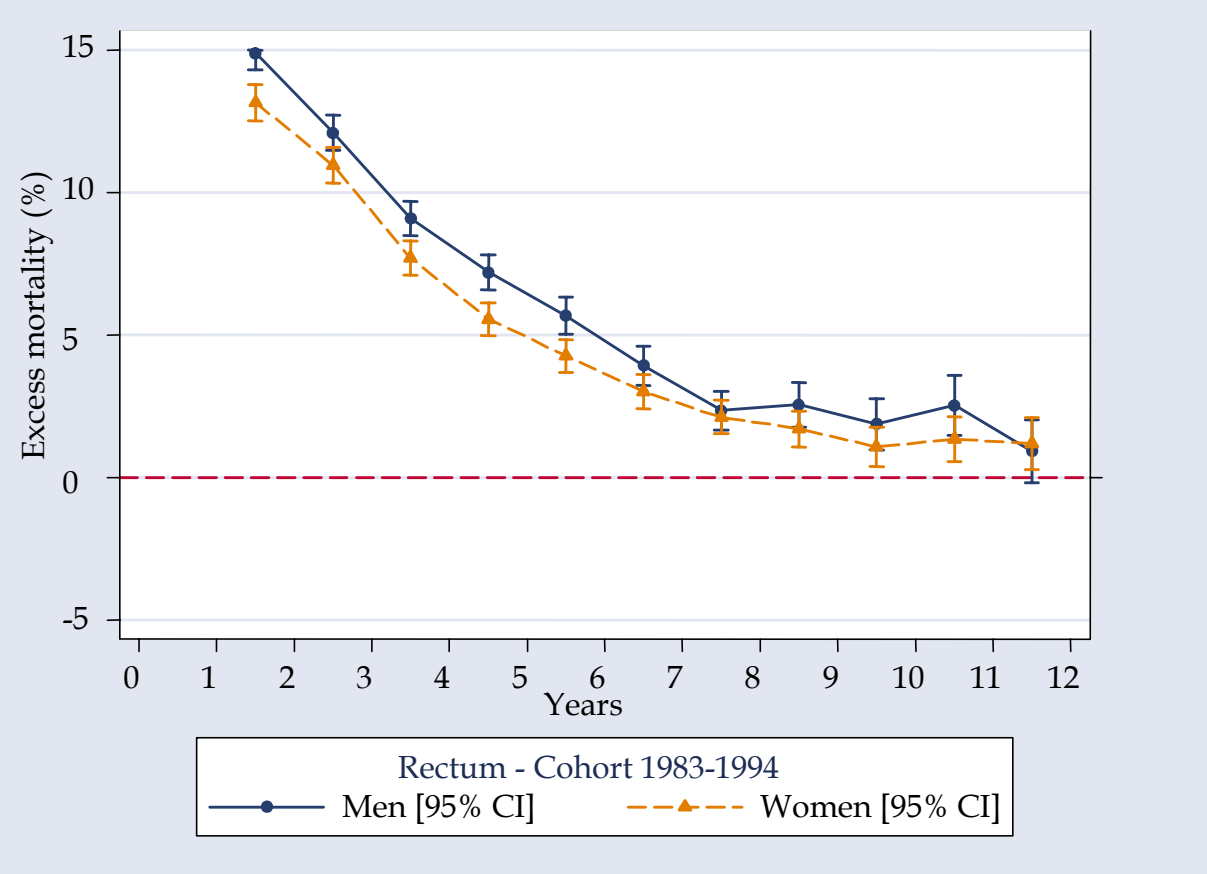

Figure 12.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 12.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) 15-44 years (N = 1,816)	45-54 years (N = 4,493)	55-64 years (N = 11,001)	65-74 years (N = 17,680)
0-1	14.48 [12.85-16.11]	14.90 [13.84-15.95]	16.24 [15.53-16.96]	20.56 [19.92-21.19]
1-2	12.63 [10.96-14.30]	14.45 [13.32-15.59]	13.98 [13.24-14.72]	14.37 [13.73-15.02]
2-3	10.43 [8.78-12.08]	12.04 [10.90-13.19]	11.30 [10.55-12.05]	11.82 [11.15-12.50]
3-4	7.62 [6.10-9.15]	8.38 [7.33-9.44]	7.94 [7.24-8.64]	8.99 [8.31-9.66]
4-5	5.55 [4.14-6.96]	6.65 [5.62-7.68]	6.58 [5.87-7.28]	6.40 [5.72-7.07]
5-6	4.66 [3.24-6.09]	5.05 [4.04-6.06]	5.24 [4.52-5.97]	4.86 [4.15-5.58]
6-7	3.45 [2.06-4.84]	2.85 [1.94-3.77]	3.74 [3.00-4.49]	3.45 [2.66-4.24]
7-8	1.78 [0.69-2.88]	2.64 [1.70-3.58]	2.21 [1.52-2.90]	2.10 [1.30-2.91]
8-9	2.27 [0.96-3.59]	1.65 [0.76-2.54]	2.27 [1.50-3.05]	2.11 [1.18-3.04]
9-10	0.19 [-0.48-0.85]	2.00 [0.90-3.11]	1.63 [0.78-2.49]	1.29 [0.20-2.38]
10-11	0.74 [-0.29-1.77]	1.97 [0.78-3.15]	1.11 [0.24-1.99]	2.81 [1.48-4.14]
11-12	0.32 [-0.59-1.23]	0.71 [-0.34-1.76]	1.14 [0.11-2.17]	1.12 [-0.37-2.61]

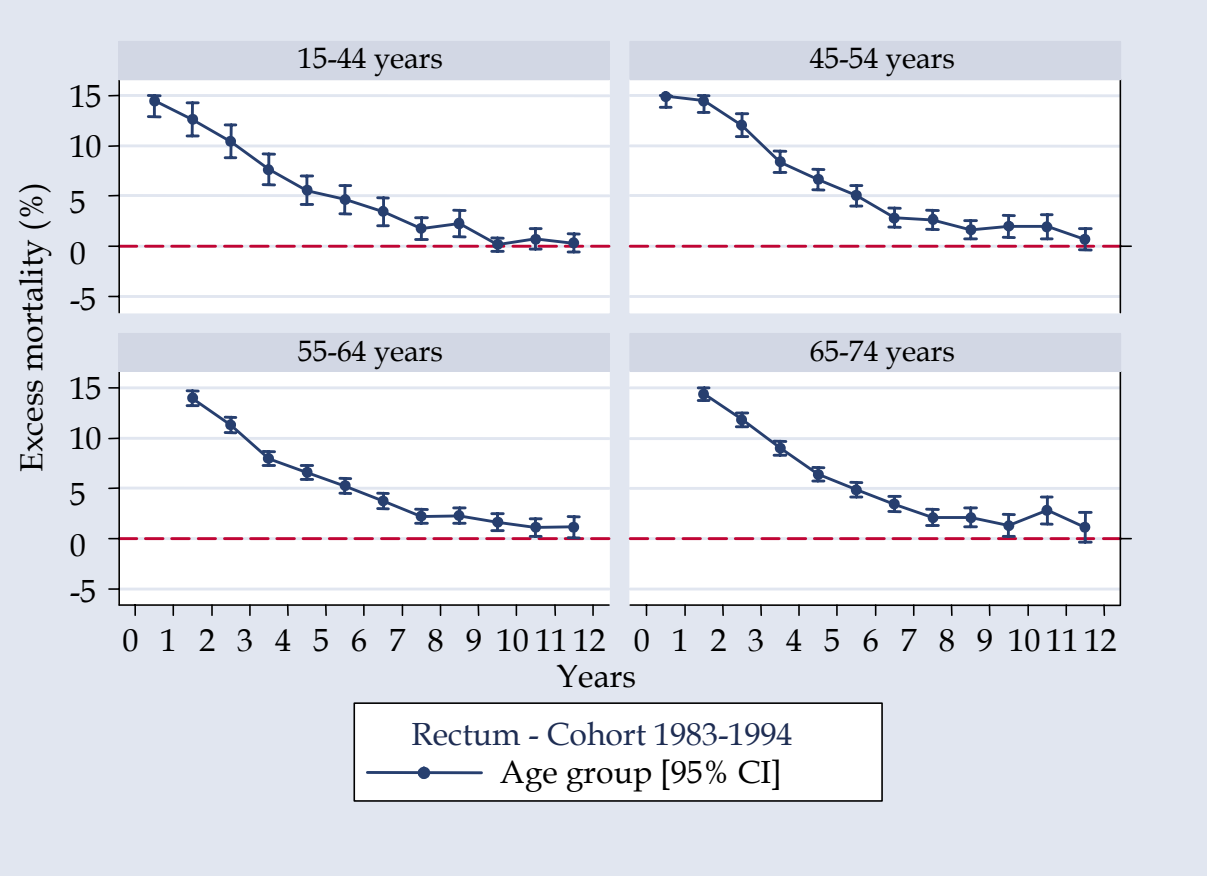

Figure 12.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 12.IV: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 1983-1985 (N = 7,921)	Cohort 1986-1988 (N = 8,684)	Cohort 1989-1991 (N = 8,948)	Cohort 1992-1994 (N = 9,437)
0-1	20.39 [19.46-21.32]	19.17 [18.30-20.04]	17.53 [16.71-18.36]	15.87 [15.09-16.64]
1-2	15.67 [14.70-16.64]	15.09 [14.19-15.99]	13.91 [13.06-14.76]	12.37 [11.59-13.16]
2-3	12.86 [11.86-13.86]	12.50 [11.58-13.43]	11.28 [10.42-12.14]	10.17 [9.38-10.96]
3-4	8.79 [7.83-9.74]	8.81 [7.92-9.70]	8.55 [7.71-9.39]	7.89 [7.11-8.66]
4-5	7.37 [6.41-8.33]	6.53 [5.67-7.39]	6.27 [5.47-7.08]	5.70 [4.89-6.51]
5-6	4.84 [3.95-5.74]	5.17 [4.33-6.02]	5.49 [4.68-6.31]	4.04 [3.04-5.03]
6-7	4.10 [3.20-5.01]	3.44 [2.65-4.23]	2.97 [2.25-3.70]	-
7-8	1.64 [0.86-2.43]	2.59 [1.81-3.36]	2.27 [1.48-3.07]	-
8-9	2.71 [1.81-3.61]	1.44 [0.71-2.17]	2.32 [1.23-3.42]	-
9-10	1.09 [0.27-1.91]	1.75 [0.95-2.55]	-	-
10-11	1.49 [0.59-2.39]	2.30 [1.34-3.26]	-	-
11-12	1.09 [0.18-1.99]	0.82 [-0.34-1.98]	-	-

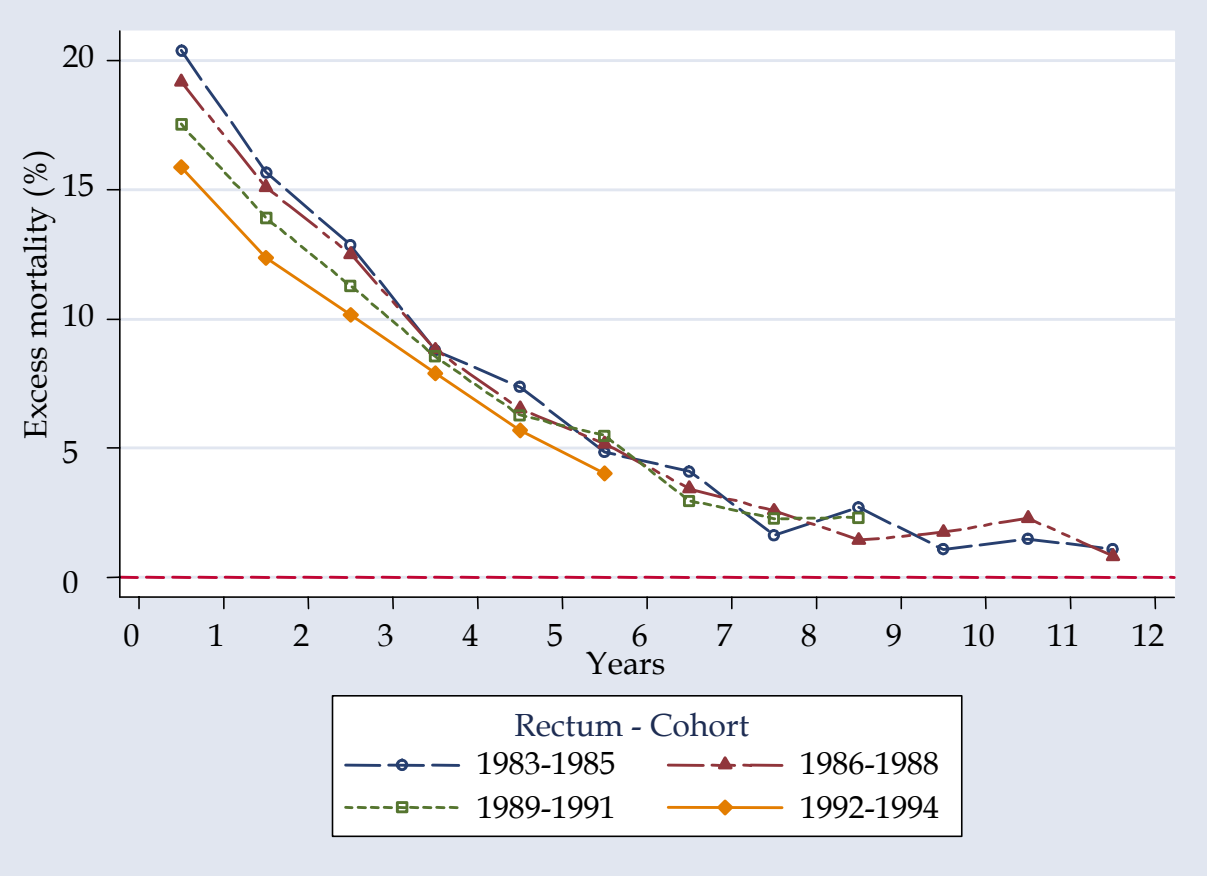

Figure 12.4: Time course of annual excess mortality by cohort

13

Lung cancer

In France, the number of new cases of primary lung cancer in 2000 was about 23,000 in men and 4,600 in women. In terms of frequency, lung cancer ranks second among male cancers and fourth among female cancers (Remontet *et al*., 2003).

In 2000, the median age of lung cancer diagnosis was 67 years for men and 68 years for women. Lung cancer remains rare before age 40 years. However, an increasing number of young men and women develop lung cancer due to the generalization and early start of smoking among young people.

In males, the incidence is increasing moderately while in women the increase is very marked. The increase affects all female cohorts. Moreover, an acceleration has been observed in the more recent cohorts.

In Western countries, lung cancer is the leading cause of cancer death for men. In women, lung cancer constitutes the third cause of cancer death, after breast and colorectal cancer. In Europe, male lung cancer-related mortality has reached a peak and even begun to fall except in Hungary, France and Spain. In contrast, female mortality is increasing. In France, the mean annual mortality growth rate is 0.67% in men and 2.86% in women.

On the basis of the Eurocare study data, the estimated 5-year relative survival is 12.13% for patients in diagnostic cohort 1992-1994 for all diseases stages taken together and the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 13.I shows the overall annual excess mortality estimates with their 95% confidence intervals. The data take into account all the patients in diagnostic cohorts 1983-1994 in Europe (8 countries). The annual excess mortality, which was high in the first year post-diagnosis (over 60%), decreased rapidly subsequently. As of 5 years post-diagnosis, the annual excess mortality was of the order of 7%. Figure 13.1 illustrates the rapid falloff in annual excess mortality.

Table 13.II shows the annual excess mortality estimates by gender. Five years post-diagnosis, the annual excess mortality was lower for women than for men. The annual excess mortality continued to fall reaching 3-4% as of years 10 to 12 post-diagnosis (figure 13.2). However, between year 6 and 9, the confidence intervals overlap.

Table 13.III shows the annual excess mortality results for the various age groups. The patients aged less than 45 years at the time of diagnosis have lower late annual excess mortality: less than 2% from 10 to 12 years post-diagnosis. Figure 13.3 shows a more marked decrease in annual excess mortality for the age groups 15-54 years.

The annual excess mortality data for the 4 cohorts are shown in table 13.IV. There is no difference between them (figure 13.4).

Very long-term annual excess mortality (all stages considered): other studies

Three sources of population data are available for evaluation of the very long-term annual excess mortality associated with lung cancer: the US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the data from the Finnish and Swedish national cancer registries.

Brenner (2002) evaluated the 10-, 15- and 20-year relative survivals for patients presenting with lung cancer diagnosed between 1973 and 1998, using the SEER program data. The relative survival estimates, calculated using the period analysis method (which takes into account the survival observed over the first years post-diagnosis for the more recent periods), were 10.6, 8.1 and 6.5%, respectively. The mean annual excess mortality estimate was of the order of 4.4% for the period, 15-20 years.

Brenner and Hakulinen (2001) estimated the long-term relative survival of patients presenting with lung cancer using the data from the Finnish national cancer registry. For the patients in diagnostic cohort 1985-1997, the 10-, 15- and 20-year relative survivals estimated using the period analysis method were 6.6, 4.9 and 3.7%, respectively. The mean annual excess mortality estimate was of the order of 5.6% for the period, 15-20 years.

For patients presenting with lung cancer diagnosed between 1965 and 1996, Talbäck *et al.* (2004) evaluated the 5-, 10- and 15-year relative survivals using the data from the Swedish national cancer registry. Using the period analysis method, the authors estimated the 5-, 10- and 15-year relative survivals to be 11.9, 7.6 and 6.9%, respectively. The data are similar to the 5-, 10- and 15-year relative survivals observed for patients in the most recently diagnosed cohort. The survivals were 12.9, 7.2 and 6.7%, respectively. The mean annual excess mortality estimate was of the order of 1.9% for the period 10-15 years.

Relative survival or long-term annual excess mortality by stage

In the PETRI study (Ile-de-France, 2004), the 5-year relative survival in France was 22% for men and women (tracheal and bronchial cancer were pooled with lung cancer in the study). For patients presenting with stage I cancer, the 5-year survival was 47%; for stage II, 32%; and for stage III, 22%. The survival rate fell to 5% for patients presenting with stage IV disease.

The 5-year relative survival, estimated from the Hérault tumor registry (2005) (929 cases reported in Hérault in 2002), was 55% for men presenting with stage I and 29% for men presenting with stage II lung cancer (lungs, bronchi and trachea). The survival fell to 10% for stage III (30% of cases) and 4% for stage IV (49% of cases) disease. In women, the relative 5-year survival was 80% for stage I, falling to 16, 10 and 2% for stages II, III and IV, respectively. The 5-year survival rate in women (80%) was markedly higher than the corresponding survival for men (55%) for stage I disease.

The US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated data on relative survival per year for three stages of cancer—localized, regional and metastatic (distant metastases)—and a non-determined stage (insufficient information in the base to determine the stage). Annual excess mortality by lung and bronchial cancer stage has been calculated from the relative survival data (table 13.V). The lung cancer distribution by stage (local, regional and metastatic) was as follows: 15.9, 36.0 and 38.7%. The results cover both genders and all ages for the diagnostic period from 1988 to 2001.

Table 13.V: Annual excess mortality by stage at diagnosis for the period 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease	Metastatic disease
0-1	20.2	51.6	81.2
1-2	17.2	42.4	68.1
2-3	12.4	25.8	45.0
3-4	8.8	15.9	27.3
4-5	7.2	11.5	20.8
5-6	6.3	8.4	15.8
6-7	5.0	7.8	12.5
7-8	4.8	7.7	7.1
8-9	4.3	6.7	7.7
9-10	4.3	5.4	16.7

The results show that the annual excess mortality related to localized disease stabilizes at 4.3% between year 7 and 10 post-diagnosis.

Influence of other prognostic factors on survival

The WHO classification of bronchopulmonary carcinoma was published in 1999 (3rd edition). The morphological classification is mainly based on standard light-microscopy criteria. For certain tumors, complementary information is generated by immunohistochemistry. Most tumors are usually easy to classify by histologic type. However, in certain cases, due to lack of differentiation of the tumor or tumor heterogeneity, the classification cannot be used.

The WHO classification identifies four principal histologic types in addition to more rare histologic types. The four principal types are derived from malignant transformation of bronchial epithelial cells:

- squamous-cell or malpighian carcinomas are the most frequent (50% of cases). They are related to smoking and readily develop on the main bronchi. Diagnosis is based on the presence of keratinization and intercellular junctions;
- adenocarcinomas (30% of cases) are recognized by their glandular and/or papillary structure or by histochemical evidencing of mucins. Adenocarcinomas constitute a heterogeneous group of tumors in terms of morphology, progressive profile and histogenesis;
- small-cell carcinomas (SCC) (15% of cases) are proximal, mediastinum-hilum tumors that are clinically very aggressive presenting, in 6 cases out of 10, in metastatic form. The histologic type is very chemosensitive. The malignant cells are small and show neuroendocrine differentiation;
- large-cell carcinomas (5% of cases) are undifferentiated tumors consisting of large cells. Their development is proximal or peripheral. Scientific progress (immunolabeling, electron microscopy) have enabled differentiation of the category by evidencing criteria that cannot be detected by conventional histology.

Smoking so-called light cigarettes (lower nicotine content) induces a change in smoking habits: smoke is more deeply inhaled and carcinogen exposure thus extends from the upper airways to the pulmonary alveoli. This phenomenon, together with the different carcinogens present in light cigarettes explains a change in the type of malignant lesions: proximal tumors (squamous-cell and small-cell) become less frequent than peripheral adenocarcinomas.

Fry *et al*. (1999) reported the 10-year relative survivals for 713,043 patients in the US whose lung cancer, of the 4 histologic types, was diagnosed between 1985 and 1995. For squamous-cell or malpighian carcinoma, the 10-year relative survival was 8%. For adenocarcinoma, the survival was 10%. For small-cell carcinoma, the survival was 2% and for large-cell carcinoma, the survival was 6%.

In practice, it remains convenient and very useful in clinical and prognostic terms to reduce the large number of histologic types or subtypes to two main prognostic groups with different management strategies: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). This simple classification, which is more clinical than histologic, is used by clinicians in everyday practice.

For non-small-cell lung cancer, the 5-year survival post-diagnosis (initial record) has been calculated as a function of clinical (cTNM) and pathologic (pTNM) stage by the International association for the study of lung cancer (IASLC). The survivals were calculated on 50,454 cases of lung cancer (Asia, Australia, Europe and North America).

Table 13.VI: 5-year relative survival by pathologic and clinical stage taken from the IASLC staging project (personal communication)

Disease stage p(TNM)	IA (T1N0)	IB (T2N0)	IIA (T1N1)	IIB (T2N1, T3N0)	IIIA (T3N1, T1N2, T2N2, T3N3)	IIIB (T4N0, T4N1, T4N2)	IV
5-year survival (%)	71	54	53	41	28	18	18

Clinical stage c(TNM)	IA	IB	II	IIIA	IIIB	IV
5-year survival (%)	63	40	32	20	8	2

For non-small-cell lung cancer, the 10-year survival of patients having survived 5 years post-complete resection is estimated to be 91% (Okada *et al*., 2003).

For small-cell lung cancer, the survival rates 2 and 5 years post-diagnosis (initial record) were determined by the IASLC (2005) for localized and extensive disease. The survivals were 20 and 6% at 2 years and 13 and 1% at 5 years.

The long-term residual annual excess mortality is related to the neoplastic disease itself but also to other risk factors. The annual excess mortality in women is reported to be related to the predominance of adenocarcinoma and non-smoking-related forms.

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Excess mortality data from the Eurocare study

Table 13.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 84,382)
0-1	62.64 [62.31-62.97]
1-2	45.07 [44.51 -45.64]
2-3	25.26 [24.57 -25.95]
3-4	15.66 [14.96 -16.36]
4-5	10.72 [10.03 -11.41]
5-6	7.75 [7.05 -8.46]
6-7	6.54 [5.77 -7.32]
7-8	6.24 [5.40 -7.07]
8-9	5.15 [4.26 -6.05]
9-10	5.64 [4.54 -6.74]
10-11	6.03 [4.79 -7.28]
11-12	6.35 [4.85 -7.85]

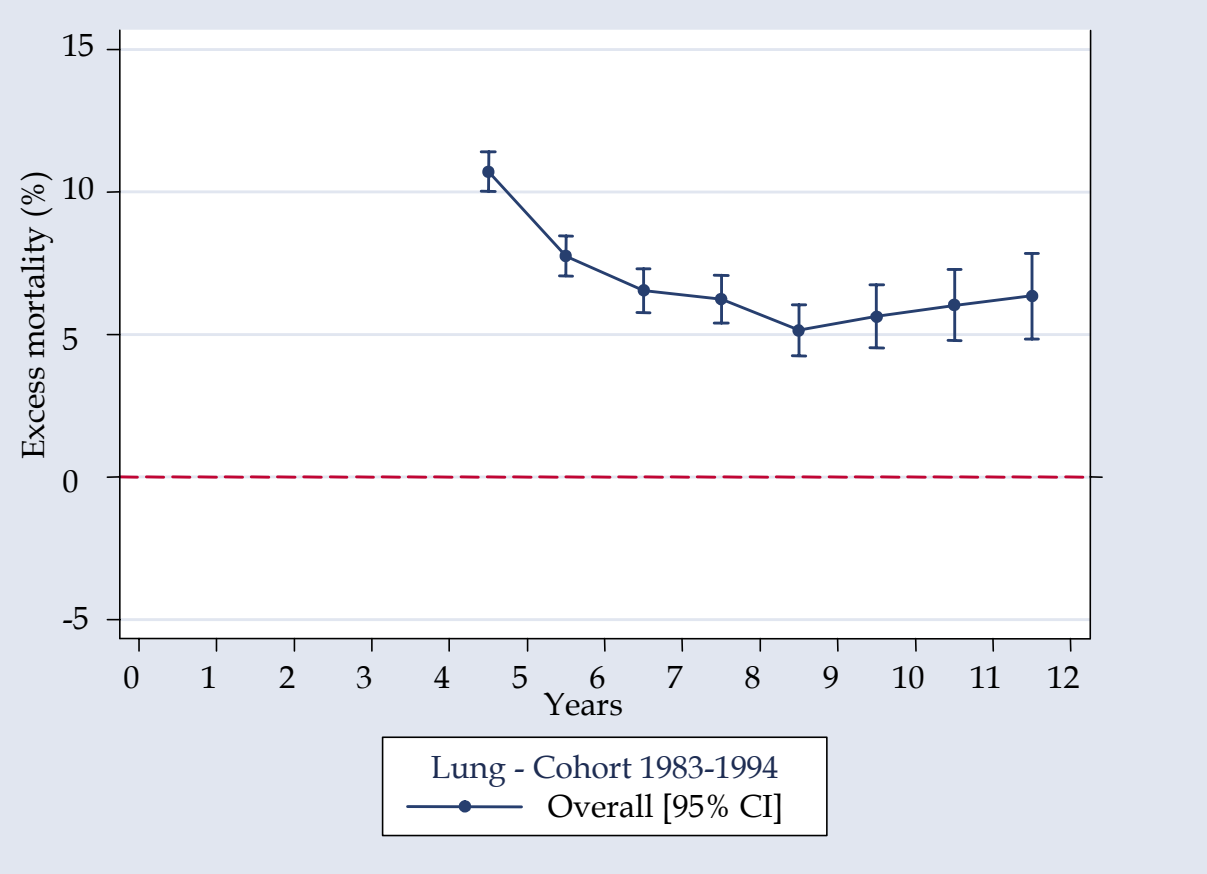

Figure 13.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 13.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 16,923)	Men (N = 67,459)
0-1	61.62 [60.88-62.35]	62.90 [62.53-63.27]
1-2	42.20 [40.98-43.42]	45.84 [45.20-46.48]
2-3	22.25 [20.87-23.63]	26.15 [25.36-26.95]
3-4	14.61 [13.26-15.97]	16.00 [15.19-16.81]
4-5	10.37 [9.04-11.71]	10.86 [10.07-11.67]
5-6	5.30 [4.11-6.48]	8.51 [7.67-9.36]
6-7	5.48 [4.10-6.86]	6.92 [6.00-7.84]
7-8	5.70 [4.18-7.22]	6.46 [5.48-7.45]
8-9	3.82 [2.32-5.32]	5.63 [4.55-6.71]
9-10	5.66 [3.61-7.71]	5.70 [4.40-7.00]
10-11	3.04 [1.18-4.89]	7.03 [5.51-8.56]
11-12	4.04 [1.70-6.38]	7.20 [5.36-9.04]

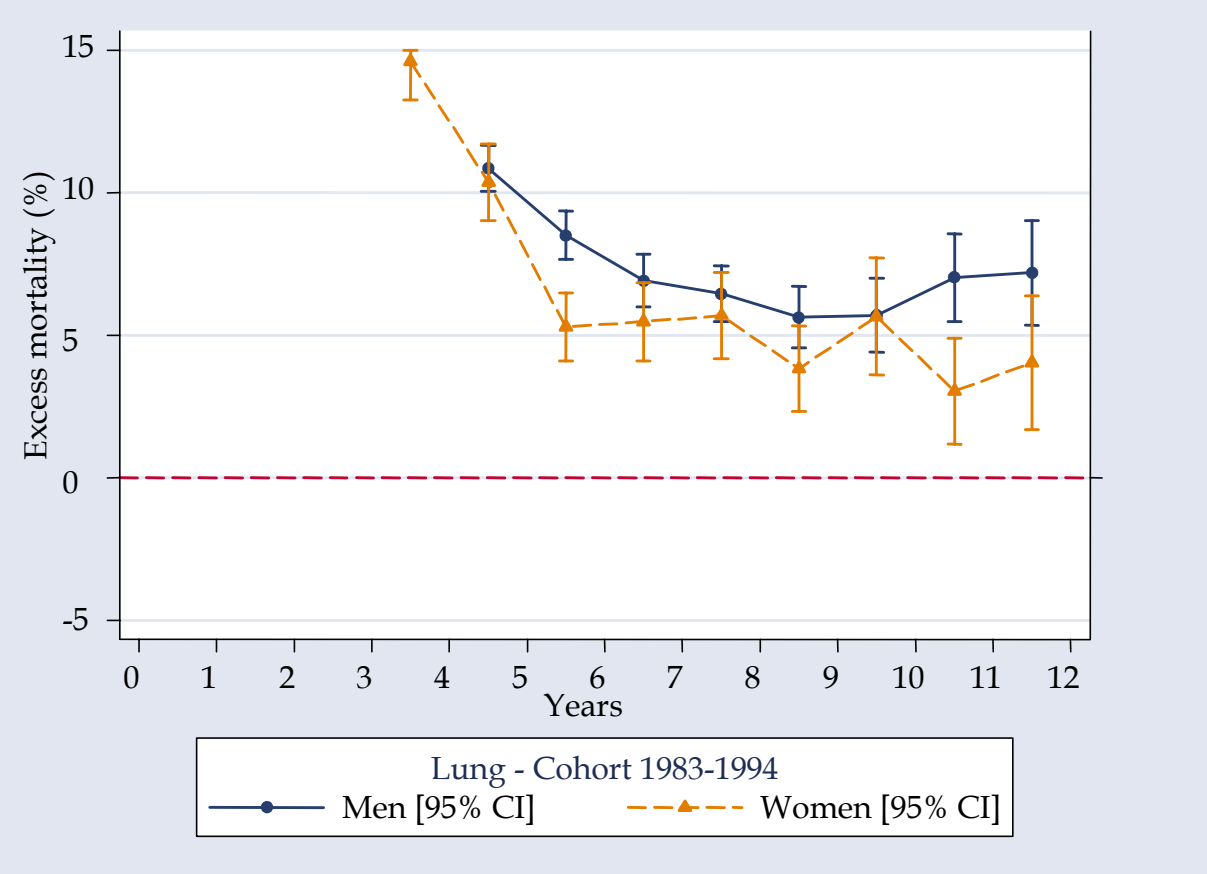

Figure 13.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 13.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (Years)	15-44 years (N = 3,051)	45-54 years (N = 10,897)	55-64 years (N = 30,144)	65-74 years (N = 40,290)
0-1	55.63 [53.86-57.40]	58.08 [57.15-59.01]	60.92 [60.36-61.48]	65.76 [65.29-66.24]
1-2	38.80 [36.19-41.42]	44.04 [42.58-45.49]	44.20 [43.28-45.12]	46.87 [45.99-47.75]
2-3	15.47 [12.97-17.96]	22.56 [20.90-24.21]	25.01 [23.91-26.11]	27.74 [26.61-28.87]
3-4	8.24 [6.15-10.32]	13.09 [11.55-14.63]	15.06 [13.98-16.14]	18.46 [17.24-19.68]
4-5	6.58 [4.54-8.62]	8.11 [6.71-9.51]	10.41 [9.35-11.47]	12.98 [11.70-14.26]
5-6	3.74 [1.98-5.50]	5.65 [4.31-6.98]	7.81 [6.74-8.89]	9.51 [8.14-10.89]
6-7	1.80 [0.37-3.23]	5.43 [3.95-6.91]	6.73 [5.56-7.90]	7.99 [6.38-9.59]
7-8	3.11 [1.21-5.01]	4.67 [3.18-6.17]	6.23 [4.99-7.47]	8.02 [6.22-9.82]
8-9	2.38 [0.53-4.24]	4.05 [2.47-5.62]	6.18 [4.79-7.57]	5.16 [3.22-7.10]
9-10	3.31 [0.81-5.81]	4.65 [2.70-6.61]	6.52 [4.84-8.21]	5.66 [3.18-8.15]
10-11	1.72 [-0.33-3.77]	5.06 [2.87-7.25]	7.43 [5.49-9.37]	5.95 [3.07-8.83]
11-12	1.66 [-0.68-4.00]	5.22 [2.66-7.77]	7.18 [4.89-9.46]	7.64 [3.90-11.38]

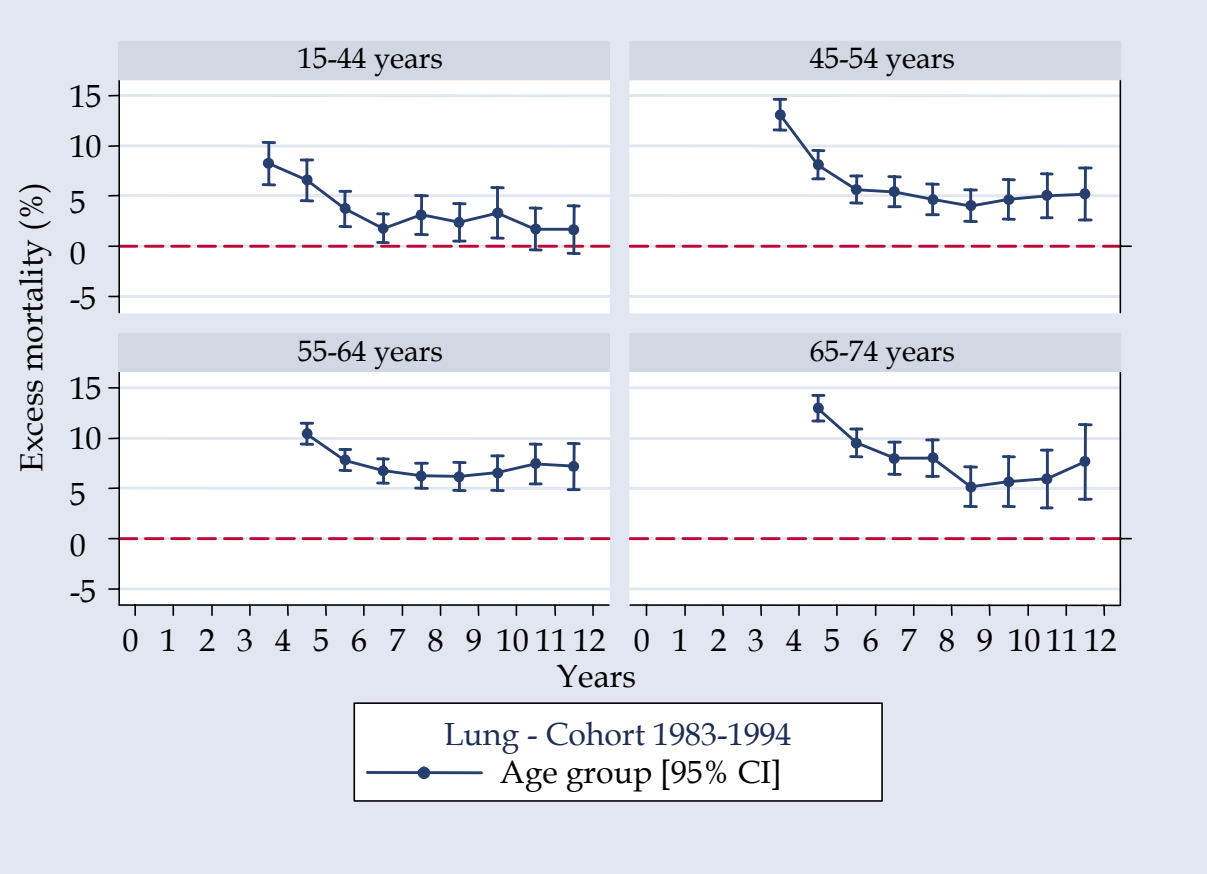

Figure 13.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 13.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 1983-1985 (N = 19,068)	Cohort 1986-1988 (N = 21,801)	Cohort 1989-1991 (N = 21,708)	Cohort 1992-1994 (N = 21,805)
0-1	61.98 [61.28-62.69]	62.83 [62.18-63.49]	63.34 [62.69-64.00]	62.32 [61.67-62.98]
1-2	46.15 [44.96-47.35]	45.54 [44.41-46.66]	45.00 [43.87-46.14]	43.75 [42.64-44.86]
2-3	27.05 [25.56-28.55]	25.62 [24.24-27.00]	23.90 [22.55-25.25]	24.71 [23.39-26.04]
3-4	16.40 [14.88-17.93]	15.37 [13.99-16.75]	15.43 [14.07-16.79]	15.55 [14.22-16.89]
4-5	11.70 [10.18-13.21]	10.46 [9.12-11.79]	10.81 [9.48-12.14]	9.95 [8.57-11.33]
5-6	7.87 [6.43-9.32]	7.27 [5.99-8.54]	8.20 [6.89-9.50]	7.58 [5.83-9.34]
6-7	7.45 [5.94-8.96]	6.61 [5.30-7.92]	5.73 [4.50-6.97]	-
7-8	6.60 [5.06-8.15]	6.49 [5.11-7.87]	5.55 [4.14-6.96]	-
8-9	5.62 [4.05-7.18]	5.08 [3.72-6.44]	4.50 [2.69-6.32]	-
9-10	5.38 [3.74-7.01]	5.85 [4.36-7.34]	-	-
10-11	6.14 [4.34-7.94]	5.91 [4.18-7.64]	-	-
11-12	6.53 [4.59-8.47]	6.03 [3.67-8.38]	-	-

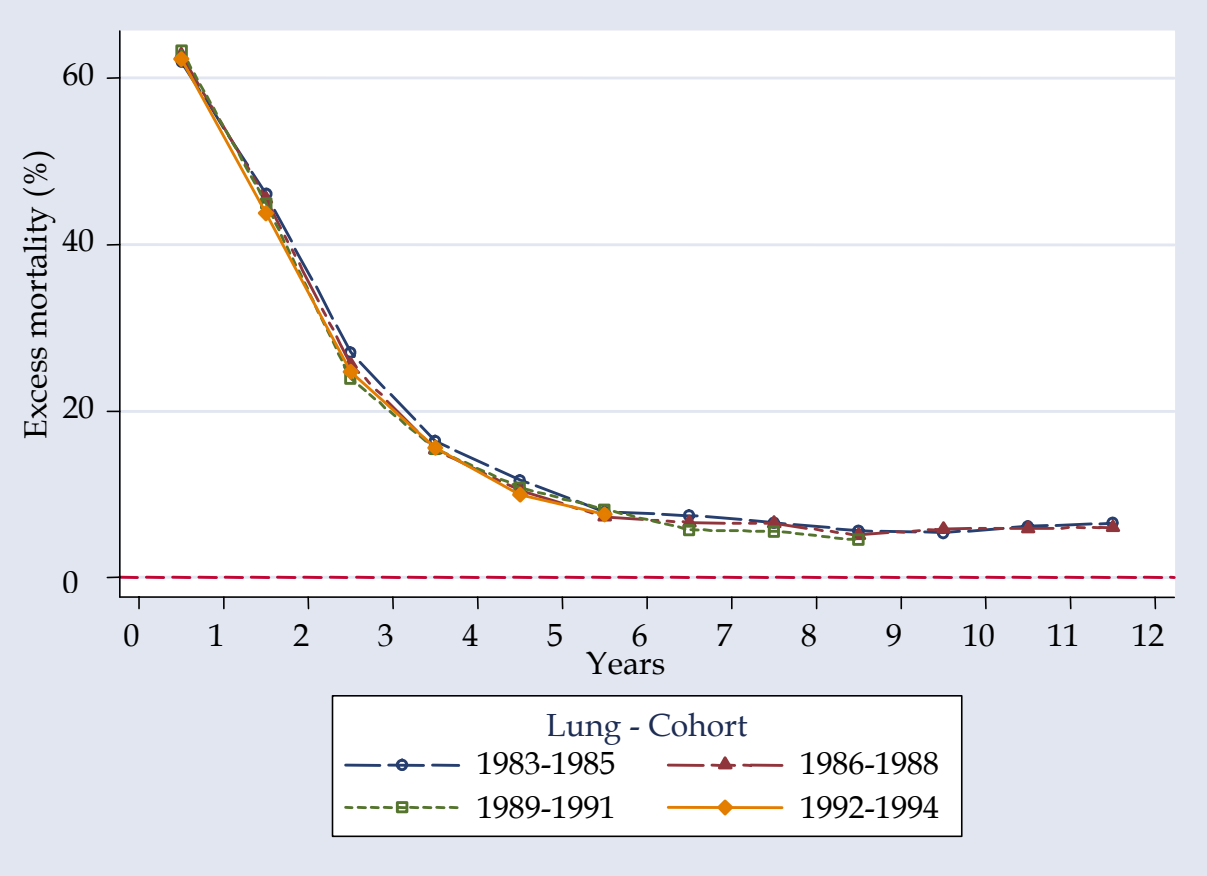

Figure 13.4: Time course of annual excess mortality by cohort

14

Laryngeal cancer

In France, 4,226 new cases of laryngeal cancer were diagnosed in 2000. Laryngeal cancer accounted for 1.5% of all incident cancers (Remontet *et al*., 2003). The age-standardized incidence rates (world population) were 9.3/100,000 for men and 0.7/100,000 for women. The sex ratio is 13.3 (Remontet *et al*., 2003). The incidence decreased from the oldest birth date cohorts to the most recent.

In the last two decades, the incidence has decreased 1.66% per year for men but remained unchanged for women. Similarly, the annual mortality rate has decreased very regularly in a more marked manner for men than for women. The age-standardized mortality rates were 4.5/100,000 for men and 0.3/100,000 for women.

The median age at diagnostic is 62 years for men and 64 years for women. The incidence peaks at around 60 years.

According to the Eurocare data for disease diagnosed between 1992 and 1994, the 5-year relative survival was 68.11% for all stages taken together and the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 14.I shows the overall annual excess mortality estimates with their 95% confidence intervals. The data take into account all the patients whose disease was diagnosed between 1983 and 1994 in Europe (eight countries). The annual excess mortality was less than 5% as of year 4 post-diagnosis, falling subsequently to 3.5% between 6 and 12 years post-diagnosis (figure 14.1).

Table 14.II shows the annual excess mortality estimates by gender. The annual excess mortality was slightly lower for women in the first years post-diagnosis (although the confidence intervals of the two genders overlap). After the first years, the time courses of annual excess mortality for men and women were similar (figure 14.2). The small population of women presenting with laryngeal cancer prevents confirmation of the trend toward lower annual excess mortality in women.

Table 14.III shows the annual excess mortality results for various age groups. The age at the time of diagnosis influenced both the early and late annual excess mortalities. The annual excess mortality was less than 2% as of 8 years post-diagnosis for the age group 15-44 years and subsequently tended towards zero. For the other 3 age groups, between 8 and 12 years post-diagnosis, the annual excess mortality remained greater than 2% (figure 14.3).

The annual excess mortality data for the 4 cohorts are shown in table 14.IV. The diagnostic period only slightly influenced the early annual excess mortality rate (figure 14.4).

Very long-term annual excess mortality (all stages considered): other studies

Two population data sources are available for evaluation of the very long-term annual excess mortality: the US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the data of the Swedish national cancer registry.

Brenner (2002) evaluated the 10-, 15- and 20-year relative survivals for patients with laryngeal cancer diagnosed between 1973 and 1998 using the data from the US SEER program. The relative survival estimates, calculated using the period analysis method (which takes into account the survival observed during the first years post-diagnosis for the most recent periods) were 56.7, 45.8 and 37.8%, respectively. The mean annual excess mortality rates were 4.2 and 3.8% for the periods 10-15 years and 15-20 years post-diagnosis, respectively.

Talbäck *et al*. (2004) studied patients with laryngeal cancer diagnosed between 1965 and 1996. The 5-, 10- and 15-year relative survivals were estimated from the data of the Swedish national cancer registry. The authors used the period analysis method. The 5-, 10- and 15-year relative survivals were 69.4, 57.4 and 49.1%, respectively. The results are similar to the 5-, 10- and 15-year relative survivals observed in the patients whose disease was diagnosed in the most recent period. The survivals were 68.3, 56.2 and 48.1%. The mean annual excess mortality estimate was of the order of 3% 10 and 15 years post-diagnosis.

Long-term relative survival or excess mortality by stage

The PETRI (2004) study determined 5-year survival data for France. The data were overall, by stage and/or by age.

In that study of laryngeal cancer, the 5-year relative survivals were 57% for men and 55% for women. For patients presenting with stage I laryngeal cancer, the 5-year survival rate was 82%. The survival rate fell to 73, 25 and 46% for patients presenting with stage II, III and IV disease, respectively.

The US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated relative survival data by year and by disease stage—localized, regional and metastatic (distant metastases)—and a non-determined stage (insufficient information in the base to determine the stage). The annual excess mortality by laryngeal cancer stage has been calculated from the relative survival data (table 14.V). The distribution of laryngeal cancer by stage (localized, regional and metastatic) was as follows: 50.0, 41.8 and 3.8%, respectively. The results are for men and women, all ages taken together, and the diagnostic period 1988-2001.

Table 14.V: Annual excess mortality by stage at diagnosis for the period 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease (N+)	Metastatic disease (M+)
0-1	3.3	18.6	49.7
1-2	4.1	18.2	35.8
2-3	4.3	10.8	22.3
3-4	3.9	9.1	14.3
4-5	2.9	7.2	7.4
5-6	2.8	7.4	11.6
6-7	2.4	5.0	1.7
7-8	2.9	6.6	6.9
8-9	3.0	6.8	5.0
9-10	3.0	6.3	17.0

The results show that for the localized stage of laryngeal cancer, the annual excess mortality remained relatively stable throughout the period (about 3%).

Influence of site on survival

An analysis of the Eurocare 2 data (Berrino *et al*., 1998) demonstrated differences in survival as a function of the anatomic site of laryngeal cancer. Glottic tumors have a superior prognosis to other forms of laryngeal cancer (RR < 0.5 relative to other sites). The poor prognosis of tumors of the proximal larynx is to be compared to that of tumors of the hypopharynx and is related to the risk factors for those tumors (alcohol abuse and smoking) which give rise to substantial comorbidity.

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Excess mortality data from the Eurocare study

Table 14.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 9,694)
0-1	10.98 [10.31-11.65]
1-2	10.37 [9.66 -11.08]
2-3	7.19 [6.52 -7.86]
3-4	5.57 [4.93 -6.22]
4-5	4.33 [3.69 -4.97]
5-6	3.65 [2.98 -4.32]
6-7	3.91 [3.14 -4.68]
7-8	3.02 [2.24 -3.80]
8-9	3.18 [2.30 -4.07]
9-10	2.74 [1.73 -3.76]
10-11	4.02 [2.79 -5.24]
11-12	3.56 [2.15 -4.96]

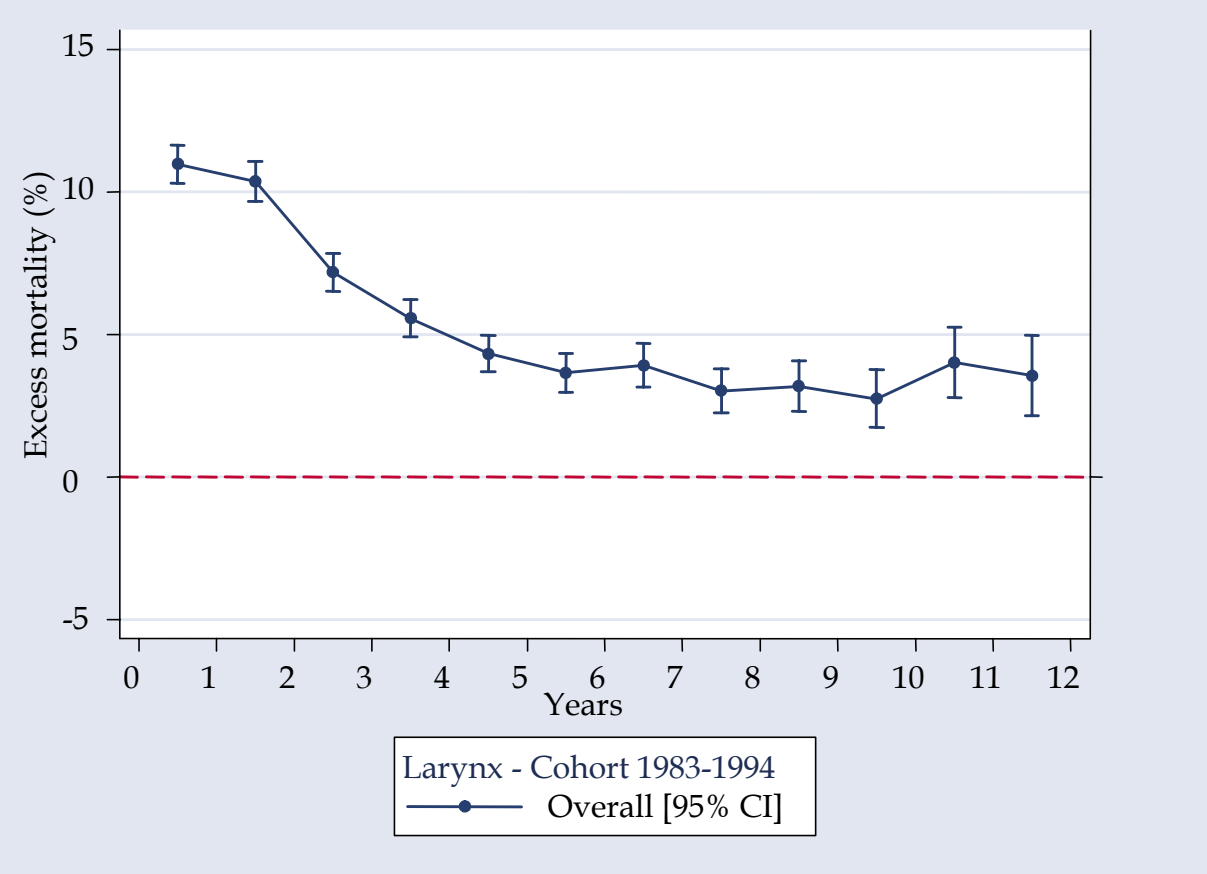

Figure 14.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 14.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 770)	Men (N = 8,921)
0-1	9.75 [7.56-11.94]	11.06 [10.35-11.76]
1-2	8.94 [6.70-11.19]	10.49 [9.74-11.23]
2-3	6.73 [4.61-8.84]	7.22 [6.52-7.92]
3-4	6.25 [4.09-8.41]	5.49 [4.82-6.17]
4-5	3.14 [1.34-4.95]	4.42 [3.74-5.10]
5-6	2.76 [0.87-4.64]	3.67 [2.97-4.38]
6-7	1.21 [-0.49-2.91]	4.09 [3.26-4.91]
7-8	3.00 [0.66-5.33]	3.00 [2.18-3.82]
8-9	1.94 [-0.38-4.26]	3.31 [2.37-4.25]
9-10	4.29 [0.92-7.66]	2.54 [1.48-3.60]
10-11	3.06 [-0.36-6.47]	4.01 [2.71-5.31]
11-12	2.21 [-1.56-5.99]	3.55 [2.07-5.04]

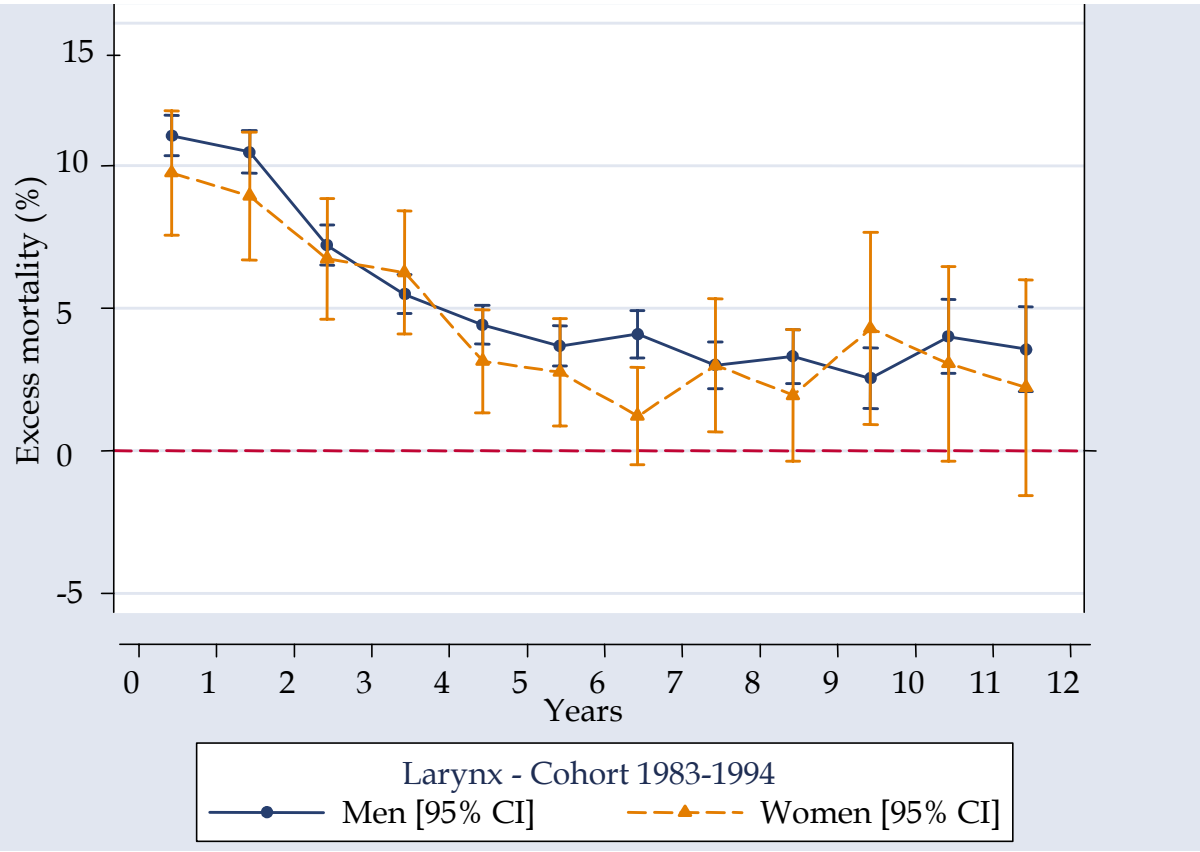

Figure 14.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 14.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) 15-44 years (N = 522)	45-54 years (N = 1,738)	55-64 years (N = 3,914)	65-74 years (N = 3,520)
0-1	7.66 [5.35-9.97]	9.70 [8.27-11.13]	10.26 [9.24-11.27]	12.96 [11.72-14.20]
1-2	9.36 [6.72-11.99]	10.00 [8.47-11.53]	10.06 [8.99-11.14]	11.10 [9.80-12.40]
2-3	6.45 [4.10-8.80]	7.48 [6.04-8.92]	6.86 [5.87-7.86]	7.56 [6.30-8.82]
3-4	5.44 [3.18-7.71]	5.11 [3.82-6.40]	4.93 [4.00-5.86]	6.68 [5.37-7.99]
4-5	1.65 [0.24-3.06]	3.93 [2.71-5.15]	3.99 [3.06-4.92]	5.56 [4.19-6.92]
5-6	2.81 [0.92-4.71]	2.62 [1.50-3.75]	4.28 [3.25-5.32]	3.64 [2.23-5.04]
6-7	1.84 [0.13-3.55]	3.32 [1.97-4.67]	4.33 [3.16-5.51]	4.22 [2.53-5.91]
7-8	2.02 [0.15-3.89]	1.88 [0.70-3.06]	2.12 [1.08-3.16]	5.54 [3.56-7.53]
8-9	1.51 [-0.30-3.33]	2.50 [1.07-3.94]	3.85 [2.52-5.19]	3.08 [1.00-5.17]
9-10	1.38 [-0.61-3.38]	1.41 [0.01-2.80]	3.18 [1.66-4.70]	3.62 [0.97-6.28]
10-11	0.94 [-0.93-2.81]	4.29 [2.11-6.46]	4.59 [2.75-6.44]	3.82 [0.75-6.90]
11-12	-0.45 [-2.32-1.42]	2.85 [0.65-5.05]	3.69 [1.64-5.75]	5.75 [1.65-9.86]

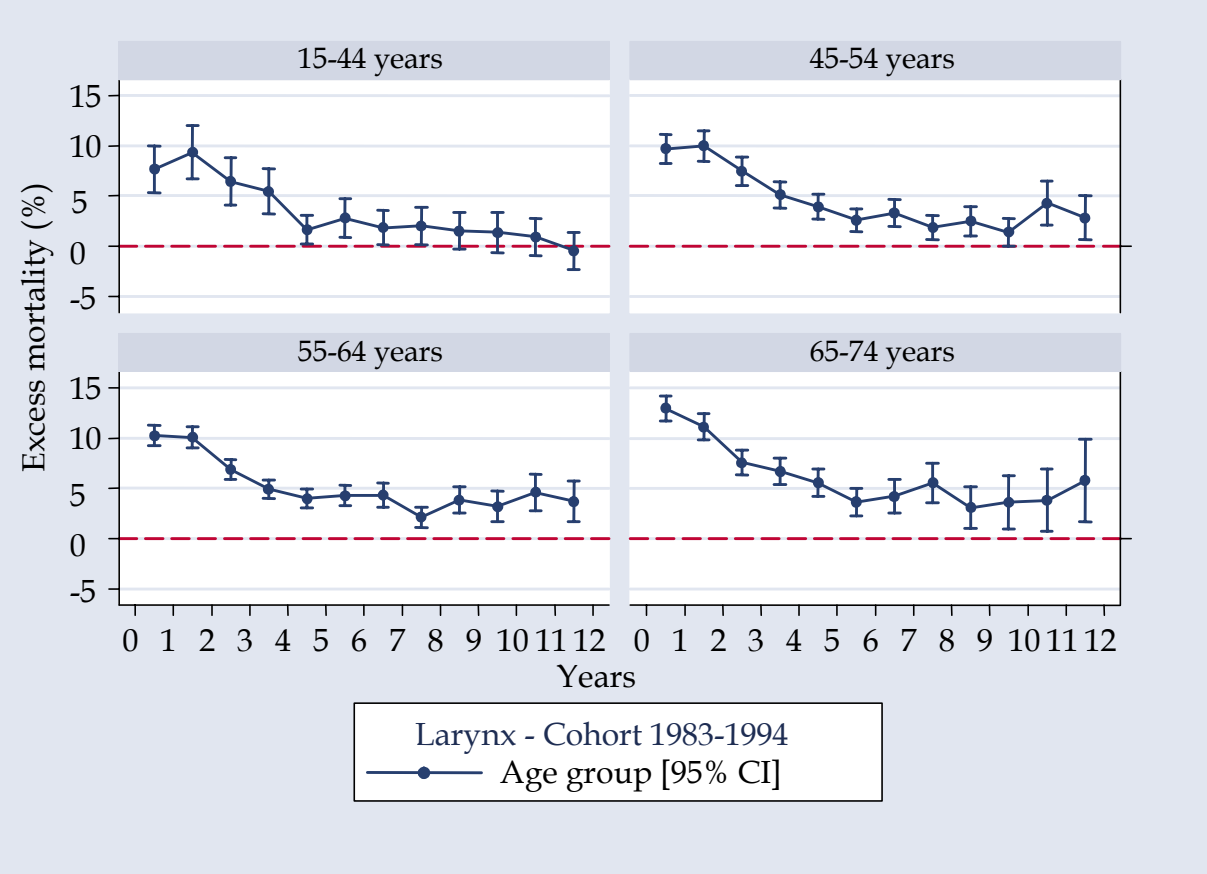

Figure 14.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 14.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 1983-1985 (N = 2,143)	Cohort 1986-1988 (N = 2,717)	Cohort 1989-1991 (N = 2,472)	Cohort 1992-1994 (N = 2,362)
0-1	12.16 [10.66-13.66]	11.66 [10.36-12.96]	9.46 [8.20-10.72]	10.72 [9.38-12.07]
1-2	11.89 [10.28-13.50]	10.45 [9.10-11.80]	10.04 [8.67-11.41]	9.28 [7.92-10.65]
2-3	7.54 [6.05-9.02]	7.21 [5.94-8.48]	7.00 [5.72-8.29]	7.06 [5.74-8.38]
3-4	6.46 [4.97-7.96]	5.68 [4.44-6.91]	5.17 [3.95-6.40]	5.12 [3.87-6.37]
4-5	4.22 [2.83-5.60]	4.50 [3.29-5.72]	3.98 [2.80-5.17]	4.62 [3.23-6.02]
5-6	3.83 [2.42-5.23]	3.90 [2.68-5.12]	3.39 [2.21-4.57]	3.33 [1.61-5.06]
6-7	4.02 [2.53-5.52]	2.89 [1.71-4.07]	4.88 [3.51-6.25]	-
7-8	2.80 [1.37-4.24]	2.76 [1.54-3.98]	3.54 [2.11-4.98]	-
8-9	3.03 [1.50-4.55]	3.61 [2.26-4.96]	2.52 [0.75-4.28]	-
9-10	2.05 [0.57-3.52]	3.27 [1.88-4.66]	-	-
10-11	3.57 [1.83-5.30]	4.42 [2.69-6.15]	-	-
11-12	3.56 [1.74-5.38]	3.50 [1.30-5.71]	-	-

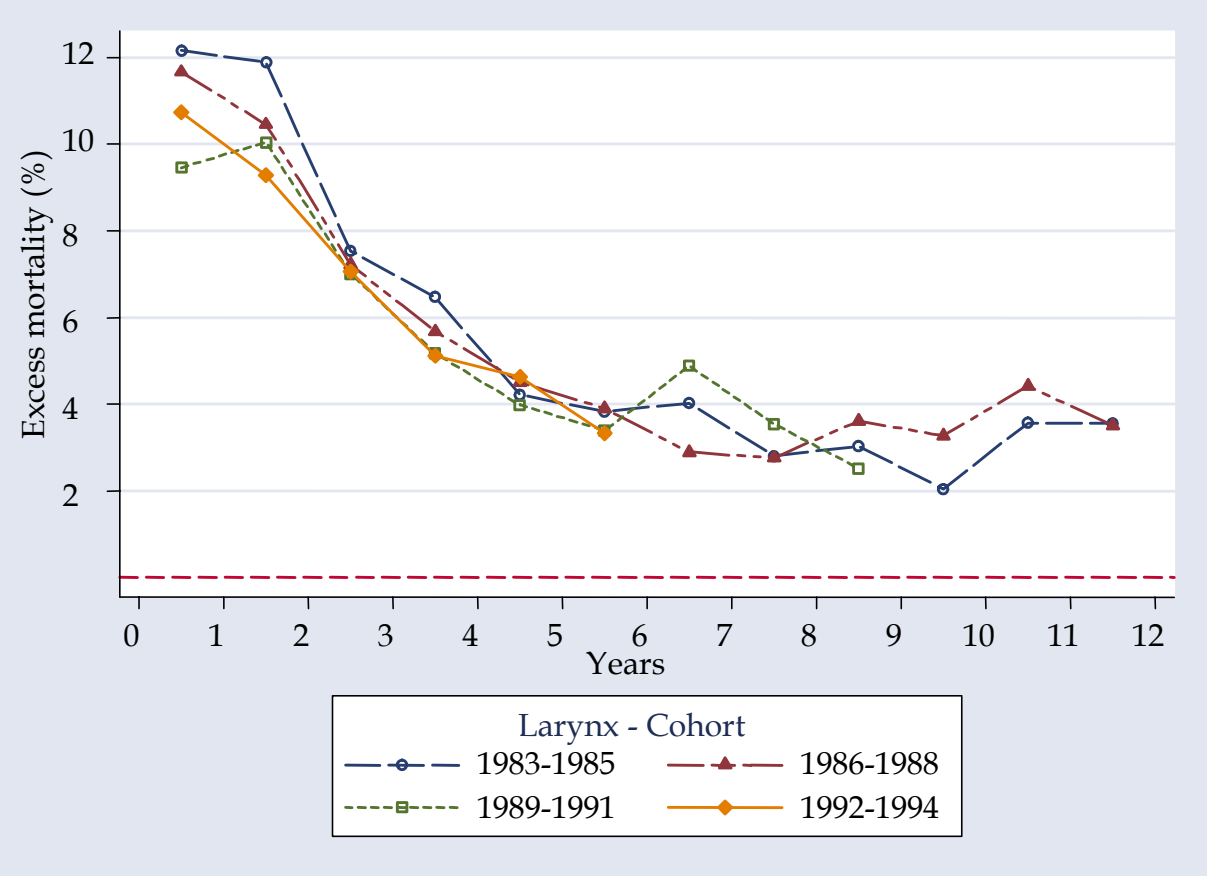

Figure 14.4: Time course of annual excess mortality by cohort

15

Hypopharyngeal cancer

Hypopharyngeal tumors are coded C12.x (piriform sinus) and C13.x (post-cricoid region and hypopharynx proper) in the CIM-O 2.

With reference to the data for the period 1980-1993 (Ménégoz *et al*., 2002), hypopharyngeal tumors accounted for only 25% of the 12,990 cases or oral and pharyngeal tumors diagnosed in men in France in 2000 (Remontet *et al*., 2003), i.e. 3,248 new cases. In women, the tumor is much rarer. It accounted for 5% of the 2,400 new cases of oral and pharyngeal cancer in France in 2000, i.e. 120 new cases.

A study of the period 1980-1993 showed a significant decrease in the incidence and mortality rates in men but no decrease in incidence. For women, a significant increase in mortality was observed. However, no change in incidence was detected (Ménégoz *et al*., 2002).

The incidence truly begins to increase after age 35 years and peaks between 55 and 65 years, before falling off fairly rapidly. The median age at diagnosis is close to 60 years for both men and women.

On the basis of the Eurocare data for the diagnostic cohort 1992-1994, the 5-year relative survival is 25.4% for all stages taken together and the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 15.I shows overall annual excess mortality estimates with their 95% confidence intervals. The data take into account all the patients whose hypopharyngeal cancer was diagnosed between 1983 and 1994 in Europe (eight countries). The annual excess mortality was greater than 20% for the first 3 years post-diagnosis. Subsequently, it fell to 10% and became relatively stable as of year 5 post-diagnosis (figure 15.1).

Table 15.II shows the annual excess mortality estimates by gender. The annual excess mortality was higher for men. From year 5 post-diagnosis, the annual excess mortality for men fluctuated around 10% while it was close to or less than 5% for women (figure 15.2). However, since the population was relatively small, the confidence intervals for the two genders show marked overlap.

Table 15.III shows the annual excess mortality results by age group. Age at diagnosis influenced both the early and late excess mortality. The annual excess mortality was higher for the age group 65-74 years, particularly in the first years post-diagnosis (figure 15.3).

The annual excess mortality data for the 4 cohorts are shown in table 15.IV. The diagnostic period had no influence on early annual excess mortality (figure 15.4).

Influence of site on survival

The poor prognosis of hypopharyngeal tumors is generally considered related to late diagnosis of the disease since the anatomical site is such that symptoms emerge late. For the same reasons, the prognoses of the various sub-sites differ. Work on the Eurocare 2 data (Berrino *et al*., 1998) has shown that post-cricoid region tumors have a more pejorative prognosis than other hypopharyngeal sites.

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Excess mortality data from the Eurocare study

Table 15.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 2,887)
0-1	37.02 [35.22-38.82]
1-2	34.34 [32.08 -36.60]
2-3	20.36 [17.92 -22.81]
3-4	16.07 [13.50 -18.63]
4-5	12.21 [9.58 -14.84]
5-6	11.32 [8.38 -14.27]
6-7	7.74 [4.80 -10.69]
7-8	8.01 [4.73 -11.29]
8-9	7.31 [3.59 -11.02]
9-10	9.11 [4.22 -13.99]
10-11	8.70 [3.19 -14.21]
11-12	10.85 [3.75 -17.95]

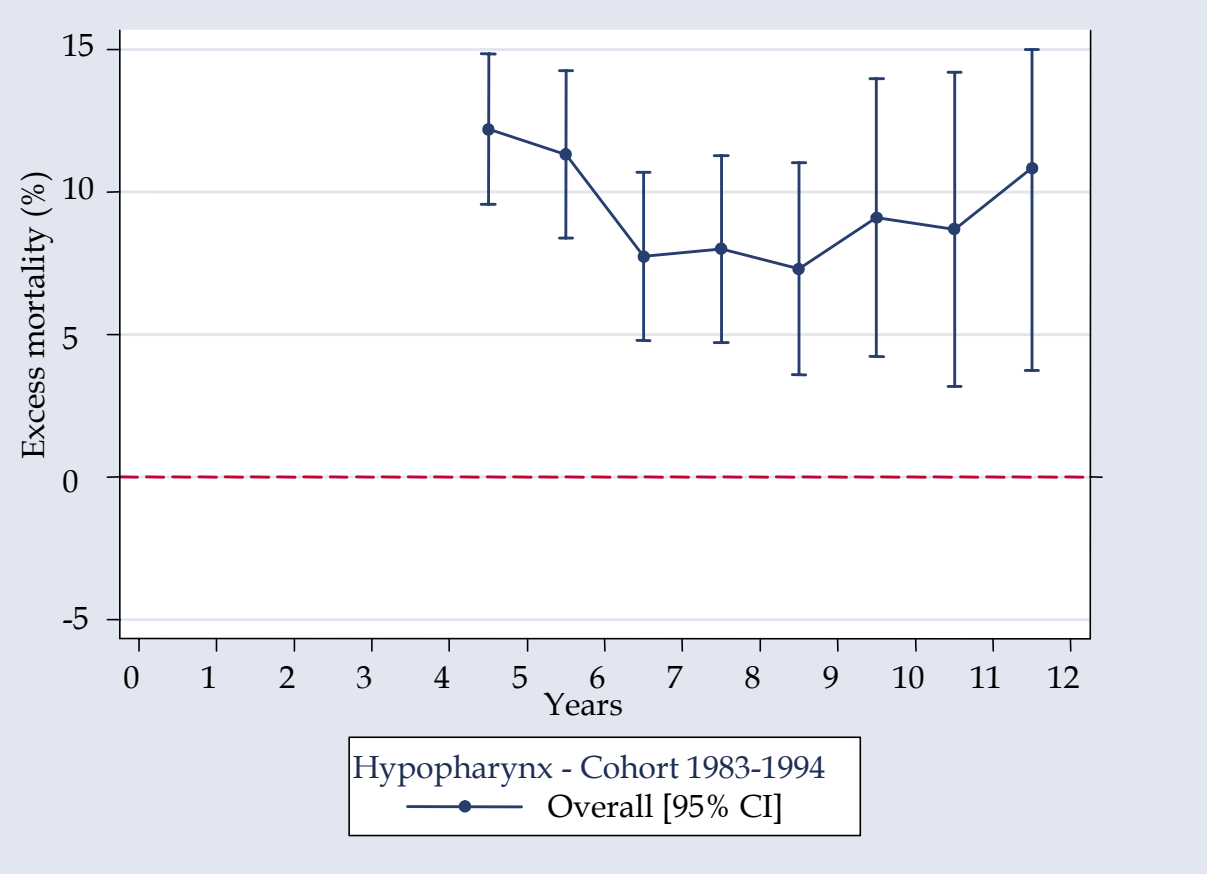

Figure 15.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 15.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 272)	Men (N = 2,594)
0-1	30.62 [25.04-36.19]	37.21 [35.31-39.12]
1-2	22.84 [16.36-29.32]	34.96 [32.56-37.36]
2-3	17.12 [10.03-24.21]	19.57 [17.00-22.14]
3-4	7.52 [1.72-13.32]	16.77 [14.01-19.53]
4-5	5.31 [-0.26-10.89]	12.63 [9.77-15.48]
5-6	3.87 [-1.85-9.60]	11.36 [8.20-14.52]
6-7	4.50 [-1.93-10.92]	8.25 [5.01-11.49]
7-8	0.96 [-3.77-5.70]	8.49 [4.87-12.12]
8-9	1.60 [-4.34-7.53]	7.85 [3.72-11.98]
9-10	2.63 [-6.25-11.51]	8.29 [3.17-13.42]
10-11	3.34 [-6.64-13.31]	9.69 [3.45-15.92]
11-12	4.90 [-7.54-17.33]	11.09 [3.14-19.04]

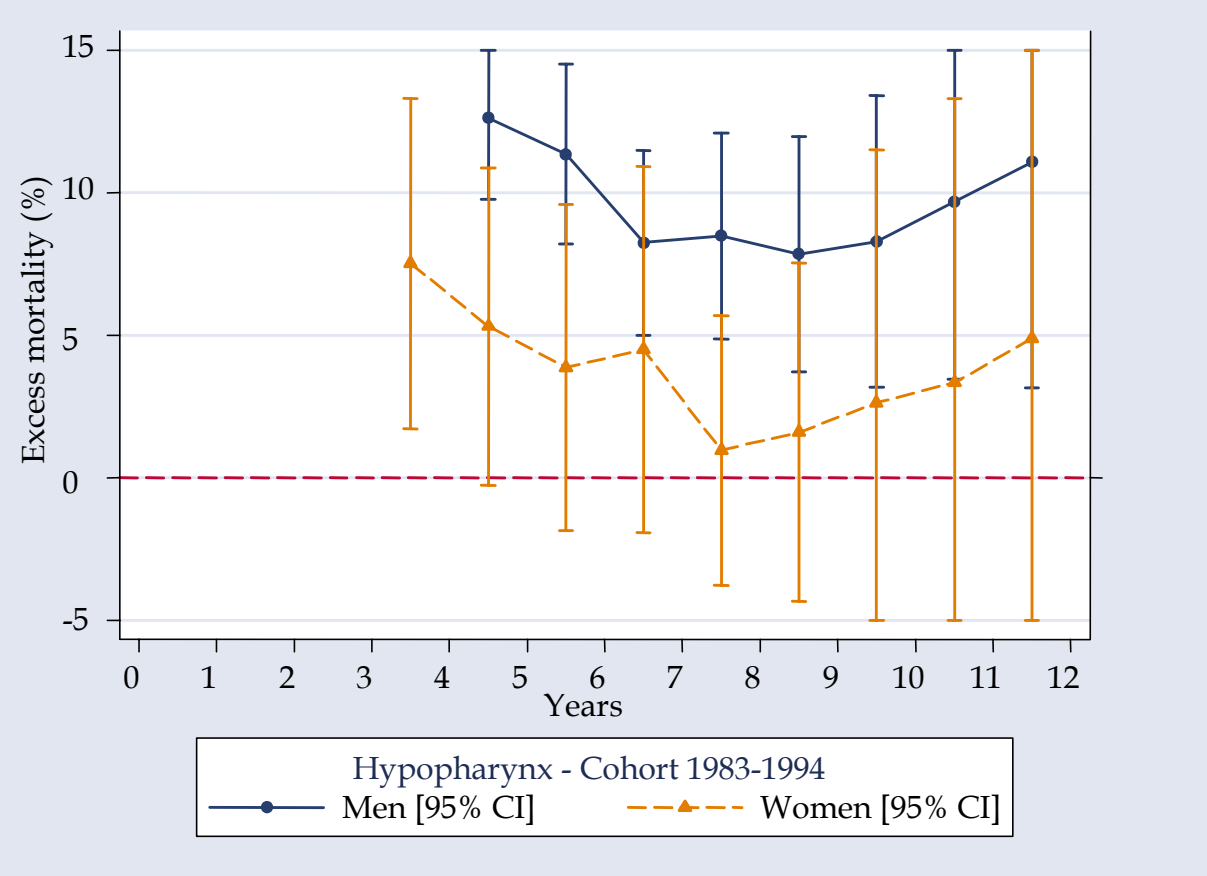

Figure 15.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 15.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) 15-44 years (N = 202)	45-54 years (N = 713)	55-64 years (N = 1,142)	65-74 years (N = 830)
0-1	33.49 [26.95-40.02]	31.46 [28.01-34.90]	37.10 [34.25-39.96]	42.69 [39.20-46.18]
1-2	27.83 [20.14-35.51]	34.71 [30.43-39.00]	35.66 [32.04-39.28]	33.82 [29.29-38.35]
2-3	15.12 [7.68-22.56]	15.47 [11.36-19.58]	22.87 [18.82-26.92]	23.58 [18.31-28.84]
3-4	15.61 [7.34-23.89]	15.60 [11.07-20.13]	16.43 [12.26-20.61]	16.22 [10.67-21.78]
4-5	4.75 [-0.88-10.38]	11.00 [6.56-15.43]	13.22 [8.84-17.59]	14.94 [8.74-21.15]
5-6	1.62 [-2.24-5.47]	9.36 [4.60-14.12]	9.61 [5.13-14.09]	21.54 [13.30-29.79]
6-7	11.83 [1.77-21.89]	5.98 [1.61-10.35]	8.24 [3.38-13.09]	7.55 [-0.18-15.27]
7-8	8.82 [-1.17-18.82]	2.49 [-0.89-5.87]	17.32 [10.39-24.26]	-2.05 [-6.81-2.70]
8-9	3.62 [-4.25-11.49]	6.39 [1.05-11.73]	12.95 [5.18-20.71]	0.61 [-6.81-8.03]
9-10	-0.54 [-8.42-7.34]	7.14 [0.12-14.17]	13.44 [3.71-23.17]	11.44 [-1.91-24.78]
10-11	10.01 [-3.87-23.89]	10.87 [1.74-19.99]	4.84 [-3.66-13.35]	9.72 [-5.73-25.16]
11-12	6.32 [-6.80-19.44]	7.17 [-2.11-16.45]	13.67 [0.11-27.24]	-

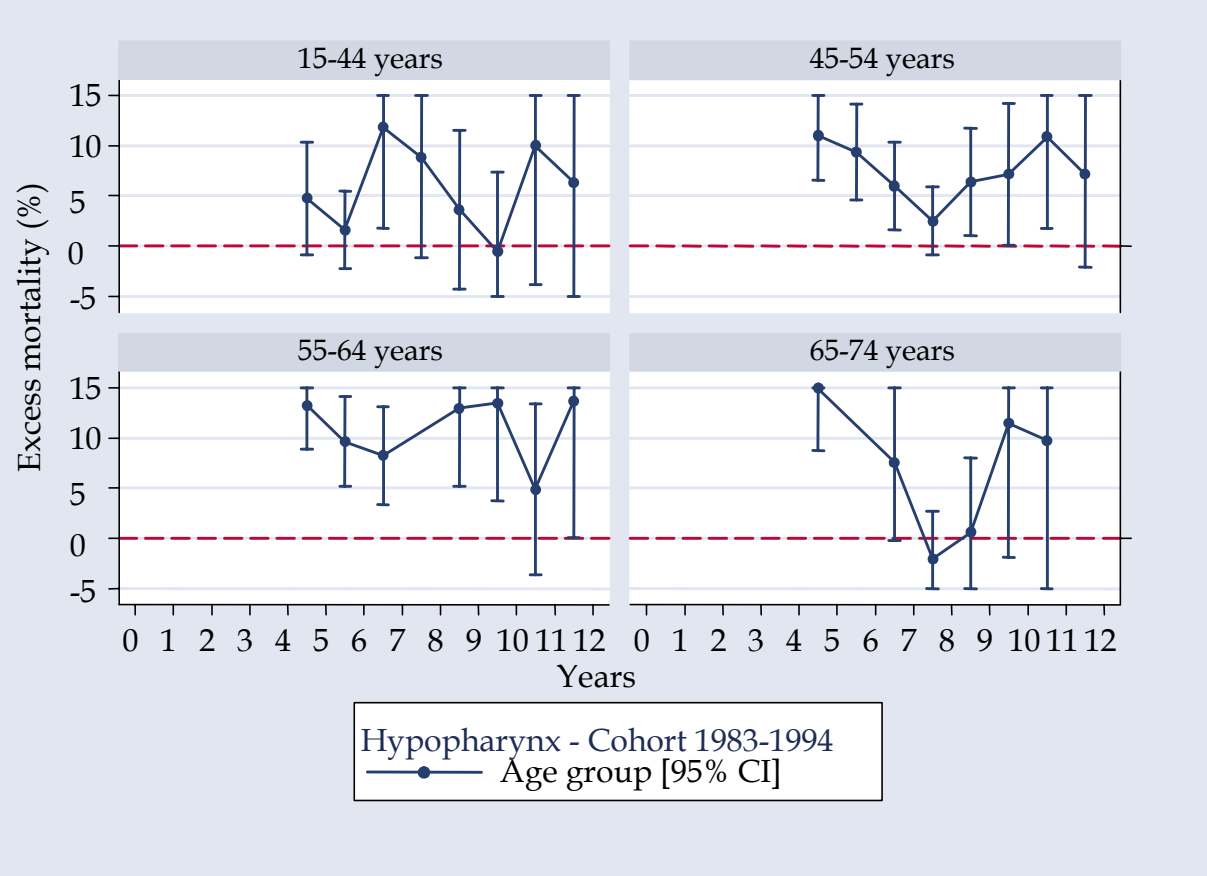

Figure 15.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 15.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 1983-1985 (N = 669)	Cohort 1986-1988 (N = 730)	Cohort 1989-1991 (N = 767)	Cohort 1992-1994 (N = 721)
0-1	37.19 [33.44-40.94]	38.29 [34.69-41.89]	34.50 [31.06-37.95]	38.26 [34.64-41.89]
1-2	34.11 [29.41-38.81]	34.18 [29.63-38.73]	34.88 [30.57-39.19]	34.11 [29.56-38.66]
2-3	21.53 [16.36-26.69]	20.08 [15.17-24.99]	21.01 [16.31-25.70]	18.82 [14.02-23.63]
3-4	19.57 [13.83-25.30]	16.87 [11.61-22.13]	14.99 [10.25-19.74]	13.21 [8.42-18.00]
4-5	10.74 [5.48-16.01]	12.37 [7.14-17.61]	13.78 [8.72-18.84]	11.47 [5.99-16.94]
5-6	11.08 [5.38-16.79]	13.95 [8.03-19.88]	7.01 [2.69-11.33]	17.20 [7.37-27.03]
6-7	6.21 [1.19-11.23]	9.15 [3.56-14.73]	7.79 [3.07-12.51]	-
7-8	8.66 [2.74-14.57]	6.85 [1.42-12.28]	8.48 [2.79-14.16]	-
8-9	9.93 [3.27-16.59]	6.77 [1.05-12.48]	3.48 [-2.83-9.78]	-
9-10	6.68 [0.37-13.00]	11.48 [4.08-18.87]	-	-
10-11	7.80 [0.74-14.86]	9.87 [1.12-18.63]	-	-
11-12	10.99 [2.46-19.52]	10.33 [-2.37-23.04]	-	-

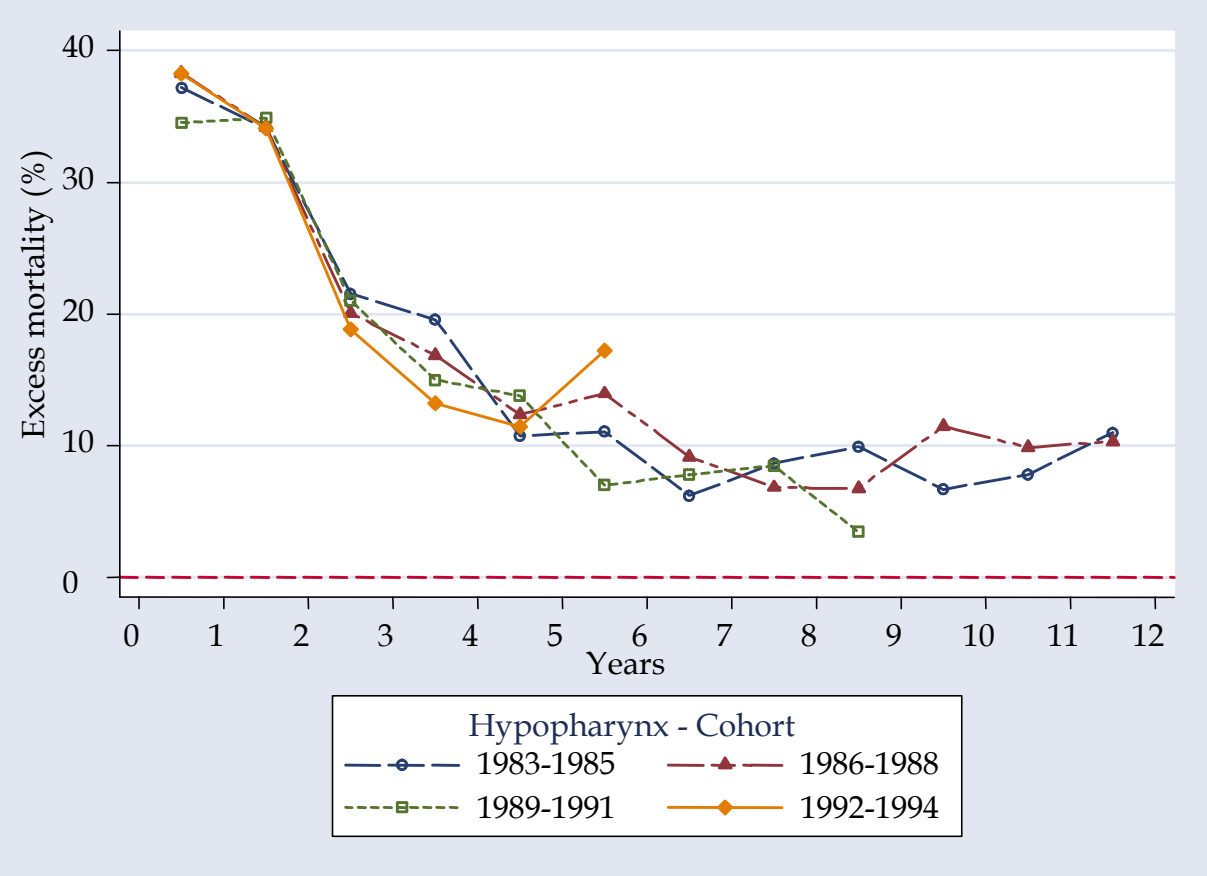

Figure 15.4: Time course of annual excess mortality by cohort

16

Oropharyngeal cancer

The oropharyngeal tumors addressed below are coded C09.x (tonsil and tonsillar fossa) and C10.x (glosso-epiglottal sulcus and oropharynx proper) in the CIM-O 2. On the basis of the data for the period 1980-1993 (Ménégoz *et al*., 2002), oropharyngeal tumors accounted for 25% of the 12,990 new cases of cancer of the mouth and pharynx diagnosed in men in France in 2000 (Remontet *et al*., 2003), i.e. 3,248 new cases. In women, oropharyngeal cancer was less frequent, accounting for about 20% of the 2,400 cases of oral and pharyngeal cancer incident in 2000, i.e. 480 new cases.

A French study of the period 1980-1993 showed a decrease in the mortality rate for men but no significant decrease in incidence. In women, no significant change was detected (Ménégoz *et al*., 2002).

The incidence truly begins to increase after age 35 years and peaks between 55 and 60 years before falling off fairly rapidly. The median age at diagnosis was close to 60 years for both men and women.

On the basis of the Eurocare data for diagnostic cohort 1992-1994, the 5-year relative survival was 40.3% for all stages taken together and the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 16.I shows the overall annual excess mortality estimates with their 95% confidence intervals. The data take into account all patients whose oropharyngeal cancer was diagnosed between 1983 and 1994 in Europe (8 countries). The annual excess mortality was less than 5% as of year 8 post-diagnosis (figure 16.1).

Table 16.II shows the annual excess mortality estimates by gender. The annual excess mortality was higher for men. However, the small population of women suffering from oropharyngeal cancer prevents confirmation of the lower annual excess mortality in women (figure 16.2).

Table 16.III shows the annual excess mortality rates by age group. The annual excess mortality was lower for age group 15-44 years. It was not significantly different from zero as of year 6 post-diagnosis for age group 15-44 years. The annual excess mortality is less than 5% for age group 45-54 years as of year 9 post-diagnosis and for age group 65-74 years as of year 5 post-diagnosis. The annual excess mortality remained greater than 5% for the age group 55-64 years (figure 16.3). However, since the confidence intervals are very large, the above trends are not reliable.

The annual excess mortality data for the 4 cohorts are shown in table 16.IV. The diagnostic period slightly influenced the early annual excess mortality rate (figure 16.4).

Influence of site on survival

Work on the Eurocare 2 data (Berrino *et al*., 1998) has shown differences in survival as a function of the exact anatomical site of oropharyngeal cancer. Tumors of the tonsil and tonsillar fossa have a better prognosis than those of the other oropharyngeal sites. The differences are probably due to the earliness of diagnosis and the scope for surgical treatment.

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Excess mortality data from the Eurocare study

Table 16.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 3,177)
0-1	27.02 [25.44-28.61]
1-2	25.89 [24.04 -27.74]
2-3	16.06 [14.21 -17.91]
3-4	11.01 [9.23 -12.80]
4-5	10.19 [8.28 -12.10]
5-6	5.84 [4.07 -7.61]
6-7	5.95 [3.87 -8.03]
7-8	5.94 [3.66 -8.21]
8-9	4.54 [2.16 -6.92]
9-10	2.76 [0.31 -5.21]
10-11	5.15 [1.92 -8.37]
11-12	4.79 [0.99 -8.59]

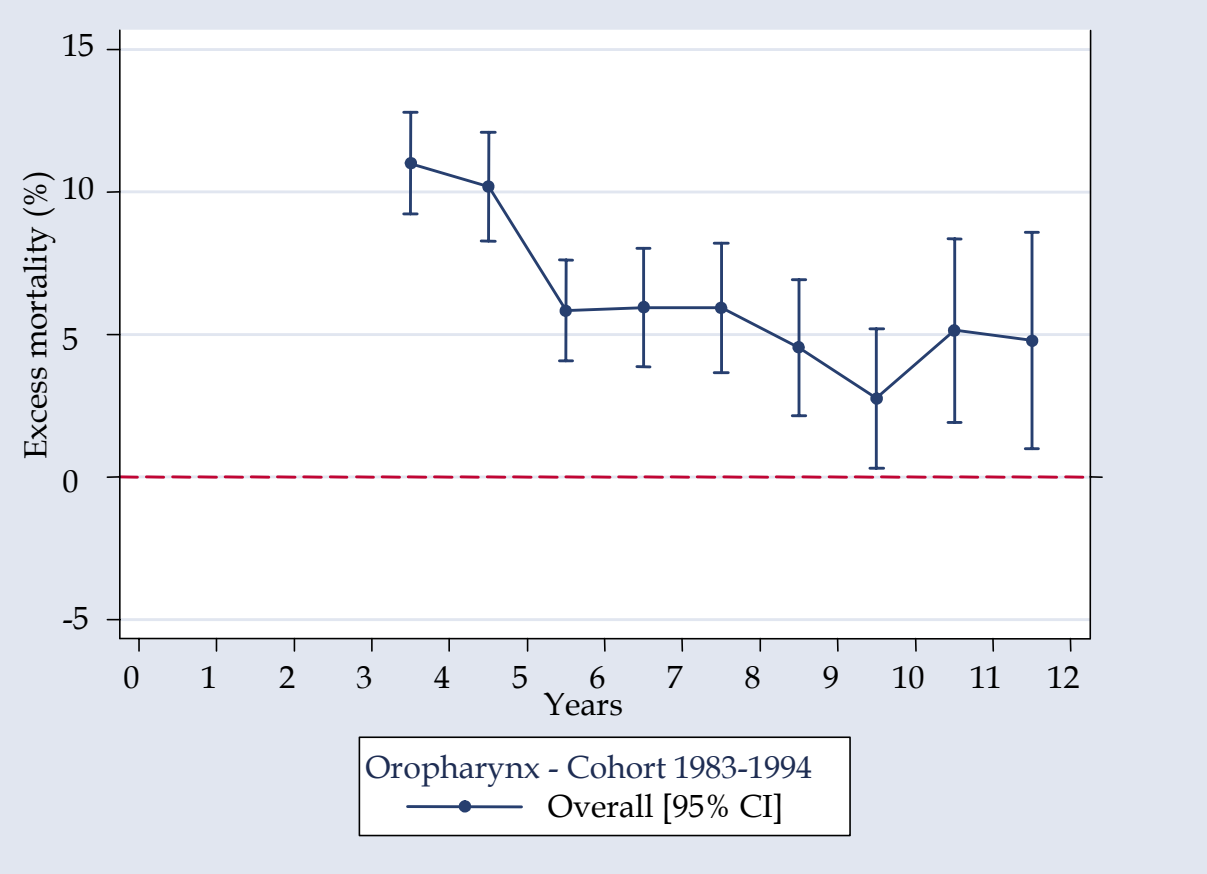

Figure 16.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 16.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 543)	Men (N = 2,630)
0-1	18.54 [15.20-21.88]	28.67 [26.90-30.45]
1-2	18.43 [14.70-22.16]	27.36 [25.26-29.46]
2-3	9.45 [6.24-12.66]	17.76 [15.59-19.93]
3-4	9.76 [6.29-13.23]	11.19 [9.14-13.25]
4-5	9.17 [5.44-12.89]	10.51 [8.29-12.72]
5-6	3.48 [0.56-6.41]	5.96 [3.91-8.01]
6-7	3.31 [0.03-6.59]	6.67 [4.16-9.17]
7-8	3.17 [-0.33-6.67]	6.09 [3.41-8.76]
8-9	1.36 [-1.75-4.48]	4.98 [2.07-7.88]
9-10	-0.47 [-2.76-1.82]	4.09 [0.85-7.33]
10-11	0.88 [-2.83-4.60]	6.61 [2.44-10.79]
11-12	1.91 [-3.23-7.04]	4.26 [-0.24-8.77]

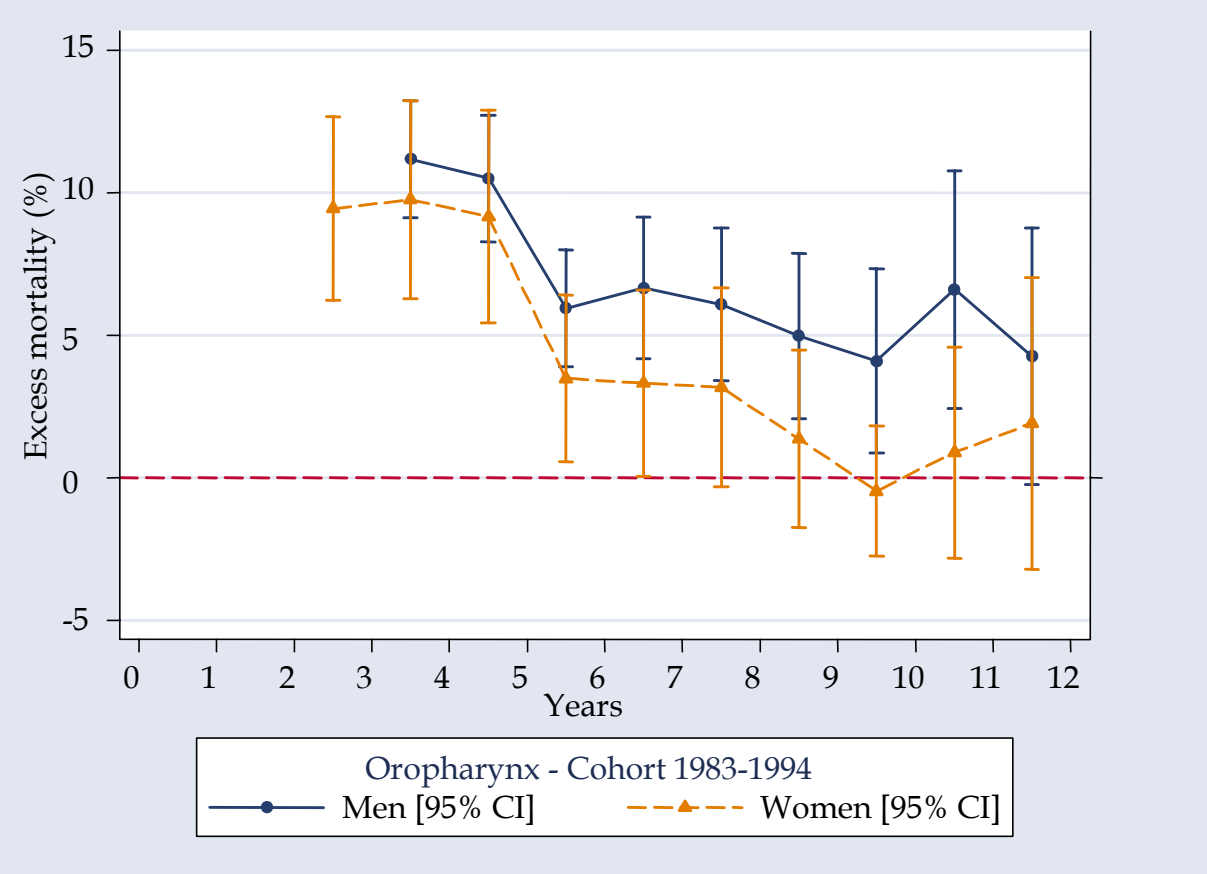

Figure 16.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 16.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	15-44 years (N = 287)	45-54 years (N = 853)	55-64 years (N = 1,219)	65-74 years (N = 818)
0-1	19.35 [14.75-23.96]	22.69 [19.85-25.54]	28.46 [25.86-31.05]	32.24 [28.89-35.59]
1-2	23.05 [17.55-28.55]	25.04 [21.67-28.40]	27.28 [24.22-30.34]	25.92 [22.00-29.85]
2-3	8.90 [4.61-13.18]	16.20 [12.85-19.54]	17.93 [14.77-21.10]	16.20 [12.14-20.26]
3-4	6.10 [2.27-9.93]	8.93 [6.03-11.83]	11.63 [8.61-14.65]	15.34 [10.86-19.81]
4-5	4.05 [0.65-7.45]	6.99 [4.15-9.83]	13.03 [9.55-16.50]	13.59 [8.66-18.52]
5-6	3.18 [-0.18-6.54]	6.45 [3.41-9.50]	7.12 [3.90-10.34]	4.38 [0.13-8.63]
6-7	0.75 [-1.38-2.88]	7.28 [3.58-10.99]	7.09 [3.28-10.90]	5.51 [0.18-10.84]
7-8	0.87 [-1.53-3.27]	6.02 [2.24-9.79]	10.03 [5.36-14.70]	2.33 [-2.73-7.39]
8-9	2.38 [-1.40-6.17]	7.13 [2.54-11.73]	4.08 [0.03-8.14]	3.03 [-3.15-9.20]
9-10	2.95 [-1.62-7.51]	3.01 [-0.93-6.95]	2.47 [-1.83-6.77]	2.67 [-4.95-10.30]
10-11	5.49 [-1.00-11.97]	5.90 [0.45-11.34]	7.32 [0.72-13.92]	-0.40 [-7.58-6.78]
11-12	-0.43 [-6.92-6.06]	1.98 [-2.43-6.40]	10.15 [1.08-19.22]	7.24 [-4.93-19.41]

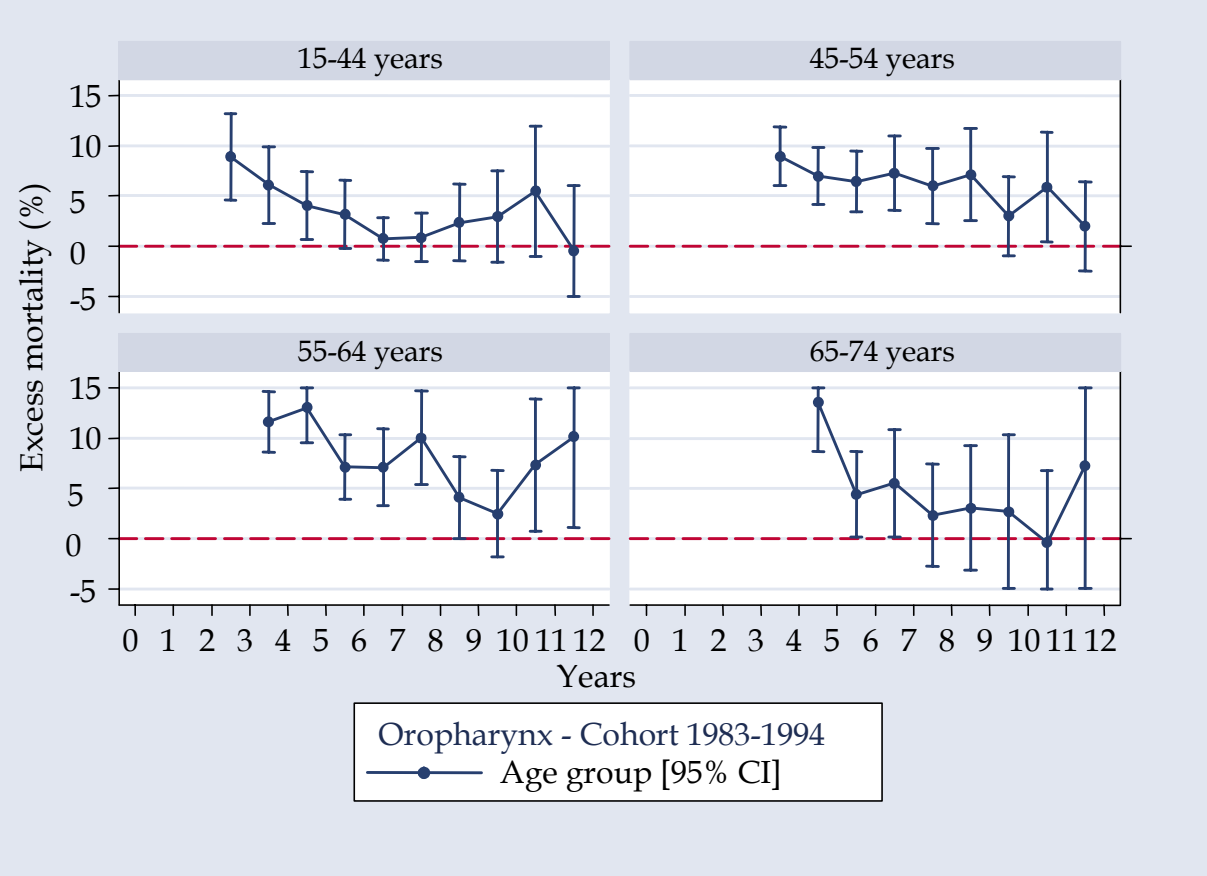

Figure 16.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 16.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (% annual) Cohort 1983-1985 (N = 659)	Cohort 1986-1988 (N = 803)	Cohort 1989-1991 (N = 835)	Cohort 1992-1994 (N = 880)
0-1	32.05 [28.40-35.70]	25.81 [22.70-28.93]	26.26 [23.20-29.33]	25.10 [22.16-28.03]
1-2	29.18 [24.80-33.56]	24.75 [21.13-28.36]	26.31 [22.71-29.91]	24.31 [20.92-27.70]
2-3	18.93 [14.33-23.53]	17.92 [14.13-21.71]	15.77 [12.20-19.35]	12.87 [9.72-16.01]
3-4	10.56 [6.37-14.74]	9.36 [6.01-12.70]	9.85 [6.53-13.17]	13.71 [10.20-17.21]
4-5	12.61 [7.81-17.41]	11.77 [7.90-15.65]	11.27 [7.55-14.99]	5.54 [2.57-8.50]
5-6	7.71 [3.35-12.08]	4.29 [1.36-7.22]	5.90 [2.75-9.05]	6.16 [1.95-10.36]
6-7	8.69 [3.87-13.50]	4.20 [1.17-7.23]	5.91 [2.55-9.27]	-
7-8	4.94 [0.73-9.15]	8.00 [4.08-11.93]	4.10 [0.59-7.60]	-
8-9	3.24 [-0.61-7.09]	3.65 [0.40-6.89]	8.30 [2.08-14.52]	-
9-10	4.97 [0.41-9.54]	1.30 [-1.42-4.01]	-	-
10-11	6.39 [1.21-11.58]	4.20 [0.13-8.27]	-	-
11-12	4.38 [-0.55-9.32]	5.33 [-0.56-11.21]	-	-

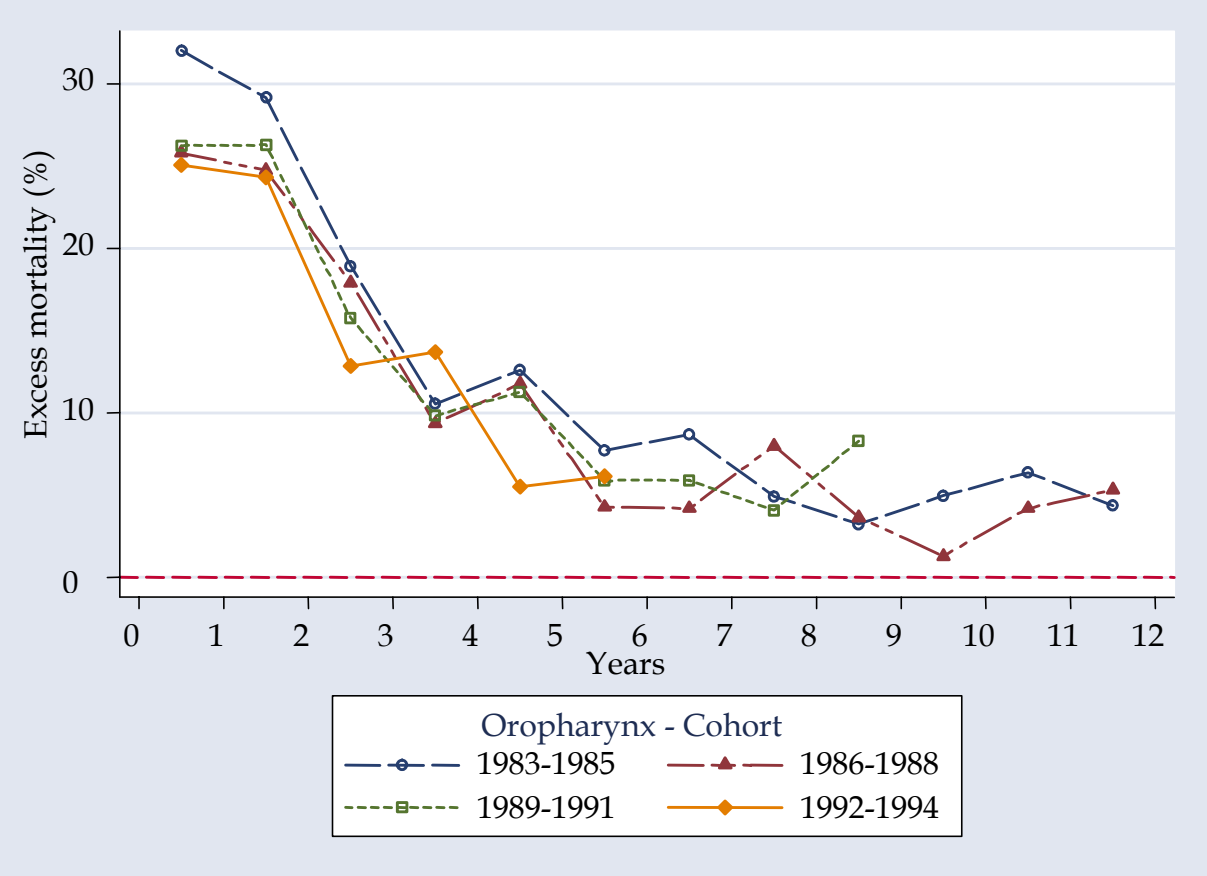

Figure 16.4: Time course of annual excess mortality by cohort

17

Nasopharyngeal cancer

Nasopharyngeal cancer is coded C11.x in the CIM-O 2. This cancer is relatively rare and only accounts for a small proportion of cancers of the "lips, mouth and pharynx". Nasopharyngeal cancer differs from other ENT tumors by the fact that its emergence is not related to alcohol abuse or smoking. However, it is frequently associated with prior Epstein-Barr virus infection.

On the basis of the French data for the period 1980-1993 (Ménégoz *et al*., 2002), nasopharyngeal cancer only accounted for 2.3% of the 12,900 new cases of oral and pharyngeal cancer diagnosed in men in France in 2000 (Remontet *et al*., 2003), i.e. 299 new cases. In women, although nasopharyngeal cancer is slightly less frequent, it accounted for about 6.4% of the 2,400 new cases of oral and pharyngeal cancer in 2000, i.e. 154 new cases.

A French study of the period 1980-1993 did not show any change in the incidence or mortality rates for men or women (Ménégoz *et al*., 2002).

Nasopharyngeal cancer occurs in young subjects. The incidence is 0.5/100,000 between age 15 and 40 years, rising subsequently to about 2/100,000 between age 40 and 75 years. The median age is 52 years for men and 49 years for women.

On the basis of the Eurocare data for patients in diagnostic cohort 1992-1994, the 5-year relative survival was 49.4% for all stages taken together and the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 17.I shows the overall annual excess mortality estimates with their 95% confidence intervals. The data take into account all the patients in diagnostic cohorts 1983-1994 in Europe (8 countries). The annual excess mortality was less than 5% as of year 8 post-diagnosis (figure 17.1).

Table 17.II shows the annual excess mortality estimates by gender. The annual excess mortality was higher for men, mainly during the first years post-diagnosis (figure 17.2).

Table 17.III shows the annual excess mortality results by age group. Age at diagnosis influences both the early and late annual excess mortality rates. For age groups 15-44 years and 45-54 years, the annual excess mortality was not significantly different from zero as of year 7 post-diagnosis. The annual excess mortality was close to zero for age groups 55-64 years and 65-74 years as of year 8 post-diagnosis. However, the precision is poor since the confidence intervals are very large (figure 17.3).

The annual excess mortality data for the 4 cohorts are shown in table 17.IV. The diagnostic period did not influence the early annual excess mortality (figure 17.4). The confidence intervals of the various cohorts overlap.

Influence of tumor morphology and treatment on survival

Work on the Eurocare 2 data (Jiong *et al*., 1998) has addressed the survival of subjects presenting with nasopharyngeal tumors as a function of tumor morphology. The most frequent forms in Europe are squamous-cell carcinomas (48%) followed by undifferentiated tumors (39%). In contrast to what is frequently observed with other tumors, the undifferentiated forms have the best prognosis (RR=0.82 adjusted for age and gender). Jiong *et al*. (1998) explain the difference by the greater sensitivity of undifferentiated tumors to radiotherapy and chemotherapy which constitute the standard treatments given that the topography of the tumors renders surgical treatment difficult.

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Excess mortality data from the Eurocare study

Table 17.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 1,074)
0-1	18.51 [16.10-20.91]
1-2	16.84 [14.24 -19.44]
2-3	14.29 [11.58 -16.99]
3-4	9.88 [7.32 -12.45]
4-5	7.35 [4.86 -9.84]
5-6	5.60 [3.13 -8.07]
6-7	7.47 [4.38 -10.57]
7-8	6.00 [2.87 -9.13]
8-9	1.58 [-0.82 -3.97]
9-10	2.96 [-0.30 -6.22]
10-11	0.93 [-1.87 -3.74]
11-12	3.75 [-0.76 -8.26]

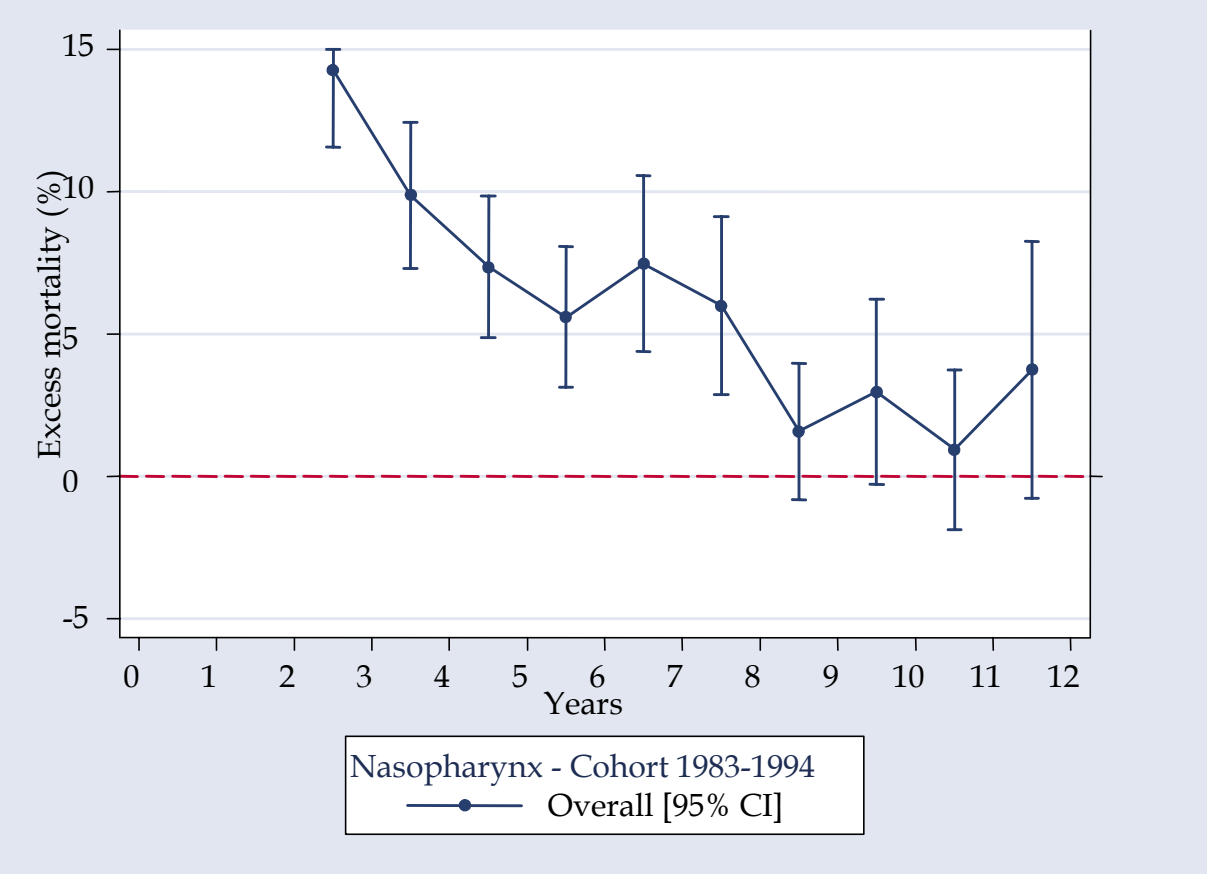

Figure 17.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 17.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 275)	Men (N = 795)
0-1	16.17 [11.72-20.62]	18.91 [16.08-21.73]
1-2	13.99 [9.31-18.68]	16.65 [13.61-19.70]
2-3	6.56 [2.77-10.35]	15.69 [12.39-18.99]
3-4	5.38 [1.69-9.07]	10.62 [7.46-13.77]
4-5	3.45 [0.12-6.77]	8.21 [5.08-11.33]
5-6	1.53 [-1.13-4.20]	6.86 [3.58-10.13]
6-7	4.74 [0.34-9.14]	7.98 [4.07-11.89]
7-8	6.87 [1.32-12.43]	4.70 [1.10-8.31]
8-9	0.52 [-2.48-3.52]	2.14 [-1.13-5.42]
9-10	2.29 [-2.23-6.80]	3.34 [-1.08-7.76]
10-11	-1.08 [-5.60-3.43]	0.84 [-2.96-4.65]
11-12	-1.24 [-5.77-3.28]	2.46 [-2.97-7.89]

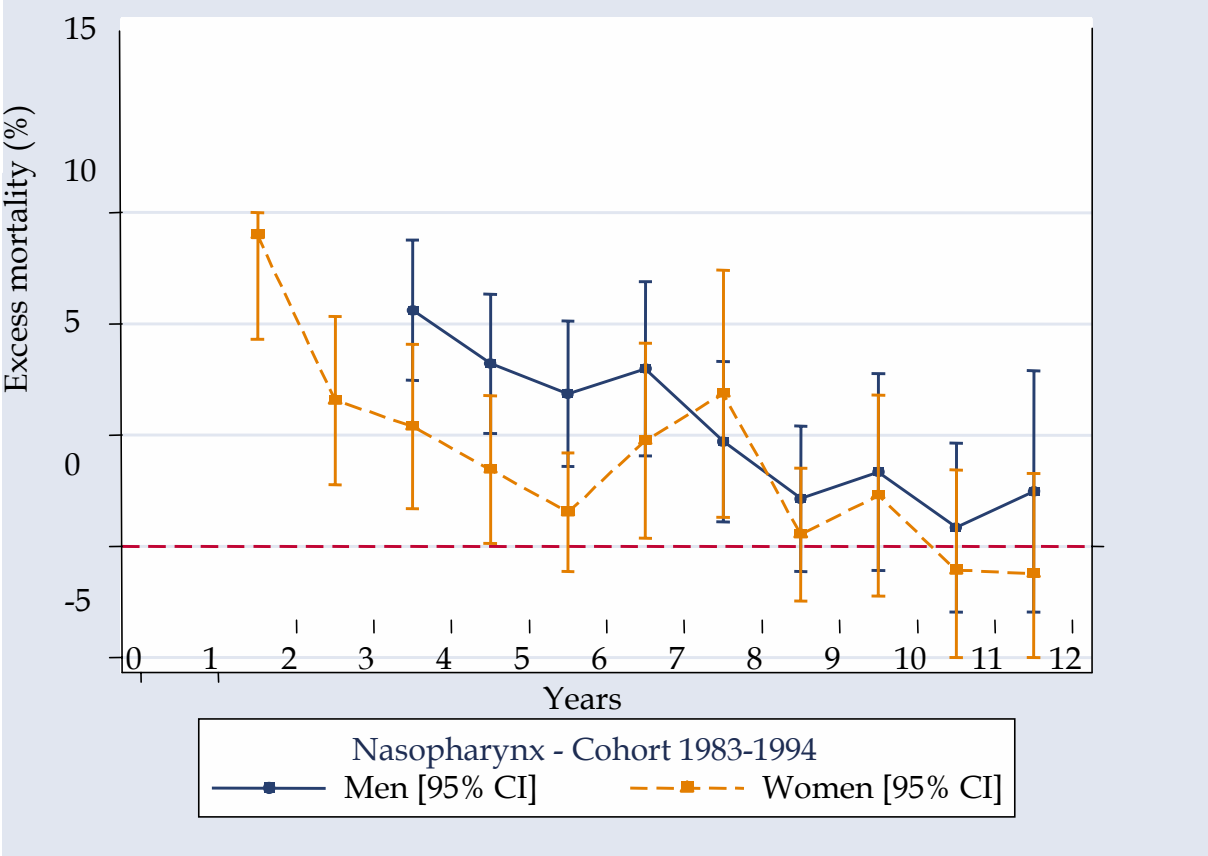

Figure 17.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 17.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	15-44 years (N = 247)	45-54 years (N = 222)	55-64 years (N = 330)	65-74 years (N = 275)
0-1	7.98 [4.56-11.39]	16.29 [11.36-21.21]	18.79 [14.44-23.15]	29.71 [24.04-35.37]
1-2	11.37 [7.20-15.53]	16.99 [11.48-22.49]	18.68 [13.78-23.58]	20.95 [14.65-27.26]
2-3	11.85 [7.34-16.37]	14.21 [8.52-19.91]	19.59 [14.01-25.17]	9.91 [4.18-15.64]
3-4	10.70 [6.08-15.31]	5.75 [1.52-9.98]	9.63 [4.80-14.45]	13.49 [6.63-20.35]
4-5	5.19 [1.57-8.82]	4.65 [0.56-8.74]	10.05 [4.70-15.40]	10.15 [3.04-17.26]
5-6	4.46 [0.82-8.11]	7.49 [2.08-12.89]	5.56 [0.70-10.41]	5.08 [-1.54-11.69]
6-7	5.44 [1.05-9.83]	6.92 [1.03-12.80]	7.41 [1.30-13.53]	11.87 [2.41-21.32]
7-8	4.14 [-0.04-8.31]	3.62 [-1.26-8.51]	6.46 [-0.01-12.92]	12.52 [1.32-23.71]
8-9	-0.24 [-4.42-3.94]	1.04 [-2.65-4.74]	5.50 [-1.76-12.77]	0.21 [-7.69-8.12]
9-10	3.14 [-1.49-7.77]	1.41 [-3.14-5.96]	2.70 [-4.22-9.62]	5.54 [-7.06-18.14]
10-11	1.89 [-2.29-6.08]	1.61 [-3.46-6.69]	-2.57 [-9.50-4.36]	3.50 [-10.24-17.23]
11-12	-0.28 [-4.46-3.90]	2.50 [-4.45-9.45]	4.12 [-5.21-13.45]	-

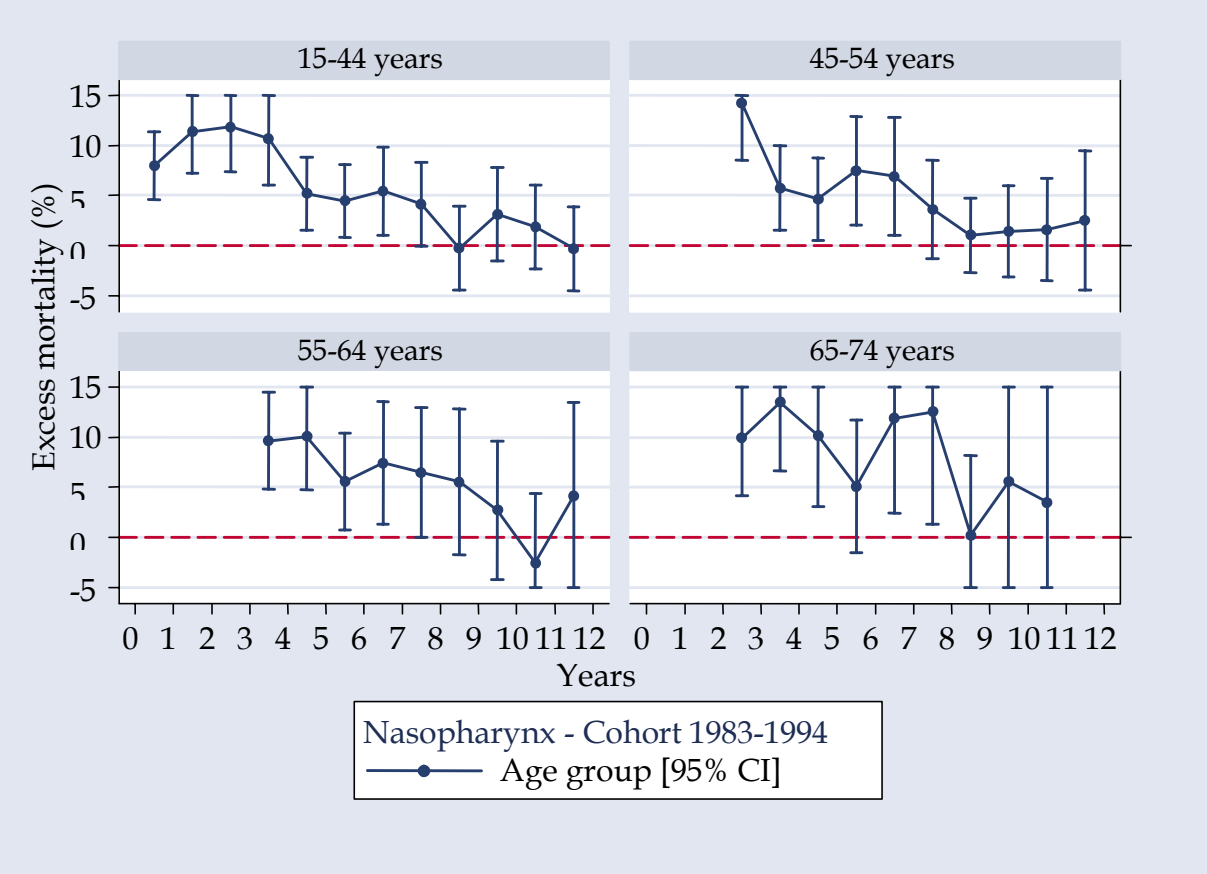

Figure 17.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 17.IV: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 1983-1985 (N = 253)	Cohort 1986-1988 (N = 291)	Cohort 1989-1991 (N = 286)	Cohort 1992-1994 (N = 244)
0-1	19.42 [14.37-24.47]	17.95 [13.38-22.52]	18.03 [13.43-22.63]	18.77 [13.73-23.81]
1-2	14.06 [8.98-19.15]	19.29 [14.05-24.52]	18.76 [13.56-23.96]	14.46 [9.34-19.58]
2-3	18.11 [12.03-24.20]	11.90 [7.00-16.80]	15.47 [10.04-20.89]	11.80 [6.63-16.97]
3-4	11.44 [5.70-17.18]	9.43 [4.61-14.25]	8.80 [4.00-13.60]	10.08 [4.83-15.33]
4-5	6.30 [1.35-11.25]	6.45 [2.02-10.88]	6.89 [2.25-11.54]	10.31 [4.15-16.48]
5-6	8.78 [2.93-14.63]	4.72 [0.59-8.85]	1.90 [-1.23-5.02]	9.97 [1.48-18.46]
6-7	5.65 [0.30-11.00]	8.47 [3.13-13.81]	7.89 [2.61-13.17]	-
7-8	5.04 [-0.39-10.47]	8.71 [2.96-14.45]	3.44 [-1.14-8.03]	-
8-9	1.78 [-2.52-6.08]	1.60 [-1.89-5.08]	1.06 [-3.85-5.97]	-
9-10	1.80 [-2.68-6.27]	3.91 [-0.75-8.56]	-	-
10-11	3.37 [-2.04-8.79]	-1.67 [-6.33-2.99]	-	-
11-12	5.21 [-1.19-11.60]	1.07 [-4.10-6.24]	-	-

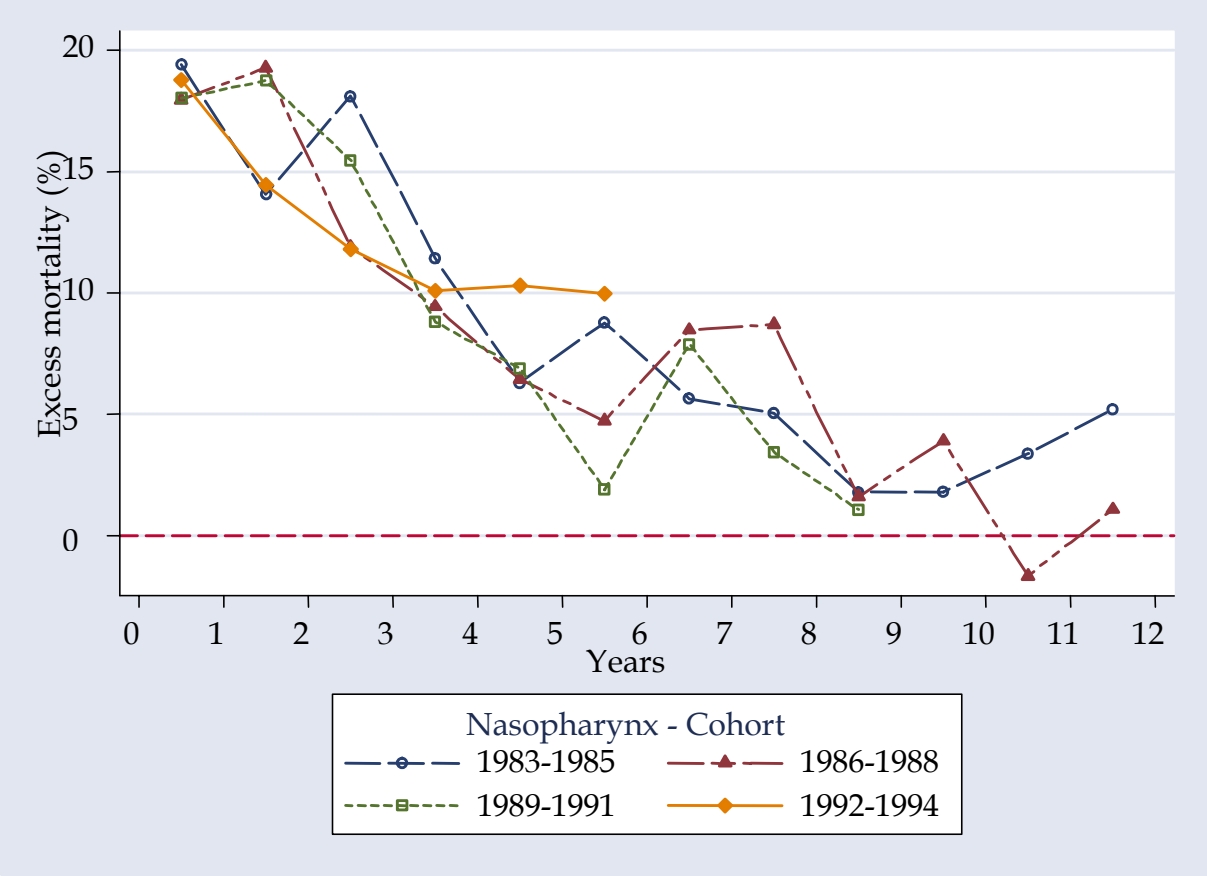

Figure 17.4: Time course of annual excess mortality by cohort

18

Thyroid cancer

With 3,711 cases incident in France in 2000, thyroid cancer accounted for 1% of all incident cancer cases (Remontet *et al*., 2003).

The incidence of thyroid cancer has increased over the last two decades. In men, the age-standardized incidence rate (world population) was 1.2/100,000 in 1980 and 2.12/100,000 in 2000, i.e. a mean annual increase of 2.89%. For women, the age-standardized incidence rate (world population) increased from 2.7/100,000 in 1980 to 7.5/100,000 in 2000, i.e. a mean annual increase of 4.80% (Remontet *et al*., 2003). The sex ratio was 0.3.

The risk of developing thyroid cancer by birth cohort is increasing. The pronounced cohort effect is observed in both men and women, with an acceleration from the 1928 cohort. The mortality by birth cohort shows a decrease in the risk of death from thyroid cancer.

The median age at diagnosis was 51 years for women and 52 years for men. Incidence decreased from age 65 years for women and 75 years for men.

Despite the increase in incidence, the mortality has been falling off regularly. The mean annual change was -1.37% for men and -1.87% for women.

On the basis of the Eurocare data, the 5-year relative survival for all stages of thyroid cancer was 90.1% for the patients in diagnostic cohort 1992-1994 and for the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 18.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates take into account all the patients whose thyroid cancer was diagnosed between 1983 and 1994 in Europe (8 countries). The annual excess mortality was 1.65% as of the first year post-diagnosis. Annual excess mortality fell thereafter, stabilizing at 0.5% for year 5 post-diagnosis (figure 18.1).

Table 18.II shows the annual excess mortality data by gender. The annual excess mortality was approximately 2-fold higher for men than for women in the first years post-diagnosis. The difference decreases with time (figure 18.2).

Table 18.III shows the annual excess mortality results by age group. For the age group 15-44 years, the excess mortality was 0.71% from 0 to 1 year post-diagnosis. Subsequently, it fell rapidly to zero as of year 4 post-diagnosis. The profile for age group 45-54 years was very similar (figure 18.3). For age groups 55-64 years and 65-74 years, the excess mortality did not reach zero but fluctuated around 1.3 and 1.5%, respectively, over the terminal portion of the curve.

The annual excess mortality data for the 4 cohorts are shown in table 18.IV. The annual excess mortality estimates appear lower for the last cohort, 1992-1994, over the first 2 years post-diagnosis (figure 18.4).

Very long-term annual excess mortality (all stages considered): other studies

Two population data sources are available for evaluation of the very long-term excess mortality: the data generated by the US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the data in the Swedish national cancer registry.

Brenner (2002) evaluated the 5-, 10-, 15- and 20-year relative survivals for patients presenting with thyroid cancer diagnosed between 1973 and 1998 using the US SEER program data. Using the period analysis method (which takes into account the survival observed during the first years post-diagnosis for the most recent periods), the relative survival estimates were 96, 95.8, 94 and 95.4%, respectively. The mean annual excess mortality estimate was close to zero for the period as a whole.

For patients presenting with thyroid cancer diagnosed between 1960 and 1998, Talbäck *et al.* (2004) evaluated the 5-, 10- and 15-year relative survivals using the Swedish national cancer registry data. Using the period analysis method, the authors estimated the 5-, 10- and 15-year relative survivals to be 83.8, 81.7 and 85.1%, respectively. The data are similar to the 5-, 10- and 15-year relative survivals observed for patients whose disease was diagnosed in the most recent period: 85.2, 84.4 and 81.7%. The mean annual excess mortality estimate was close to zero over the whole period. The results were similar to those obtained with the US data. They show that there was no long-term excess mortality related to thyroid cancer.

Long-term relative survival or excess mortality by stage

The PETRI study (Ile-de-France, 2004) showed 5-year relative survivals of men and women with thyroid cancer in France of the order of 95%. The analysis by stage showed that most of the cases diagnosed were stage I and that the 5-year relative survival was 98%. Since few cases are diagnosed at stages II, III and IV, sufficiently precise survival data cannot be generated. In contrast, the analysis of survival by histology shows the good prognosis of papillary forms (5-year relative survival: 100%). The data on follicular forms (7 cases) are not sufficient to enable sufficiently precise survival data to be generated.

The US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated relative survival data by year and for three stages of the disease—localized, regional and metastatic (distant metastases)—and a non-determined stage (insufficient information in the base to determine the stage). Annual excess mortality rates by thyroid cancer stage have calculated from those data (table 18.V). The thyroid cancer stage distribution (localized, regional and metastatic) was as follows: 55.1, 36.5 and 5.5%. The results are for men and women of all ages for the diagnostic period 1988-2001.

Table 18.V: Annual excess mortality by stage at diagnosis for the period 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease (N+)	Metastatic disease (M+)
0-1	0.50	2.60	30.1
1-2	0.00	0.62	6.01
2-3	0.00	0.41	4.26
3-4	0.00	0.31	2.38
4-5	0.00	0.31	3.58
5-6	0.00	0.31	0.00
6-7	0.00	0.10	1.69
7-8	0.00	0.31	0.52
8-9	0.00	0.00	0.00
9-10	0.00	0.63	0.00

The results show nil annual excess mortality as of the first year post-diagnosis for the localized stage. For the other stages, the excess mortality falls very rapidly reaching 0 in all cases between 6 and 8 years post-diagnosis.

Influence of other prognostic factors and treatment on survival

The most frequent thyroid tumors derive from thyroglobulin-secreting (TG) follicular cells. The predominant group (over 80% of cases) consists in differentiated tumors: papillary tumors and follicular tumors. Little differentiated tumors (about 2% of cases) and undifferentiated or anaplastic tumors (4-5%) are rarer. In addition (7% of cases), C cell-derived (secreting calcitonin, CT) tumors or medullary tumors exist. One quarter of those cases are hereditary. Early screening for familial forms results in 100% recovery. Anaplastic tumors are more frequent in subjects aged over 60 years.

Prognosis is based on histologic type, age at diagnosis (greater than or less than 45 years), tumor size (greater than or less than 3 cm), local/regional status (confined or not confined to the gland), the presence or absence of lymph node metastases and the presence or absence of distant metastases.

For a subject aged less than 45 years presenting with a tumor measuring less than 3 cm and that is differentiated with no lymph node invasion, lymph node metastasis or remote metastasis, the 20-year survival is 100%.

The Champagne-Ardennes registry observed a very marked increase in frequency (from 29.1 to 43%) of papillary small tumors (0 to 1 cm) concomitantly with a significant decrease in large-diameter tumors (from 52.5 to 40.9% for tumors measuring less than 4 cm and from 17.7 to 15.9% for tumors measuring more than 4 cm or extending outside the capsule) for the period 1978-1982 and 1999-2001.

The American joint committee on cancer (AJCC) has reported 5-year relative survivals for stages I, II, III and IV papillary cancer in patients whose thyroid cancer was diagnosed between 1985 and 1990: 100, 100, 94 and 48%, respectively. For follicular cancer, the 5-year relative survivals were 99, 99, 82 and 47%, respectively. The 5-year relative survivals have also been estimated by histologic grade (table 18.VI) (Hundhal *et al*., 1998).

Table 18.VI: 5- and 10-year relative survivals by histologic subgroup and grade taken from Hundahl *et al*. (1998)

	5-year/10-year relative survivals (%) (number of patients)		
Histologic subgroup	Histologic grade 1	Histologic grade 2	Histologic grade 3
Papillary	98/86 (2365)	93/73 (760)	70/68 (254)
Follicular	97/47 (878)	85/65 (200)	59/52 (167)

The influence of therapeutic strategy on survival is difficult to determine even by means of a randomized prospective trial since the disease is only weakly progressive and the survivals are long. Moreover, treatment protocols differ.

In the particular case of undifferentiated tumors, survival is not modified by surgery, radiotherapy or chemotherapy alone. Only protocols combining several therapeutic approaches are able to enhance local tumor control preventing death by asphyxia.

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Excess mortality data from the Eurocare study

Table 18.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 9,819)
0-1	7.63 [7.08-8.17]
1-2	1.65 [1.34 -1.97]
2-3	1.11 [0.83 -1.38]
3-4	0.83 [0.56 -1.09]
4-5	0.71 [0.45 -0.97]
5-6	0.38 [0.13 -0.63]
6-7	0.67 [0.35 -0.99]
7-8	0.90 [0.54 -1.26]
8-9	0.44 [0.10 -0.79]
9-10	0.49 [0.08 -0.90]
10-11	0.61 [0.15 -1.07]
11-12	0.48 [-0.03 -0.99]

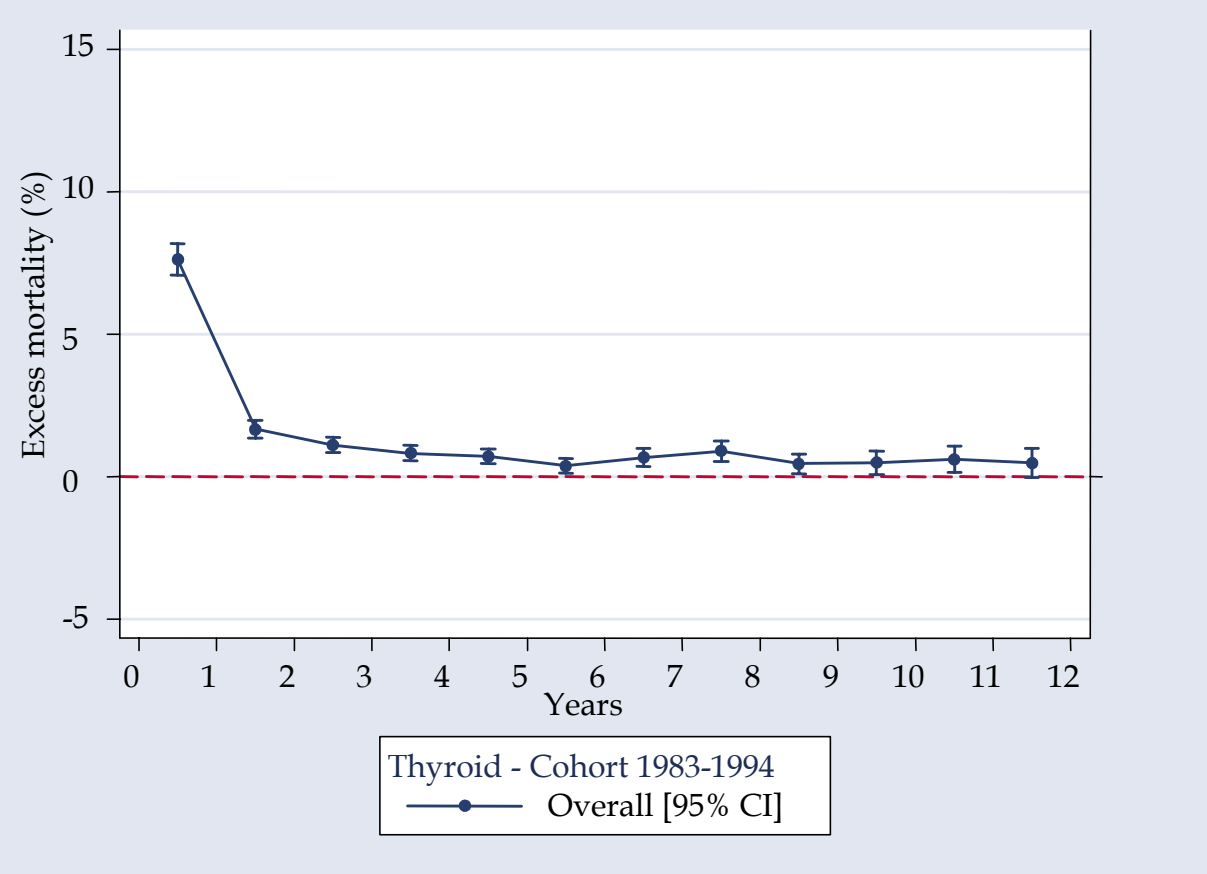

Figure 18.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 18.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 7,393)	Men (N = 2,424)
0-1	5.99 [5.42-6.55]	12.63 [11.25-14.02]
1-2	1.26 [0.95-1.57]	2.97 [2.11-3.83]
2-3	0.68 [0.42-0.94]	2.56 [1.72-3.40]
3-4	0.65 [0.39-0.91]	1.52 [0.77-2.26]
4-5	0.51 [0.26-0.77]	1.37 [0.61-2.13]
5-6	0.22 [-0.02-0.47]	1.00 [0.24-1.76]
6-7	0.63 [0.30-0.96]	0.85 [0.03-1.68]
7-8	0.63 [0.28-0.98]	1.64 [0.63-2.65]
8-9	0.31 [-0.03-0.65]	0.98 [-0.02-1.98]
9-10	0.42 [-0.00-0.84]	0.93 [-0.21-2.07]
10-11	0.50 [0.03-0.97]	1.21 [-0.08-2.50]
11-12	0.60 [0.04-1.16]	0.27 [-0.96-1.50]

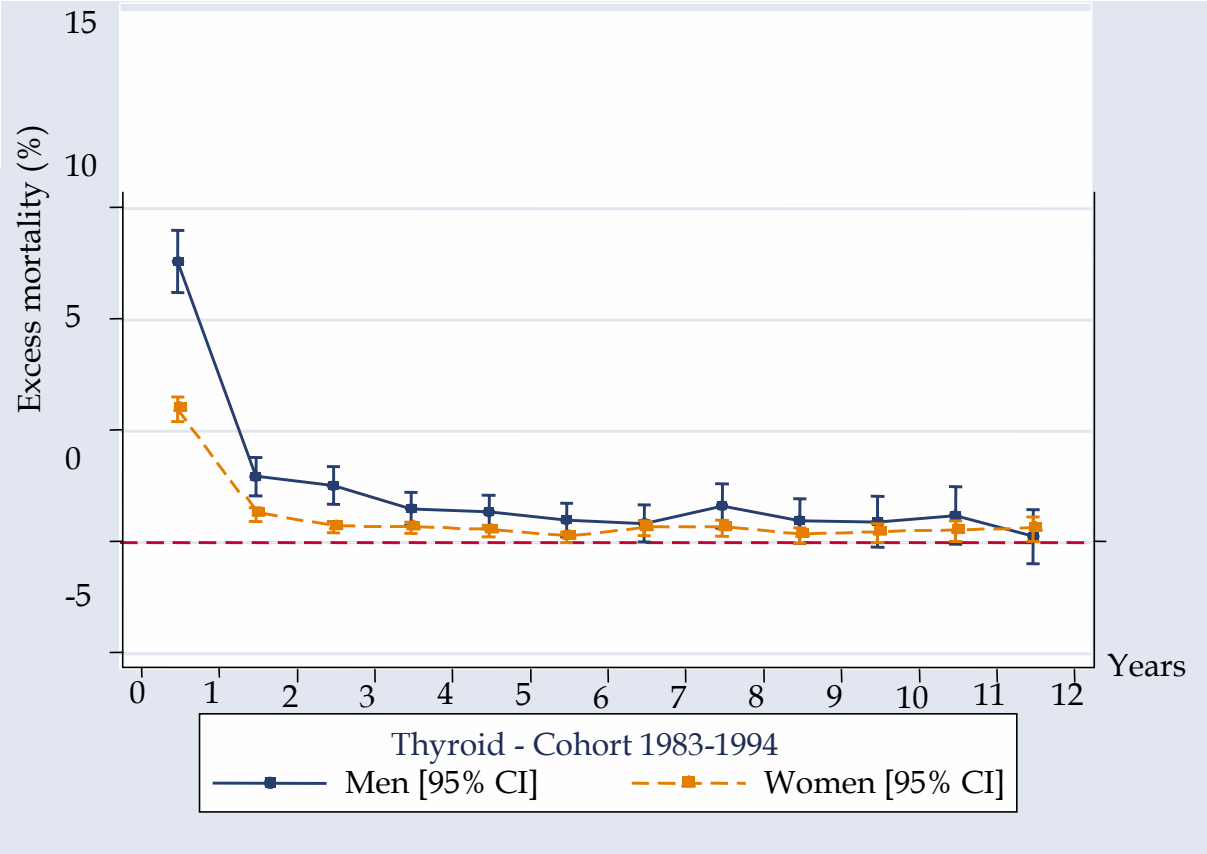

Figure 18.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 18.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	15-44 years (N = 4,229)	45-54 years (N = 1,914)	55-64 years (N = 1,850)	65-74 years (N = 1,826)
0-1	0.71 [0.44-0.98]	3.62 [2.75-4.49]	11.69 [10.18-13.21]	24.06 [22.01-26.11]
1-2	0.28 [0.10-0.47]	1.25 [0.67-1.82]	2.77 [1.84-3.69]	5.19 [3.76-6.63]
2-3	0.18 [0.02-0.34]	0.75 [0.26-1.24]	1.87 [1.04-2.70]	3.81 [2.43-5.19]
3-4	0.25 [0.06-0.43]	0.40 [-0.01-0.81]	1.89 [1.03-2.75]	2.19 [0.91-3.46]
4-5	0.05 [-0.08-0.19]	0.54 [0.08-1.01]	1.39 [0.56-2.22]	2.55 [1.13-3.97]
5-6	0.06 [-0.08-0.21]	-0.04 [-0.37-0.28]	0.74 [-0.05-1.54]	1.85 [0.36-3.34]
6-7	0.13 [-0.06-0.31]	0.44 [-0.12-0.99]	1.57 [0.50-2.64]	2.15 [0.35-3.94]
7-8	0.13 [-0.07-0.33]	0.94 [0.22-1.67]	1.50 [0.38-2.63]	3.36 [1.24-5.48]
8-9	0.12 [-0.09-0.34]	0.62 [-0.09-1.33]	1.35 [0.14-2.57]	0.27 [-1.68-2.22]
9-10	0.19 [-0.08-0.47]	1.23 [0.22-2.24]	-0.12 [-1.17-0.94]	1.63 [-1.06-4.31]
10-11	-0.07 [-0.24-0.09]	1.42 [0.28-2.55]	1.29 [-0.24-2.82]	1.57 [-1.42-4.57]
11-12	0.16 [-0.16-0.48]	0.92 [-0.24-2.07]	1.62 [-0.27-3.51]	-0.65 [-3.69-2.40]

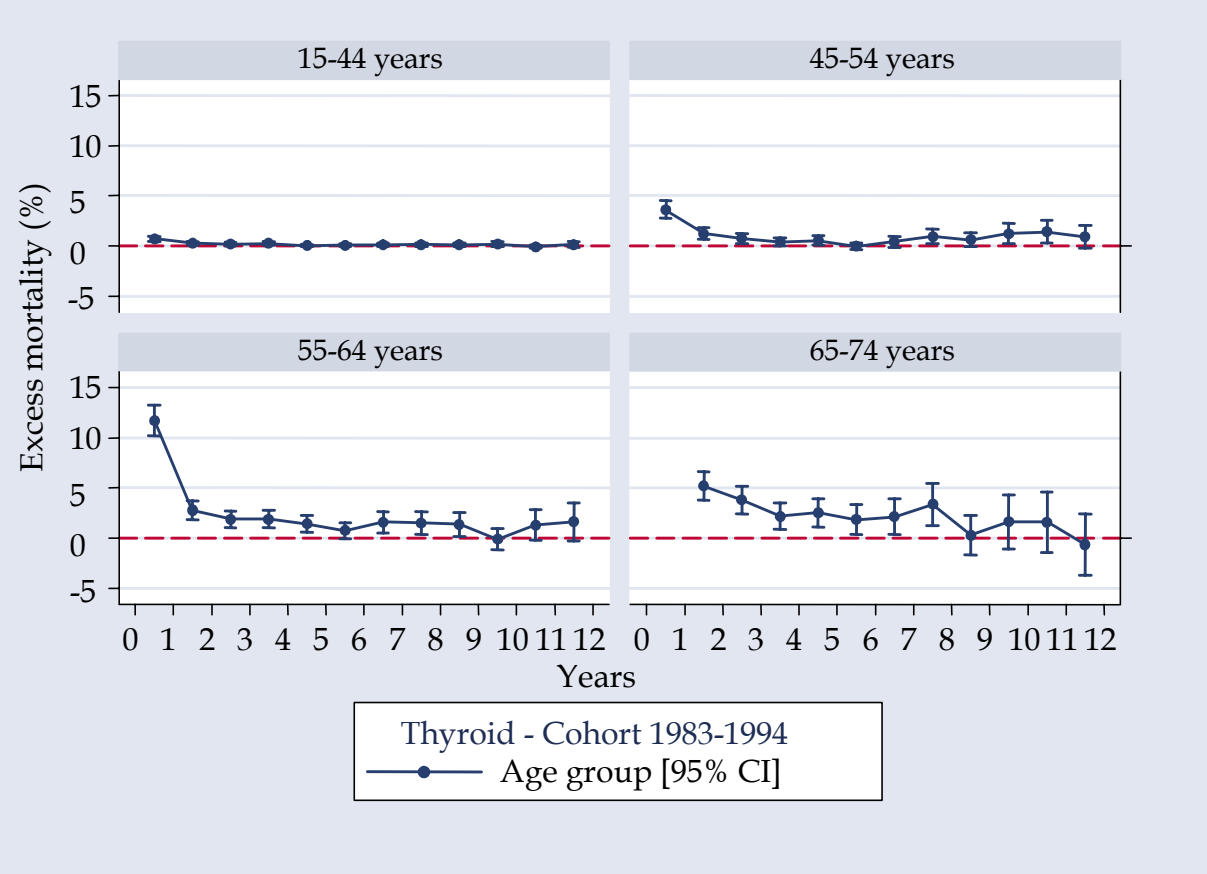

Figure 18.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 18.IV: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 1983-1985 (N = 2,119)	Cohort 1986-1988 (N = 2,465)	Cohort 1989-1991 (N = 2,464)	Cohort 1992-1994 (N = 2,771)
0-1	8.48 [7.23-9.72]	9.06 [7.88-10.24]	7.01 [5.95-8.06]	6.25 [5.31-7.19]
1-2	2.33 [1.55-3.11]	1.57 [0.96-2.19]	1.90 [1.25-2.55]	1.00 [0.52-1.48]
2-3	1.15 [0.52-1.78]	0.99 [0.45-1.53]	1.08 [0.53-1.63]	1.19 [0.68-1.71]
3-4	1.09 [0.45-1.72]	0.61 [0.12-1.10]	0.66 [0.17-1.15]	0.96 [0.47-1.46]
4-5	0.46 [-0.08-1.00]	0.93 [0.38-1.48]	0.64 [0.14-1.13]	0.77 [0.25-1.29]
5-6	0.19 [-0.31-0.69]	0.29 [-0.16-0.73]	0.43 [-0.04-0.89]	0.68 [0.02-1.34]
6-7	0.73 [0.11-1.35]	1.00 [0.42-1.59]	0.30 [-0.16-0.76]	-
7-8	1.24 [0.52-1.96]	0.63 [0.09-1.17]	0.85 [0.23-1.47]	-
8-9	0.77 [0.11-1.42]	0.37 [-0.14-0.87]	0.05 [-0.57-0.66]	-
9-10	0.76 [0.09-1.43]	0.27 [-0.24-0.77]	-	-
10-11	0.80 [0.10-1.49]	0.41 [-0.19-1.00]	-	-
11-12	0.41 [-0.23-1.05]	0.57 [-0.27-1.41]	-	-

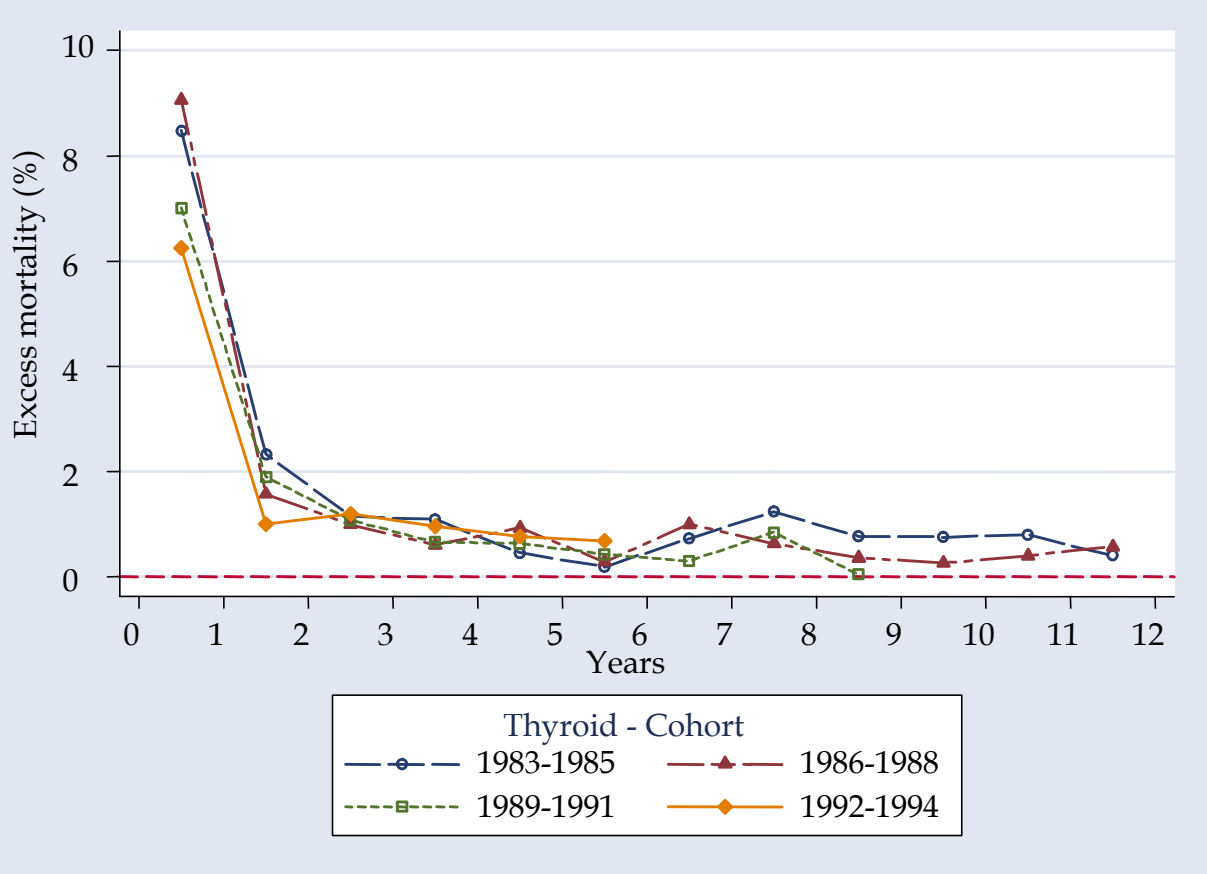

Figure 18.4: Time course of annual excess mortality by cohort

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Cuteaneous melanoma

Melanoma is a malignant melanocytic tumor which affects the skin in 90% of cases. The remaining 10% consist in mucosal, neuromeningeal or unknown primary lesions.

In 2000, 7,200 cases of invasive cutaneous melanoma were diagnosed in France. Melanoma thus accounted for 2.6% of the incident cases of cancer. Melanoma is both a little more frequent and of slightly earlier onset in women than in men. The age-standardized incidence rate (world population) was 9.5/100,000 for women and 7.6/100,000 for men. The median age at the time of diagnosis was 56 years for women and 58 years for men (Remontet *et al*., 2003).

With regard to temporal trends, a man born in 1953 has a ten-fold greater risk of developing a cutaneous melanoma than a man born in 1913. In women, the risk is 6-fold higher. The risk of death is 2.7-fold higher for men and 2.1-fold higher for women. These trends suggest that the increase in incidence is largely related to diagnosis of tumors with a superior prognosis since therapeutic progress does not in itself suffice to explain the dissociation between the incidence and mortality time courses.

In France, the number of survivors having developed melanoma of the skin less than 5 years previously is estimated to be 24,000. Among that population, 14,650 are aged less than 65 years (Pisani *et al*., 2002).

On the basis of the Eurocare study, the 5-year relative survival for the most recent cohort of patients whose melanoma was diagnosed between 1992 and 1994 was 86.63% for the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 19.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates were obtained taking into account all the cutaneous melanoma diagnoses between 1983 and 1994 in Europe (8 countries). The maximum annual excess mortality was of the order of 4% in the 2nd year post-diagnosis, and then decreased to values less than 1%. As figure 19.1 shows, the annual excess mortality plot falls below the 2% value as of year 5 post-diagnosis.

Table 19.II shows the annual excess mortality estimates by gender. For women, the excess mortality was less than 3%, peaking in the second year (2.78%). Three years post-diagnosis, the annual excess mortality fell below 2% and below 1% in years 8 and 9 post-diagnosis. In men, excess mortality peaked in the second year (6.05%). After 2 years, the excess mortality fell below 2%. It fell below 1% after year 10. The plots are shown in figure 19.2.

Table 19.III shows the annual excess mortality data obtained for various age groups. Excess mortality was lower for the young. For subjects aged less than 44 years, annual excess mortality fell below 2% after year 4 post-diagnosis and below 1% after year 10. For more elderly subjects, the annual excess mortality was higher in the initial phase, but decreased

more rapidly. Annual excess mortality fell below 1% as of year 8 post-diagnosis. The corresponding plots are shown in figure 19.3.

The annual excess mortality data for the four Eurocare cohorts are shown in table 19.IV. Annual excess mortality fell from the oldest to the most recent cohort for the first 2 years post-diagnosis (about 1% per year over the first 3 years). Beyond year 5, the improvement was less marked. Figure 19.4 shows the effect for the first years post-diagnosis.

Very long-term annual excess mortality (all stages considered): other studies

Three sources of population data are available for evaluation of the very long-term annual excess mortality associated with melanomas of the skin: the data of the US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer and the Swedish and Finnish national cancer registries.

Brenner (2002) evaluated the 5-, 10-, 15- and 20-year relative survivals for cutaneous melanoma diagnosed between 1973 and 1998 using the US SEER program data. Using the period analysis method (which takes into account the survival observed over the first years post-diagnosis for the most recent periods), the 5-, 10-, 15- and 20-year relative survivals were 89.0, 86.7, 83.5 and 82.8%, respectively. The mean annual excess mortality estimate was 0.17% for the period 15-20 years.

Brenner and Hakulinen (2001) evaluated the 10-, 15- and 20-year relative survivals for cutaneous melanoma diagnosed between 1960 and 1998 using the Finnish national cancer registry. The authors used the period analysis method. The estimates were 79.3, 78.3 and 76.1%, respectively. The mean annual excess mortality estimate was 0.56% for the period 15-20 years.

Talbäck *et al*. (2004) evaluated the 5-, 10- and 15-year relative survivals for melanoma of the skin diagnosed between 1965 and 1996 using the data of the Swedish national cancer registry. Using the period analysis method, the authors estimated the 5-, 10- and 15-year relative survivals to be 87.9, 84.1 and 76.9%, respectively. The data are similar to the 5-, 10- and 1-year relative survivals for the patients in the most recent diagnostic cohort: 87.3, 79.4 and 74.9%. The estimated mean annual excess mortality was 1.16% over the period 10-15 years.

Long-term relative survival or excess mortality by stage

The US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated relative survival data by year for three stages of cancer—localized, regional and metastatic (distant metastases)—and by a non-determined stage (insufficient information in the database to determine the stage). Annual excess mortalities have been calculated from those data (table 19.V). The distribution of cutaneous melanoma cases by stage (localized, regional and metastatic) was as follows: 82.0, 10.2 and 3.5%. The data are shown for all ages taken together at the time of diagnosis, for the diagnostic period 1988-2001.

Table 19.V: Annual excess mortality by melanoma stage at diagnosis for the period, 1988-2001 (taken from 9 registries of the Surveillance Epidemiology and End Results (SEER) program, 2004)

	Annual excess mortality (%)		
Interval (years)	Localized disease	Regional disease (N+)	Metastatic disease (M+)
0-1	0.00	7.50	60.70
1-2	0.40	13.19	35.37
2-3	0.90	11.71	22.05
3-4	0.81	8.04	17.17
4-5	0.61	5.21	9.76
5-6	0.51	4.05	4.73
6-7	0.41	3.54	1.42
7-8	0.31	2.97	7.19
8-9	0.10	0.54	4.65
9-10	0.00	1.63	6.50

For localized disease, the annual excess mortality was nil as of year 1 post-diagnosis.

Influence of prognostic factors at the time of diagnosis on survival

The prognostic factors conventionally employed for melanoma at the time of initial diagnosis are as follows: histologic type as per the 1972 Sidney classification (McGovern *et al*., 1986), tumor thickness using the Breslow index (Breslow, 1970), Clark level (Clark *et al*., 1969), the presence of ulceration, the presence of regression phenomena, site, lymph node involvement and patient age. The Breslow index (Breslow, 1970) has been the most rugged prognostic factor for 30 years, since its role has been confirmed by all the studies.

The American joint committee on cancer (AJCC) reviewed 17,600 melanoma cases and conducted a multivariate analysis of survival. The most recent prognostic classification only includes the prognostic factors: Breslow index, ulceration, Clark level of IV for tumors < 1 mm, and lymph node involvement (distinguishing the number of nodes and microscopic and gross invasion). Histologic type, gender and site had no influence compared to the other criteria (Balch *et al*., 2001). Melanoma in elderly subjects is thicker and has a more pejorative prognosis than that in young subjects (McHenry *et al*., 1992; Chamberlain *et al*., 2002).

The TNM classification and the AJCC-UICC (International Union against Cancer) prognostic classification, based on the same data, are now unanimously recognized for clinical trials. Those classifications are also used by clinicians for patient management and for updating the reference systems based on the Consensus conference (1955) and the Standards Options and Recommendations (SOR) (1998).

Influence of prognostic factors during disease course on survival

The prognostic factors that intervene during the course of the disease are, in particular, the prognostic factors for recurrence.

It is to be noted that all the descriptive data on recurrences are derived from old studies. It is probable that the data will change with the generalization of investigating for the sentinel

lymph node and with the natural or induced time course of incidence by melanoma type and stage.

The sentinel lymph node method is a relatively recent method (Morton *et al*., 1992). An initial study with median follow-up of 38 months appears to show that excision of the sentinel node at the time of initial diagnosis influences the distribution of the first recurrences (Statius Muller *et al*., 2002). Among the 18% recurrences, 52% were local or transit recurrences, 9% recurrence in the regional lymph node area and 34% distant recurrences. While the method appears to modify the time course of melanoma, it has not shown any influence on overall survival (3 trials are ongoing: the Multicenter selective adenectomy trial, the Sun belt melanoma trial and the Florida melanoma trial).

Several studies conducted in different countries concord in finding that the very marked increase in the incidence of melanoma is essentially due to superficial melanomas of limited thickness (Hall *et al*., 1999; Czarnecki and Meehan, 2000; Marks, 2002). They thus constitute a markedly preponderant subgroup of 'thin' melanomas (<0.75 mm) whose behavior is characterized by weak progression. The recurrence rate is estimated to be between 3.3 and 7.2% (Shaw *et al*., 1987; McKinnon *et al*., 2003; Schmid-Wendtner *et al*., 2003). The distribution of the recurrences sites is substantially the same for the 'thin' melanoma group (Schmid-Wendtner *et al*., 2003). Disease-free survival seems a little longer with a median of 49 months (McKinnon *et al*., 2003).

Influence of classification time course on survival

The concept of a 'thin' melanoma has evolved over the years. Up until 2001, melanoma thickness was broken down as follows: < 0.75 mm, from 0.75 to 1.5 mm, from 1.5 to 4 mm and > 4 mm. The new TNM classification has amended the melanoma group distribution: < 1 mm, from 1.01 to 2 mm, from 2.01 to 4 mm and > 4 mm (Balch *et al*., 2003). This change is likely to influence the concept of 'thin' melanoma.

The time course of melanomas < 0.75 mm is markedly different from that of melanomas from 0.75 to 1 mm. A study of the population data from the Australian New South Wales registry demonstrated the following observed survivals: 97.3% at 10 years, then 95.5% at 15 years for tumors of thickness less than 0.6 mm; 95% at 10 years and 94.4% at 15 years for tumors of thickness between 0.61 and 0.80 mm; and 93% at 10 years and 90.9% at 15 years for tumors of thickness between 0.81 and 1 mm (McKinnon *et al*., 2003). A further Australian study (South Australia registry) reported very similar 10-year survival figures: 98% for tumors < 0.5 mm, 96.6% for tumors between 0.51 and 0.75 mm and 91.5% for tumors between 0.76 and 1 mm (SACR, 2000).

In recent years, a further trend has become clear: the number of 'thick' melanomas, and hence melanomas with a poor prognosis, has stabilized in absolute terms. Moreover, patients presenting with 'thick' melanoma have grown older and there has been an increase in the number of nodular melanomas at the expense of lentigo maligna melanoma and acral-lentiginous melanoma (McHenry *et al*., 1992; Chamberlain *et al*., 2002; Crocetti et Carli, 2003; Murray *et al*., 2005).

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Excess mortality data from the Eurocare study

Table 19.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 29,441)
0-1	3.68 [3.44-3.92]
1-2	4.31 [4.05-4.57]
2-3	3.43 [3.18-3.69]
3-4	2.76 [2.52-2.99]
4-5	2.18 [1.95-2.41]
5-6	1.68 [1.44; 1.91]
6-7	1.58 [1.31-1.84]
7-8	1.04 [0.79-1.30]
8-9	0.93 [0.65-1.21]
9-10	0.91 [0.58-1.24]
10-11	0.90 [0.54-1.25]
11-12	0.66 [0.26-1.05]

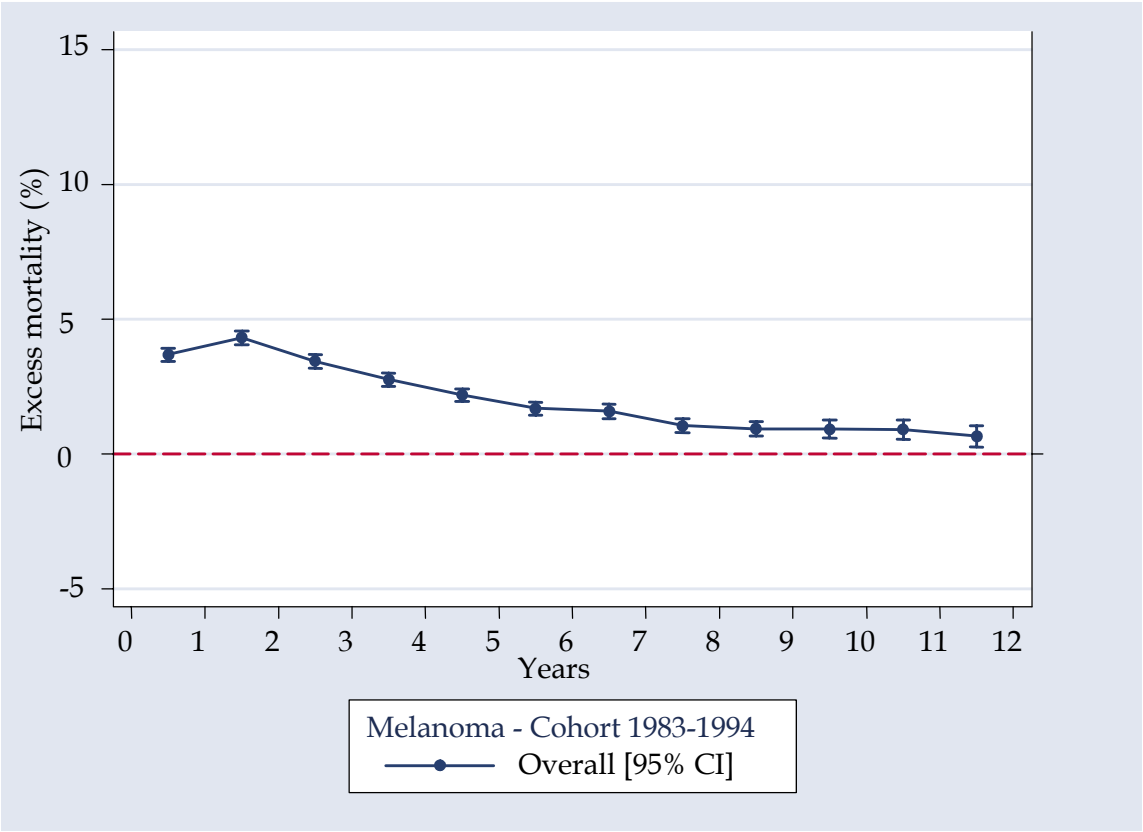

Figure 19.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 19.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (% annual) Women (N = 15,248)	Men (N = 14,193)
0-1	2.11 [1.85-2.37]	5.38 [4.96-5.79]
1-2	2.78 [2.48-3.07]	6.05 [5.60-6.50]
2-3	2.33 [2.05-2.61]	4.77 [4.33-5.20]
3-4	1.67 [1.42-1.93]	4.12 [3.69-4.54]
4-5	1.72 [1.45-1.99]	2.81 [2.40-3.21]
5-6	1.28 [1.01-1.55]	2.25 [1.84-2.67]
6-7	1.40 [1.09-1.70]	1.87 [1.42-2.32]
7-8	1.04 [0.74-1.34]	1.13 [0.69-1.56]
8-9	0.61 [0.31-0.91]	1.45 [0.94-1.96]
9-10	0.63 [0.27-0.99]	1.41 [0.80-2.01]
10-11	1.16 [0.72-1.60]	0.63 [0.04-1.22]
11-12	0.66 [0.20-1.12]	0.72 [0.01-1.42]

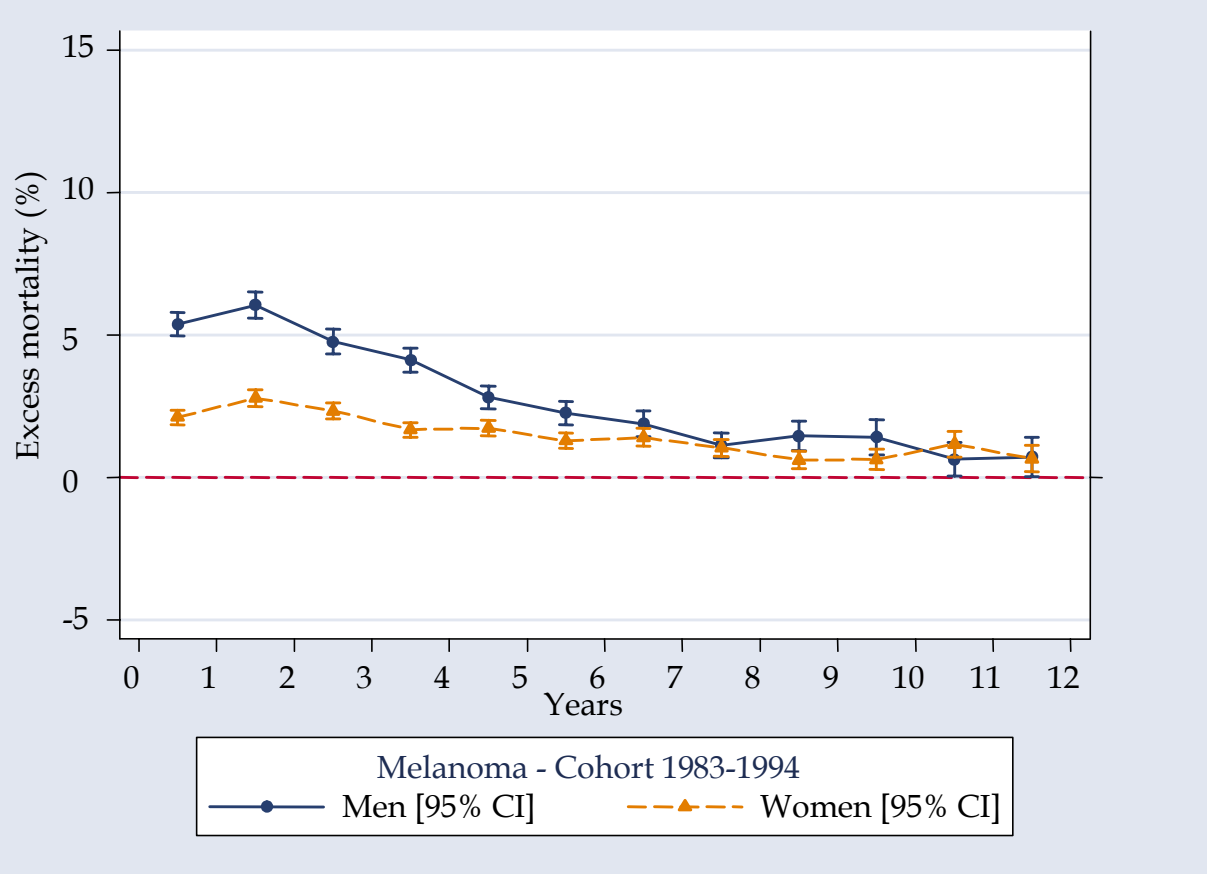

Figure 19.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 19.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	15-44 years (N = 9,451)	45-54 years (N = 6,403)	55-64 years (N = 6,751)	65-74 years (N = 6,836)
0-1	2.13 [1.83-2.43]	3.36 [2.89-3.82]	4.51 [3.96-5.05]	5.35 [4.70-6.00]
1-2	2.98 [2.63-3.34]	3.76 [3.26-4.25]	5.22 [4.62-5.82]	5.91 [5.21-6.62]
2-3	2.42 [2.09-2.75]	3.45 [2.96-3.95]	3.96 [3.40-4.53]	4.47 [3.78-5.16]
3-4	2.18 [1.87-2.50]	2.45 [2.01-2.89]	3.13 [2.59-3.66]	3.64 [2.95-4.33]
4-5	1.77 [1.47-2.07]	2.51 [2.04-2.97]	2.14 [1.63-2.64]	2.57 [1.87-3.27]
5-6	1.53 [1.23-1.83]	1.89 [1.44-2.34]	2.06 [1.51-2.61]	1.28 [0.58-1.99]
6-7	1.15 [0.85-1.44]	1.41 [0.95-1.86]	1.64 [1.06-2.23]	2.55 [1.64-3.46]
7-8	1.15 [0.84-1.45]	1.17 [0.71-1.63]	1.31 [0.72-1.91]	0.32 [-0.53-1.16]
8-9	1.03 [0.71-1.34]	0.82 [0.36-1.28]	1.08 [0.44-1.72]	0.67 [-0.34-1.68]
9-10	0.96 [0.60-1.32]	0.98 [0.41-1.55]	0.82 [0.08-1.55]	0.82 [-0.46-2.10]
10-11	1.02 [0.62-1.41]	1.25 [0.59-1.92]	0.32 [-0.42-1.07]	0.92 [-0.54-2.37]
11-12	0.72 [0.33-1.12]	0.12 [-0.41-0.65]	0.68 [-0.25-1.61]	1.29 [-0.52-3.10]

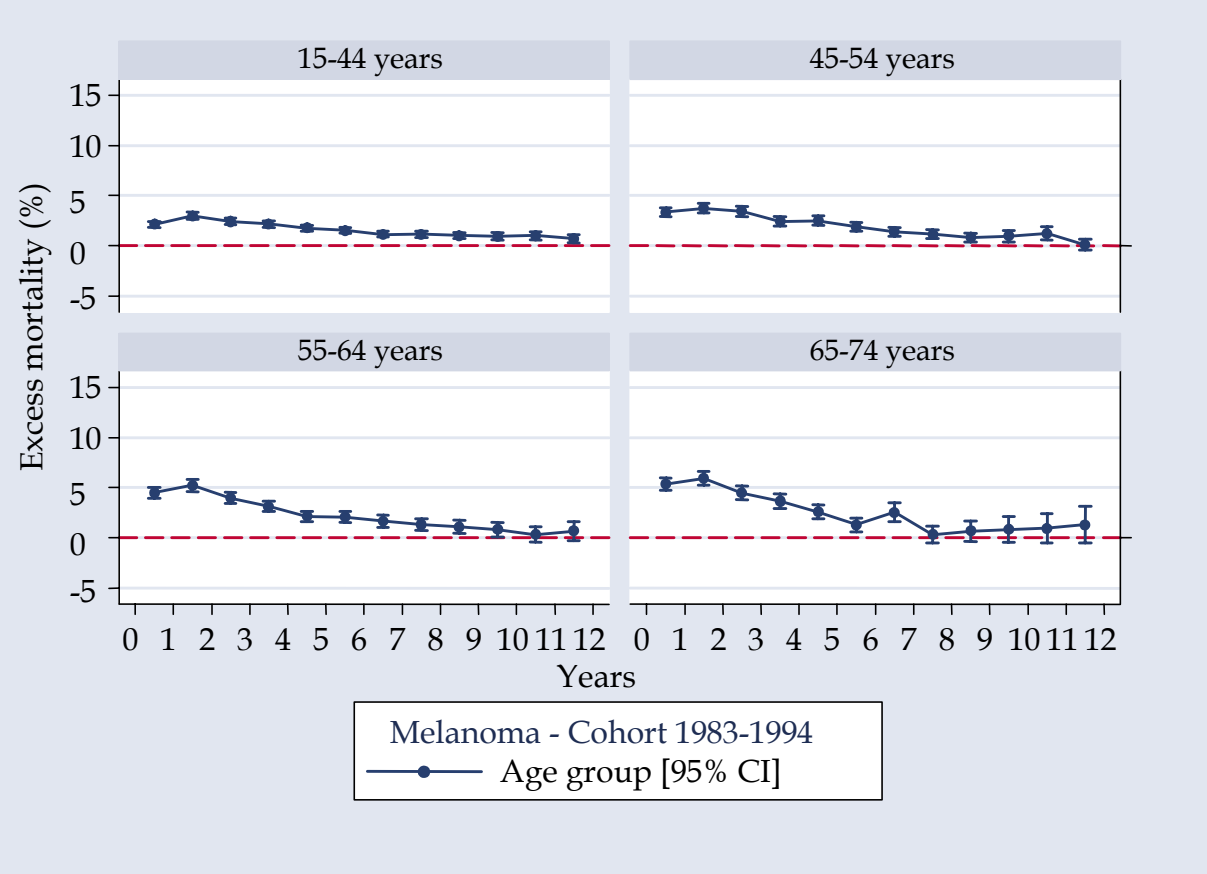

Figure 19.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 19.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 1983-1985 (N = 5,984)	Cohort 1986-1988 (N = 7,193)	Cohort 1989-1991 (N = 8,014)	Cohort 1992-1994 (N = 8,250)
0-1	4.39 [3.82-4.97]	4.21 [3.69-4.72]	3.34 [2.89-3.78]	3.03 [2.61-3.45]
1-2	5.59 [4.94-6.25]	4.69 [4.13-5.24]	3.52 [3.05-3.98]	3.83 [3.36-4.31]
2-3	4.37 [3.75-4.99]	3.67 [3.14-4.19]	2.96 [2.51-3.42]	3.04 [2.59-3.49]
3-4	2.97 [2.41-3.52]	3.34 [2.82-3.86]	2.65 [2.20-3.09]	2.22 [1.81-2.64]
4-5	3.02 [2.44-3.59]	1.93 [1.48-2.39]	1.94 [1.52-2.35]	2.01 [1.55-2.46]
5-6	1.98 [1.46-2.50]	1.80 [1.35-2.26]	1.29 [0.91-1.67]	1.80 [1.21-2.40]
6-7	1.69 [1.18-2.21]	1.62 [1.17-2.08]	1.45 [1.05-1.86]	-
7-8	1.29 [0.80-1.79]	1.02 [0.60-1.44]	0.85 [0.44-1.26]	-
8-9	1.02 [0.53-1.50]	0.76 [0.35-1.17]	1.09 [0.51-1.66]	-
9-10	0.75 [0.28-1.23]	1.04 [0.58-1.49]	-	-
10-11	1.10 [0.57-1.62]	0.70 [0.22-1.18]	-	-
11-12	0.57 [0.07-1.06]	0.81 [0.15-1.48]	-	-

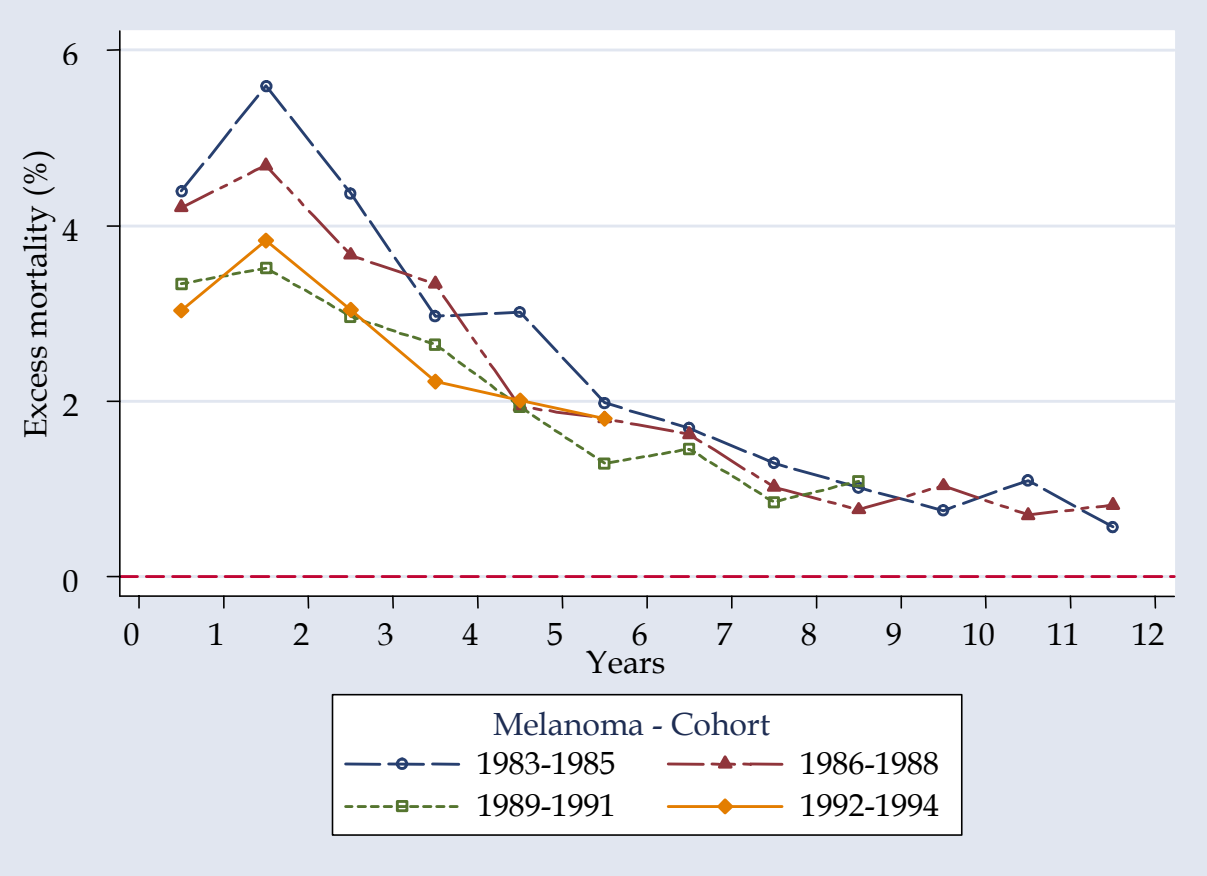

Figure 19.4: Time course of annual excess mortality by cohort

20

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) accounts for about 20% of the cases of leukemia in adults. It is more frequently observed in men than in women.

The Côte d'Or malignant blood disease registry reported a standardized incidence rate for acute lymphoblastic leukemia of 1.72/100,000 for the period 1980-2001. ALL is nonetheless essentially a childhood leukemia: before age 15 years, the standardized incident rate is 3.94/100,000.

While childhood survival of ALL is good (current 5-year relative survival of almost 80%), the prognosis is markedly more pejorative in adults: for 1980-1997, the 5-year relative survival was 50% (95% CI [40-59]) and the 10-year relative survival 43% (95% CI [33-54]), according to the Côte d'Or registry.

On the basis of the Eurocare data for diagnostic cohort 1992-1994, the 5-year relative survival was 31.3% for all stages taken together and the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 20.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates take into account all the cases diagnosed in Europe (8 countries) between 1983 and 1994. The annual excess mortality, which is relatively high in the first years post-diagnosis, falls rapidly to 3% as of year 5 and continues to fall to a mean value that is not statistically different from zero after year 8 post-diagnosis (figure 20.1).

Table 20.II shows the annual excess mortality data by gender. The data are very similar, although slightly lower for women. The two plots are superimposed with large confidence intervals (figure 20.2).

Table 20.III shows the annual excess mortality rates observed for age groups 15-44 years and 45-64 years. In the age group 15-44 years, as of year 6 post-diagnosis, there is no longer any significant annual excess mortality (figure 20.3). The annual excess mortality plot for the age group, 45-64 years, is systematically higher but no firm conclusion can be drawn given the magnitude of the confidence intervals.

Table 20.IV shows the annual excess mortality estimates for the 4 cohorts. The annual excess mortality rates appear to be the same for the 4 cohorts. Figure 20.4 confirms the absence of a cohort effect.

Impact of treatment on short-term survival

The therapeutic strategies used in adults have followed the progress in ALL treatment for children. However, the results are not as good as those obtained in pediatric settings. The complete remission rate is of the order of 75 to 91%, but the 5-year survivals remain poor

ranging from 28 to 49%, depending on the study. While the relapse-free survival rate is not satisfactory, a plateau is nonetheless observed. In young adults, no excess mortality is observed after 5 years of complete remission.

Allogeneic bone marrow transplant from a relative or unrelated donor is indicated in relapses of standard-risk ALL and as first-line treatment for ALL with a poor prognosis (essentially ALL cases with the Philadelphia chromosome). Similar results were obtained with the two types of transplant (Kiehl *et al*., 2004). The 5-year event-free survival is estimated to be 28%.

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Excess mortality data from the Eurocare study

Table 20.I: Annual excess mortality: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Overall (N = 1,172)
0-1	33.68 [30.96-36.40]
1-2	30.45 [27.17 -33.74]
2-3	16.56 [13.35 -19.77]
3-4	10.39 [7.48 -13.31]
4-5	8.10 [5.27 -10.93]
5-6	3.02 [1.00 -5.05]
6-7	2.10 [0.19 -4.02]
7-8	4.14 [1.44 -6.84]
8-9	1.27 [-0.53 -3.08]
9-10	0.33 [-1.03 -1.69]
10-11	1.22 [-0.96 -3.40]
11-12	1.76 [-1.12 -4.64]

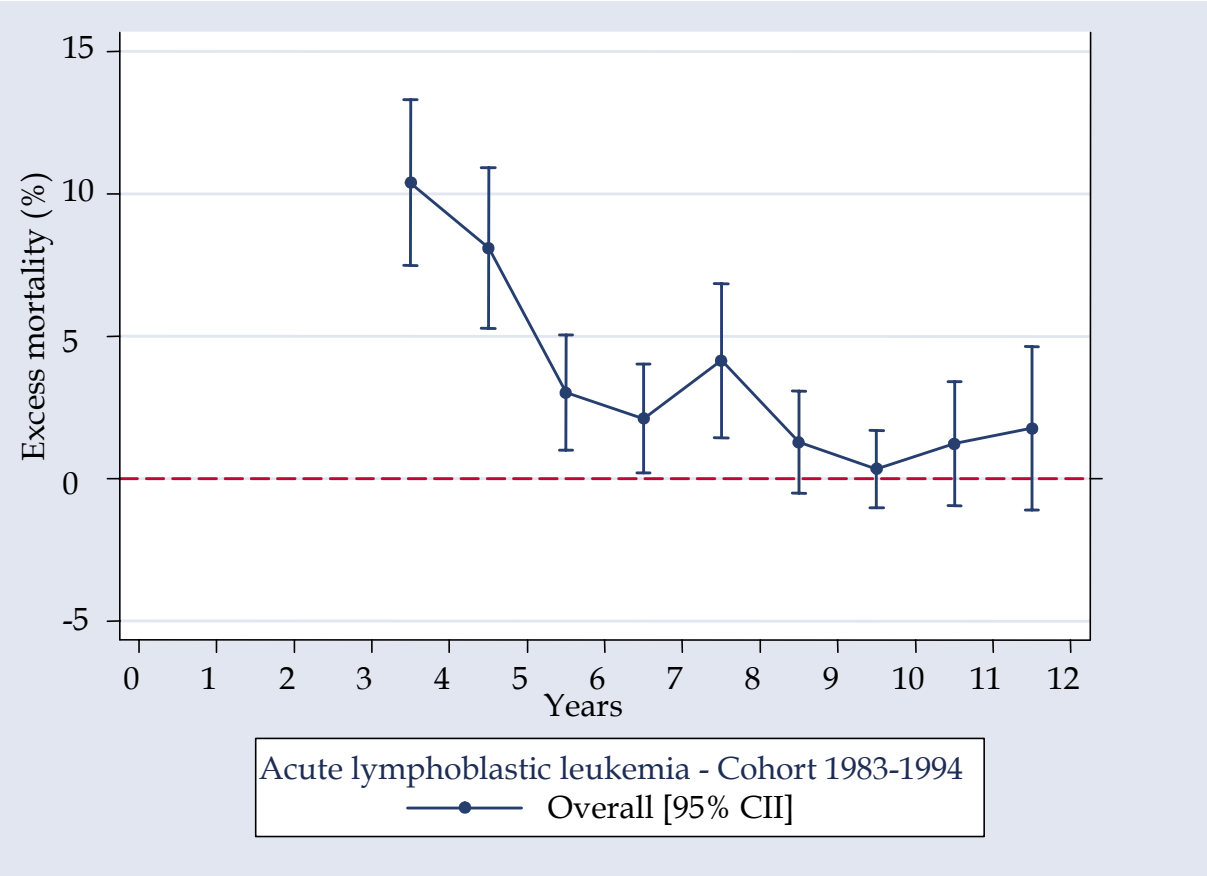

Figure 20.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 20.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 454)	Men (N = 702)
0-1	31.80 [27.50-36.09]	33.40 [29.89-36.91]
1-2	31.63 [26.31-36.94]	27.86 [23.71-32.01]
2-3	15.14 [10.08-20.19]	14.56 [10.63-18.48]
3-4	6.46 [2.65-10.28]	11.19 [7.33-15.06]
4-5	8.99 [4.22-13.76]	5.56 [2.47-8.64]
5-6	4.12 [0.37-7.88]	2.38 [0.06-4.70]
6-7	-0.27 [-4.02-3.48]	2.27 [-0.23-4.76]
7-8	-0.28 [-4.03-3.48]	5.35 [1.55-9.15]
8-9	-0.32 [-4.08-3.43]	0.61 [-1.07-2.30]
9-10	1.53 [-2.14-5.21]	-0.31 [-1.99-1.38]
10-11	3.94 [-1.91-9.80]	-0.29 [-1.97-1.40]
11-12	-0.23 [-6.07-5.62]	3.20 [-1.51-7.91]

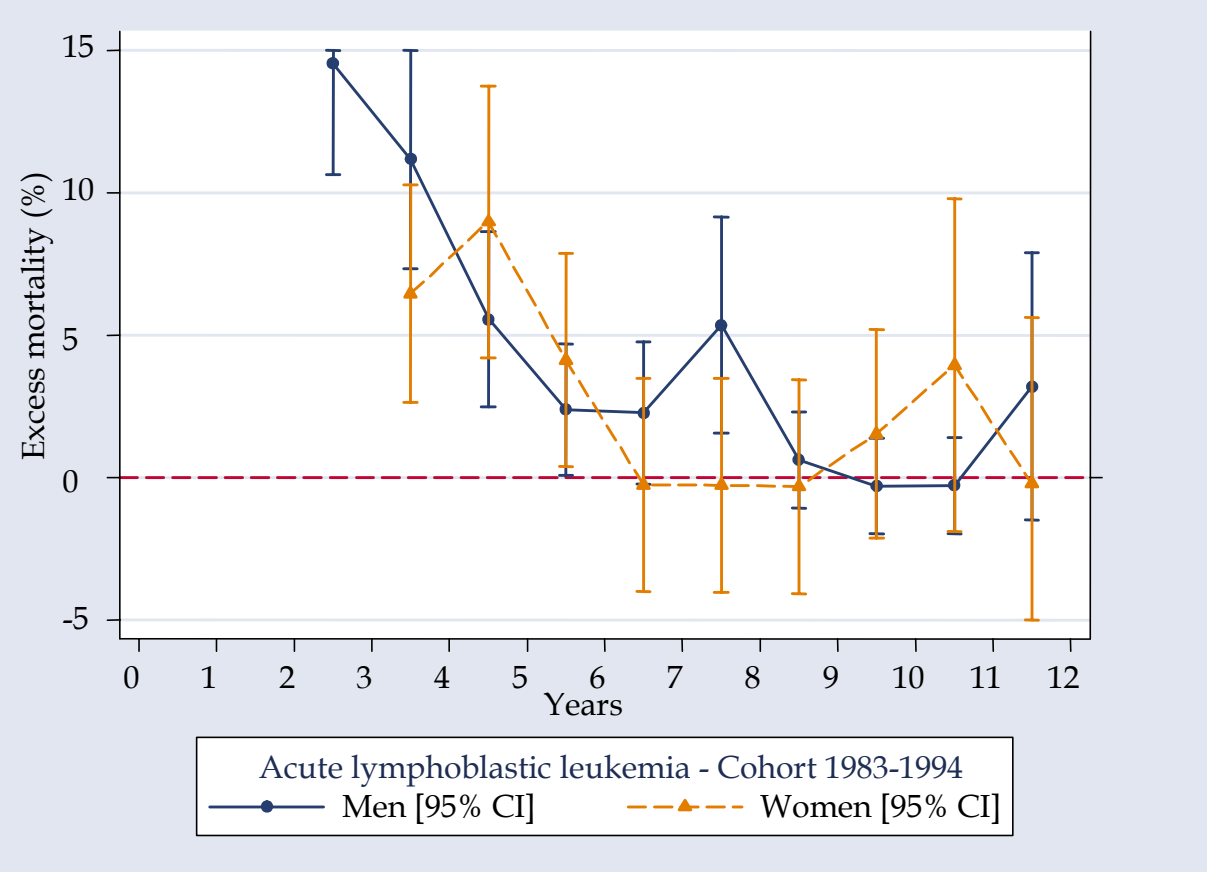

Figure 20.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 20.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)	
Interval (years)	15-44 years (N = 807)	45-64 years (N = 365)
0-1	27.70 [24.61-30.79]	46.99 [41.83-52.16]
1-2	30.64 [26.88-34.40]	29.84 [23.09-36.60]
2-3	14.87 [11.37-18.36]	22.12 [14.64-29.59]
3-4	9.57 [6.43-12.71]	13.51 [6.26-20.77]
4-5	6.64 [3.78-9.50]	13.93 [5.80-22.07]
5-6	2.74 [0.65-4.83]	4.22 [-1.59-10.02]
6-7	0.85 [-0.51-2.20]	7.83 [-0.58-16.24]
7-8	4.05 [1.21-6.90]	4.64 [-3.37-12.66]
8-9	0.47 [-0.74-1.68]	6.30 [-4.10-16.70]
9-10	-0.16 [-1.38-1.05]	3.43 [-6.28-13.14]
10-11	0.73 [-1.03-2.49]	4.72 [-7.73-17.18]
11-12	2.15 [-1.04-5.34]	-1.90 [-14.36-10.56]

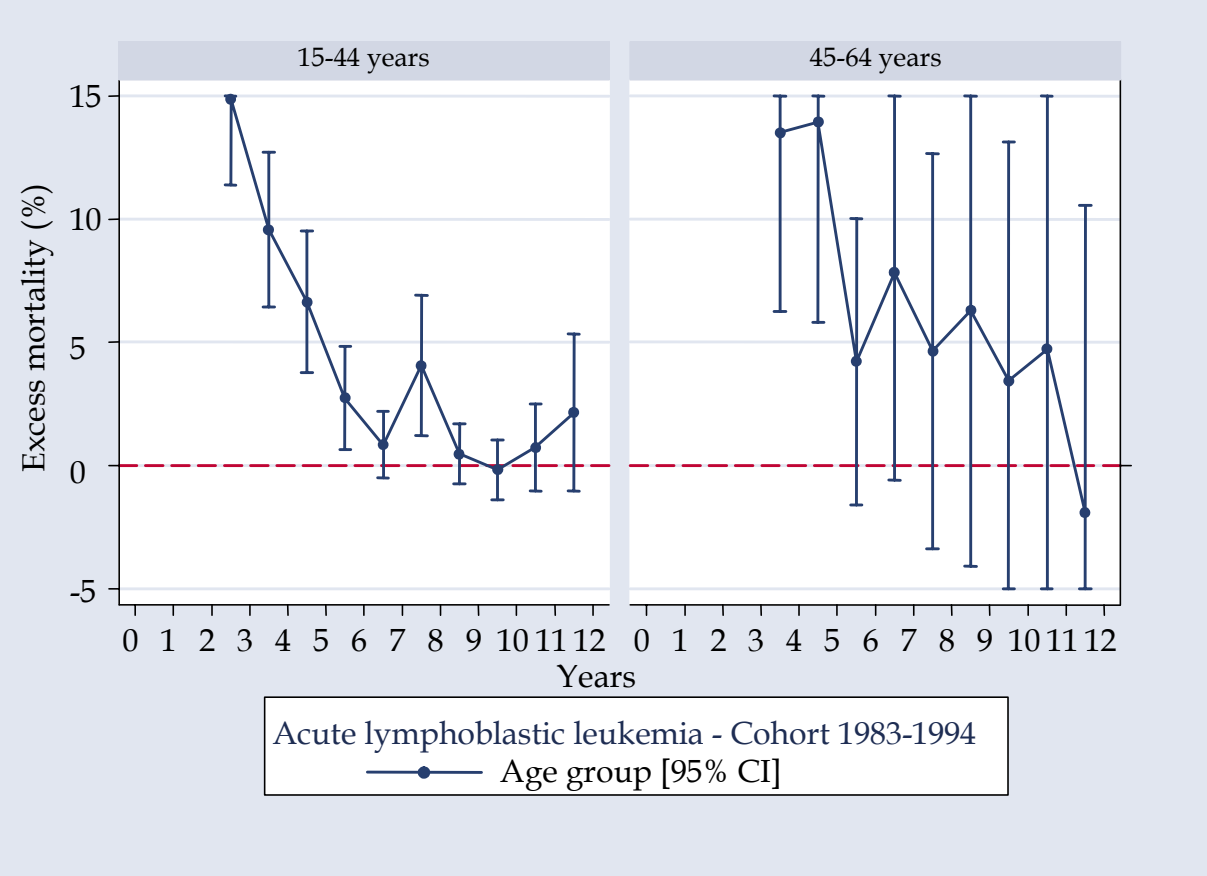

Figure 20.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 20.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 1983-1985 (N = 251)	Cohort 1986-1988 (N = 324)	Cohort 1989-1991 (N = 299)	Cohort 1992-1994 (N = 298)
0-1	36.45 [30.47-42.43]	34.35 [29.16-39.55]	34.23 [28.83-39.64]	30.07 [24.84-35.30]
1-2	30.96 [23.55-38.36]	32.66 [26.29-39.03]	23.89 [17.87-29.91]	34.07 [27.55-40.59]
2-3	18.04 [10.59-25.49]	11.05 [5.80-16.30]	17.45 [11.26-23.63]	20.28 [13.38-27.17]
3-4	7.97 [2.11-13.83]	10.09 [4.73-15.46]	15.17 [8.62-21.72]	7.39 [2.30-12.48]
4-5	7.61 [1.53-13.69]	8.60 [3.30-13.90]	7.86 [2.48-13.24]	8.16 [2.20-14.11]
5-6	5.56 [-0.05-11.18]	1.65 [-1.09-4.39]	1.95 [-1.07-4.97]	4.47 [-1.91-10.86]
6-7	4.36 [-0.84-9.55]	2.74 [-0.72-6.20]	-0.26 [-3.28-2.76]	-
7-8	3.10 [-1.53-7.73]	2.86 [-0.74-6.47]	6.61 [0.80-12.42]	-
8-9	1.52 [-1.96-5.00]	-0.40 [-4.00-3.21]	4.43 [-1.95-10.82]	-
9-10	-0.28 [-3.76-3.20]	0.71 [-1.49-2.91]	-	-
10-11	-0.31 [-3.78-3.17]	2.40 [-1.44-6.24]	-	-
11-12	3.33 [-1.63-8.29]	-0.36 [-4.19-3.48]	-	-

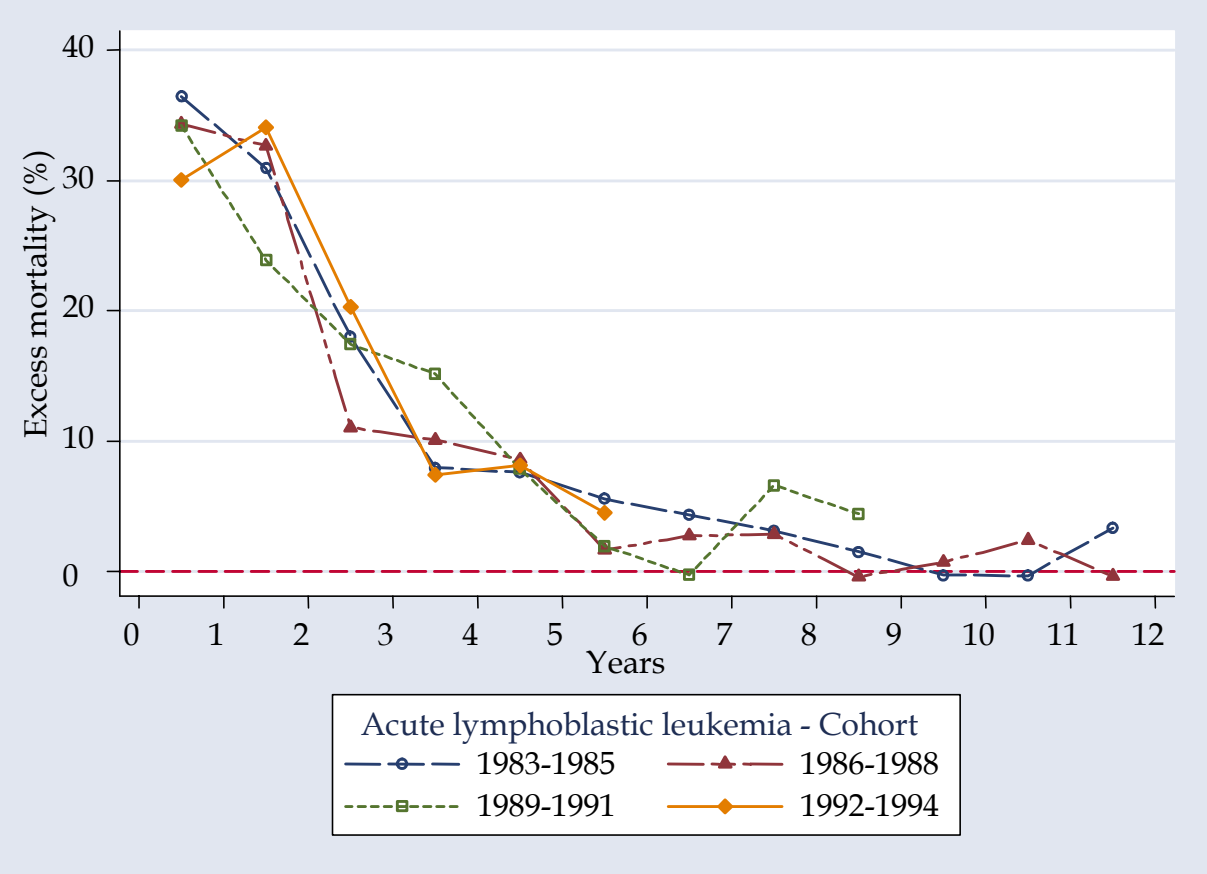

Figure 20.4: Time course of annual excess mortality by cohort

21

Acute myeloid leukemia

Acute myeloid leukemia (AML) consists of a set of very heterogeneous diseases. The annual incidence of the group of diseases is of the order of 3.4/100,000 (SEER, 2002). In 2002, in the United States, the incidence was estimated to be 10,600 new cases. Similar data have been reported in other Western countries. In France, the age standardized incidence rate was 2.4/100,000 according to the Côte d'Or malignant blood disease registry.

The disease most frequently affects the elderly. The median age of onset is 64 years and about 60% of patients are aged over 60 years. AML occurs more frequently in men than in women (Godwin and Smith, 2003).

On the basis of the Eurocare data, the 5-year relative survival of the patients in the most recent cohort (1992-1994) was 29.61% for all stages taken together and the eight countries selected. The Côte d'Or registry has reported a relative survival for the period 1980-1997 of 16% (95% CI [0-45]) at 5 years and 12% (95% CI [0-42]) at 10 years.

Promyelocytic leukemia (M3) is a rare variety of acute leukemia which differs from the other forms of leukemia, in particular because of its excellent prognosis.

The incidence of promyeolocytic leukemia varies depending on the country: 0.6 new cases per million people in Italy (Avvisati *et al.*, 1991), 2.7/100,000 in the United States (Douer, 2003) and 0.46/100,000 in France, according to the Côte d'Or malignant blood disease registry. The disease is more frequent in subjects from the Iberian Peninsula and, by extension, in the Hispanic populations of the new world, and in overweight subjects (Estey *et al.*, 1997). The disease occurs in adults at a median age of 40-45 years: 10% of patients are over 60 years. The 5- and 10- year survival rates reported by the Côte d'Or registry were both 61% (95% CI [37-78]).

Annual excess mortality (all types considered): Eurocare data

Table 21.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates were obtained by taking into account all the patients whose AML was diagnosed in Europe (8 countries) between 1983 and 1994. The annual excess mortality falls rapidly to 5% from year 5 post-diagnosis. It continues to fall thereafter tending toward zero after year 11 post-diagnosis (figure 21.1).

Table 21.II shows the annual excess mortality data by gender. The two annual excess mortality plots are superimposed (figure 21.2). There is no difference between men and women.

Table 21.III shows the annual excess mortality results for age groups 15-44 years and 45-64 years. In age group 15-44 years, from year 6 post-diagnosis, there was no longer any significant annual excess mortality (figure 21.3). The annual excess mortalities for age group 45-64 years were higher. The mean value was 2.5% between years 7 and 12 post-diagnosis.

The analysis of the annual excess mortality for the 4 cohorts (table 21.IV and figure 21.4) of the Eurocare study demonstrated a decrease in annual excess mortality for the more recent cohorts.

Very long-term annual excess mortality (all types considered): other studies

Talbäck *et al*. (2004) evaluated the 5-, 10- and 15-year relative survivals for patients whose acute myeloid leukemia diagnosed between 1960 and 1998 using the Swedish national cancer registry data, all ages taken together. Using the period analysis method (which takes into account the survival observed over the first years following diagnosis for the most recent periods), the estimates were 15.5, 11.5 and 4.7% for 5-, 10- and 15- year survivals, respectively. The data are similar to the 5-, 10- and 15-year relative survivals for the patients whose AML was diagnosed in the most recent period: 18.2, 12.8 and 7.8%. The data show that, 15 years post-diagnosis, survival did not reach a plateau. The mean annual excess mortality between 10 and 15 years post-diagnosis was 9.4%.

Impact of cytogenetic status and treatment on survival

The prognosis varies depending on the cytogenetic status of the neoplasm. The observed 3-year survivals for the favorable, intermediate and unfavorable stages were 58, 43 and 15%, respectively (Slovak *et al*., 2000). After year 3 post-diagnosis, the risk of death appears negligible and the same for the 3 groups.

The impact of treatment on survival is a function of two factors: age (greater than 70 years, treatment is only symptomatic) and cytogenetic status.

The impact of all-trans-retinoic acid (in addition to standard chemotherapy) on survival was investigated for promyelocytic leukemia (Fenaux *et al*., 2000) in a recent study (*European APL group*). The results show that all-trans-retinoic acid addition procures a gain in survival: at time point 3 years, the overall survival in the all-trans-retinoic acid group was 75% vs. 55% for the group on chemotherapy alone.

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Excess mortality data from the Eurocare study

Table 21.I: Annual excess mortality: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)
Interval (years)	Overall (N = 3,258)
0-1	47.30 [45.57-49.02]
1-2	33.94 [31.68 -36.21]
2-3	19.90 [17.53 -22.28]
3-4	13.27 [10.99 -15.55]
4-5	7.59 [5.58 -9.60]
5-6	4.65 [2.83 -6.47]
6-7	3.02 [1.25 -4.78]
7-8	1.64 [0.14 -3.13]
8-9	3.04 [0.94 -5.14]
9-10	2.75 [0.33 -5.17]
10-11	1.82 [-0.48 -4.12]
11-12	0.58 [-1.39 -2.56]

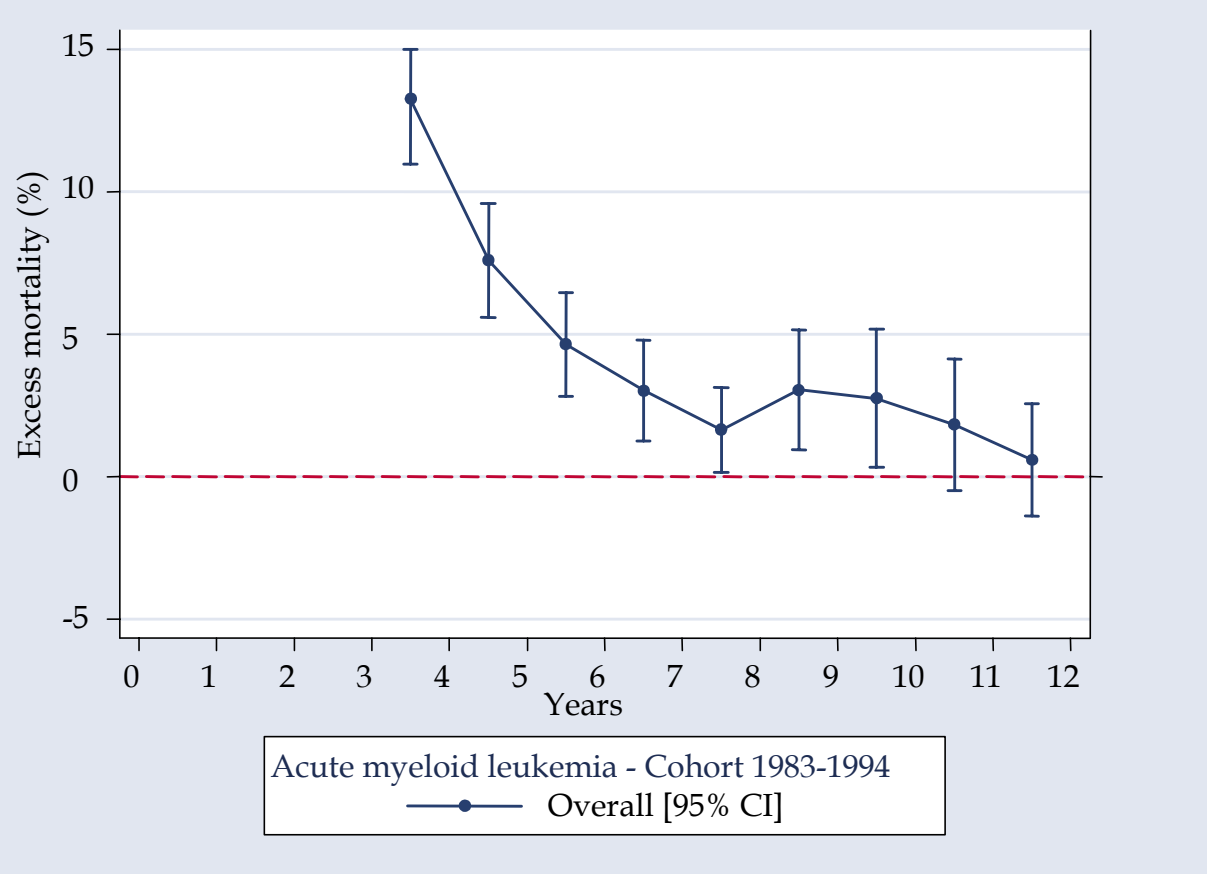

Figure 21.1: Annual excess mortality: diagnostic cohort 1993-1994

Table 21.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 1,493)	Men (N = 1,747)
0-1	45.70 [43.17-48.24]	48.12 [45.76-50.48]
1-2	33.17 [29.89-36.44]	33.86 [30.72-37.00]
2-3	20.59 [17.12-24.06]	18.73 [15.50-21.96]
3-4	13.33 [10.01-16.66]	12.86 [9.75-15.97]
4-5	5.78 [3.18-8.38]	8.65 [5.73-11.57]
5-6	3.42 [1.12-5.72]	5.41 [2.71-8.10]
6-7	4.07 [1.21-6.92]	2.11 [-0.06-4.29]
7-8	1.28 [-0.63-3.19]	1.02 [-0.83-2.88]
8-9	2.98 [-0.00-5.97]	3.17 [0.17-6.16]
9-10	5.57 [0.87-10.27]	-1.12 [-4.12-1.88]
10-11	0.72 [-1.66-3.09]	2.74 [-0.99-6.48]
11-12	-0.53 [-2.90-1.85]	1.50 [-2.16-5.17]

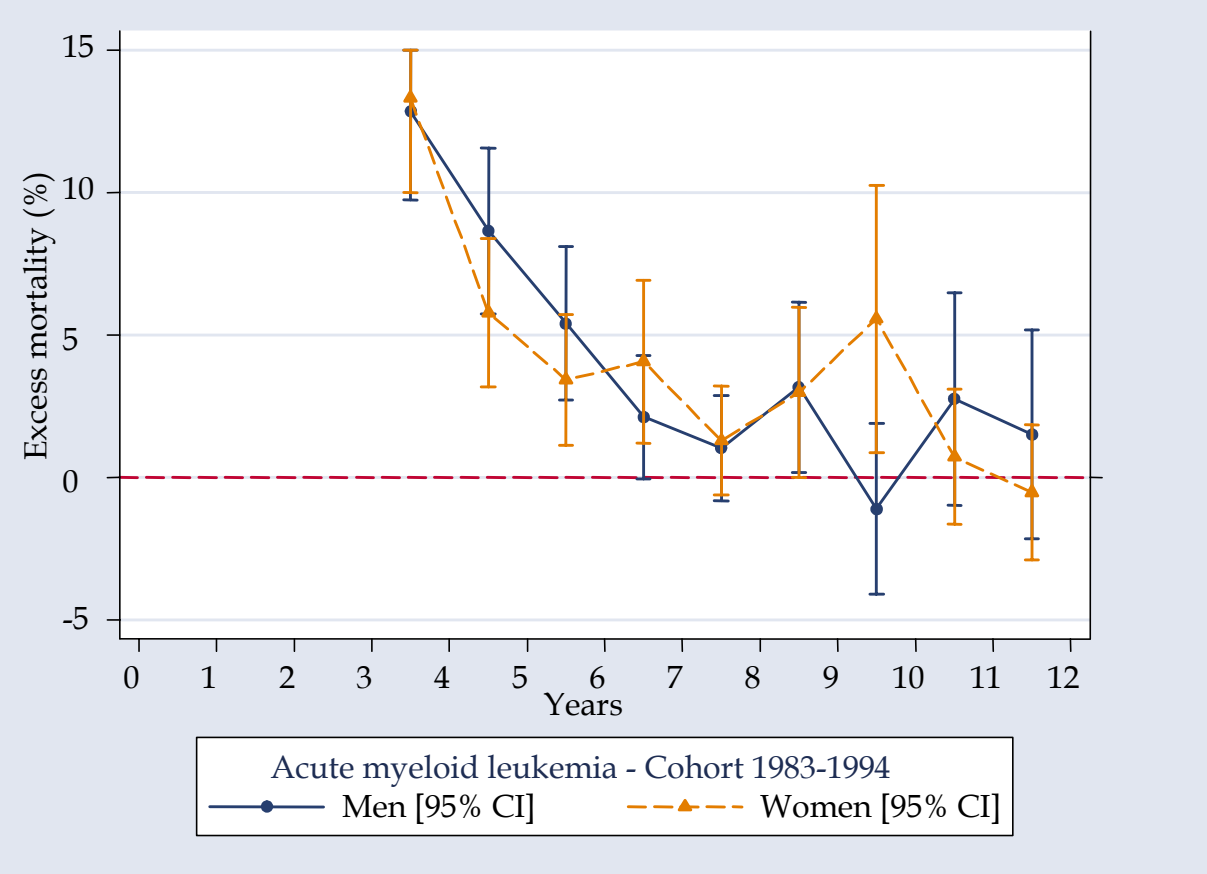

Figure 21.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 21.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)	
Interval (years)	Cohort 15-44 years (N = 1,229)	Cohort 45-64 years (N = 2,029)
0-1	37.04 [34.34-39.75]	53.55 [51.36-55.73]
1-2	30.37 [27.12-33.62]	36.93 [33.80-40.07]
2-3	16.96 [13.76-20.16]	22.63 [19.16-26.09]
3-4	11.97 [8.91-15.03]	14.56 [11.18-17.94]
4-5	5.60 [3.21-7.99]	9.69 [6.45-12.93]
5-6	2.16 [0.46-3.86]	7.39 [4.09-10.69]
6-7	1.10 [-0.35-2.56]	5.20 [1.84-8.56]
7-8	1.23 [-0.37-2.82]	2.11 [-0.54-4.76]
8-9	2.68 [0.19-5.18]	3.49 [-0.03-7.00]
9-10	2.96 [-0.11-6.03]	2.48 [-1.40-6.36]
10-11	-0.23 [-3.30-2.83]	4.68 [-0.72-10.07]
11-12	0.95 [-1.39-3.29]	-0.04 [-3.51-3.43]

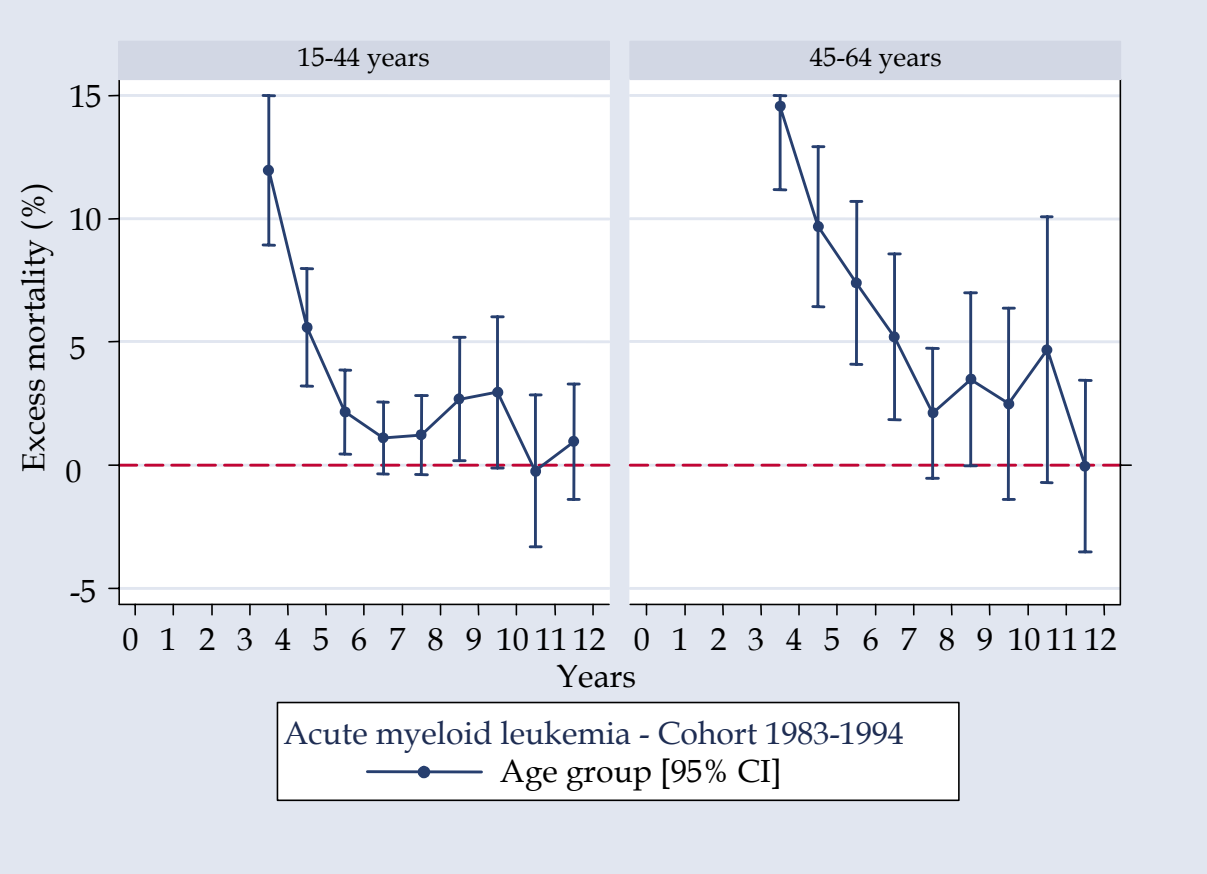

Figure 21.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 21.IV: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	1983-1985 (N = 770)	1986-1988 (N = 861)	1989-1991 (N = 813)	1992-1994 (N = 814)
0-1	53.23 [49.69-56.78]	52.33 [48.97-55.68]	42.66 [39.23-46.08]	41.00 [37.61-44.40]
1-2	38.78 [33.70-43.86]	35.70 [30.99-40.40]	31.47 [27.20-35.74]	31.22 [27.03-35.41]
2-3	26.92 [20.94-32.89]	19.69 [14.77-24.62]	19.02 [14.62-23.42]	16.27 [12.20-20.33]
3-4	20.07 [13.70-26.44]	12.12 [7.55-16.69]	15.77 [11.21-20.33]	7.83 [4.52-11.14]
4-5	9.95 [4.52-15.37]	10.73 [6.03-15.42]	5.63 [2.38-8.88]	5.46 [2.21-8.71]
5-6	3.01 [-0.50-6.51]	4.46 [0.99-7.92]	6.06 [2.58-9.53]	4.02 [0.18-7.86]
6-7	1.24 [-1.37-3.84]	3.34 [0.16-6.52]	3.78 [0.82-6.75]	-
7-8	1.23 [-1.44-3.91]	0.67 [-1.27-2.61]	2.85 [-0.12-5.83]	-
8-9	4.23 [-0.04-8.49]	4.27 [0.63-7.91]	-0.68 [-3.66-2.30]	-
9-10	2.32 [-1.19-5.83]	3.07 [-0.25-6.39]	-	-
10-11	2.39 [-1.28-6.05]	1.28 [-1.56-4.11]	-	-
11-12	0.18 [-2.03-2.40]	1.23 [-2.56-5.03]	-	-

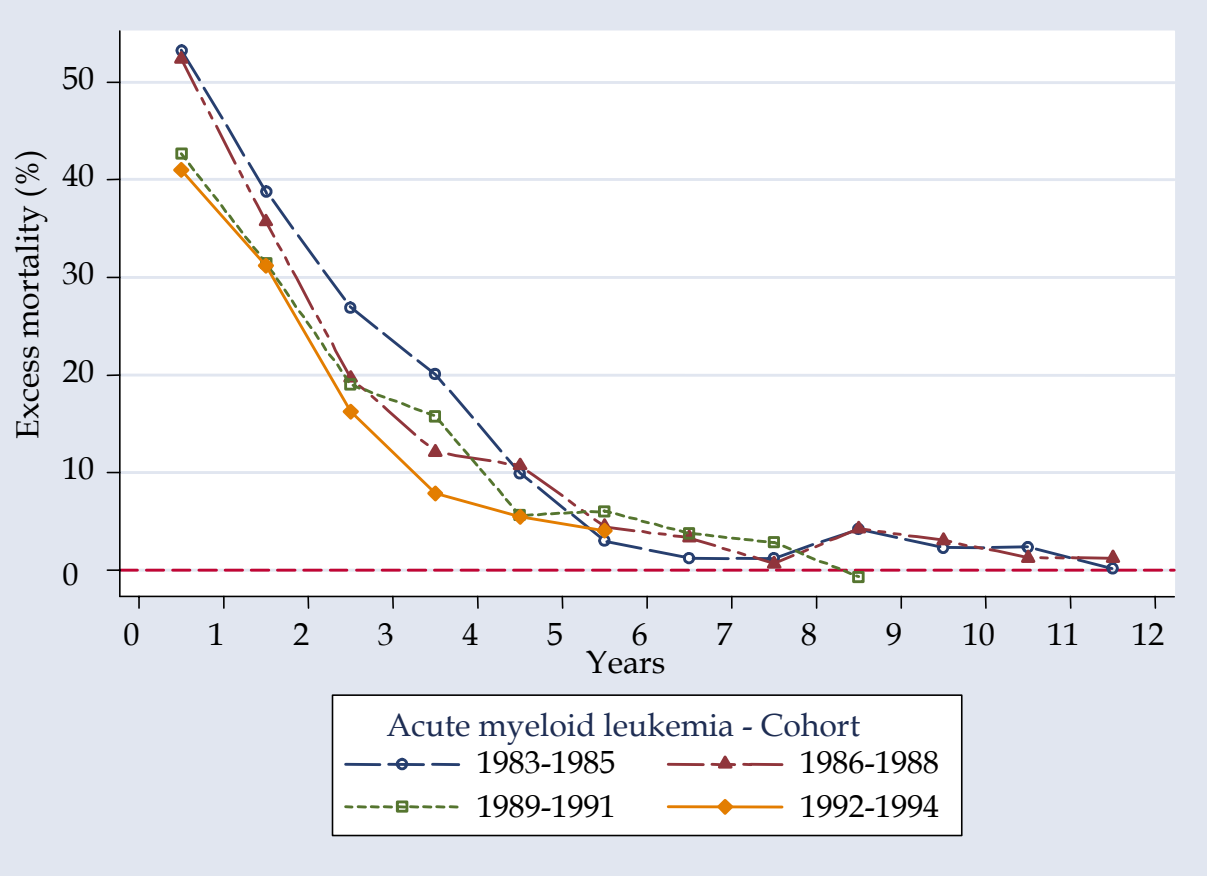

Figure 21.4: Time course of annual excess mortality by cohort

22

Chronic lymphocytic leukemia

With 2,171 incident cases in France in 2000, chronic lymphocytic leukemia (CLL) accounted for 35% of all cases of leukemia and 0.8% of all cases of cancer. The disease caused 1,112 deaths in 2000. Chronic lymphocytic leukemia does not occur in children and the incidence begins to rise as of age 45 years. The median age is about 70 years.

The Côte d'Or malignant blood disease registry has reported an age-standardized incidence rate for CLL of 3.1/100,000 for the period 1980-2001.

The same registry reports 5- and 10-year relative survivals for the period 1980-1997 of 84% (95% CI [78-91]) and 65% (95% CI [52-78]), respectively.

The Eurocare data show a 5-year relative survival of 72.7% for the most recent cohort (1992-1994) all stages taken together and for the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 22.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates take into account all the cases of CLL diagnosed in Europe (8 countries) between 1983 and 1994. Annual excess mortality fluctuating between 5 and 10% persisted throughout the entire follow-up period (figure 22.1).

Table 22.II summarizes the annual excess mortality results by gender. The annual excess mortality estimates were higher for men for all years post-diagnosis. The plot showing female annual excess mortality is lower than that for men over the greater part of the time interval. In the last 3 years, the two plots crossed. However, it is difficult to draw any conclusion in view of the increasingly large confidence intervals (figure 22.2).

Table 22.III shows the results obtained for the various age groups. The annual excess mortality profiles are fairly similar for the various age groups (figure 22.3). However, an increase in excess mortality was observed for the oldest age groups. The excess mortality rate after year 8 post-diagnosis was about 7% for subjects aged less than 65 years and 10% for those aged more than 65 years.

The annual excess mortality data on the 4 cohorts are shown in table 22.IV. Figure 22.4 shows a slight reduction in annual excess mortality for the most recent cohort (1992-1994) in the first 2 years post-diagnosis.

Very long-term annual excess mortality (all stages considered): other studies

Talbäck *et al*. (2004) evaluated the 5-, 10- and 15-year relative survivals of patients with chronic lymphocytic leukemia diagnosed between 1960 and 1998 using the Swedish national cancer registry data, all ages taken together. Using the period analysis method (which takes into account the survival observed over the first years post-diagnosis for the most recent

periods), the 5-, 10- and 15-year relative survivals were 63.3, 41.6 and 23.5%, respectively. The results were close to the observed survival rates (68.4, 41.5 and 30.6%, respectively). The authors showed that 15 years post-diagnosis survival had not reached a plateau. The estimated mean annual excess mortality from 10 to 15 years post-diagnosis was 10.8%.

Survival by prognostic stage

There are several prognostic profiles for CLL. A non-negligible contingent of patients presenting with CLL is characterized by a life expectancy equivalent to that of controls of comparable age.

Prognostic stages A, B and C are defined in Binet's classification (1981) as follows:

- stage A: no anemia, no thrombopenia, less than 3 sites involved
- stage B: no anemia, no thrombopenia, 3 or more sites involved
- stage C: anemia (Hb < 10 g) and/or thrombopenia (platelet count < 100,000/mm^3).

The French Côte d'Or registry has reported 5- and 10-year relative survivals by stage (table 22.V).

Table 22.V: Relative survival by prognostic stage taken from the Côte d'Or registry data

Prognostic stage	5-year relative survival (% - [95% CI])	10-year relative survival (% - [95% CI])
Stage A	89 [84-94]	74 [65-83]
Stage B	78 [65-91]	53 [31-75]
Stage C	89 [53-83]	37 [17-57]

The immunoglobulin gene mutation rate and karyotype anomalies are now accepted as major prognostic criteria which predominate relative to the clinical stage alone. In patients free from somatic mutation of the immunoglobulin genes of neoplastic lymphocytes, the course of the disease is less favorable (Damle *et al*., 1999; Hamblin *et al*., 2000). Similarly, the following cytogenetic anomalies: +12, del(11q), del(17p) (Dohner *et al*., 2000) are pejorative prognostic factors. It is to be noted that karyotyping is routinely conducted while testing to determine the mutant or non-mutant nature of the immunoglobulin gene sequence remains highly experimental.

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Excess mortality data from the Eurocare study

Table 22.I: Annual excess mortality: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Overall (N = 5,480)
0-1	8.01 [7.21-8.81]
1-2	5.50 [4.75-6.24]
2-3	6.23 [5.42-7.05]
3-4	6.78 [5.89-7.67]
4-5	7.54 [6.55-8.53]
5-6	8.67 [7.51; 9.84]
6-7	8.80 [7.44-10.16]
7-8	8.17 [6.70-9.63]
8-9	7.94 [6.29-9.59]
9-10	9.67 [7.59-11.76]
10-11	6.81 [4.70-8.92]
11-12	9.99 [7.23-12.74]

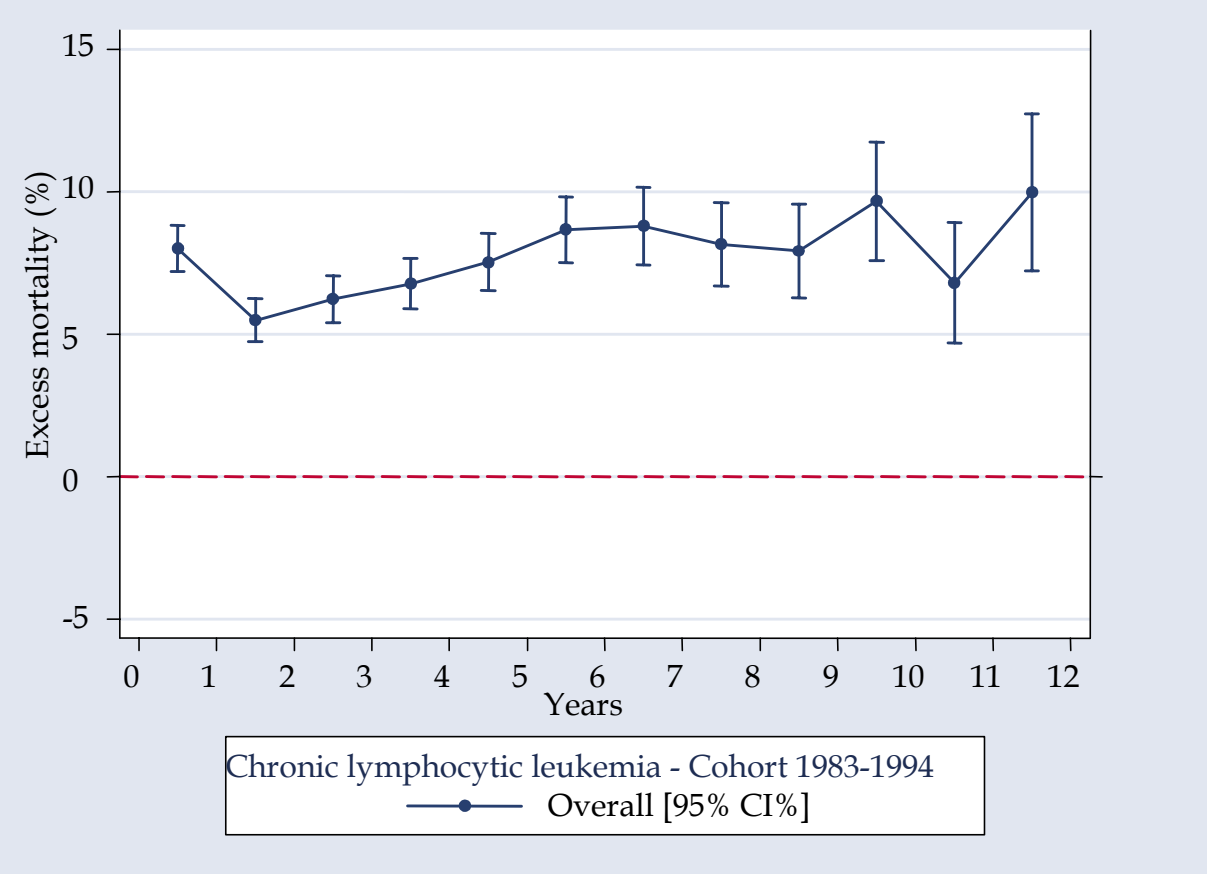

Figure 22.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 22.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 1,992)	Men (N = 3,488)
0-1	6.44 [5.27-7.62]	8.92 [7.85-9.98]
1-2	4.85 [3.74-5.96]	5.86 [4.87-6.86]
2-3	5.75 [4.52-6.98]	6.51 [5.43-7.59]
3-4	4.49 [3.31-5.67]	8.23 [7.00-9.46]
4-5	6.72 [5.26-8.18]	8.09 [6.75-9.43]
5-6	6.94 [5.30-8.58]	9.91 [8.31-11.51]
6-7	6.24 [4.41-8.07]	10.58 [8.67-12.48]
7-8	6.62 [4.60-8.63]	9.43 [7.38-11.49]
8-9	5.95 [3.76-8.13]	9.57 [7.18-11.95]
9-10	7.35 [4.58-10.13]	11.58 [8.59-14.57]
10-11	8.16 [4.96-11.35]	5.55 [2.78-8.33]
11-12	12.78 [8.39-17.17]	7.86 [4.34-11.38]

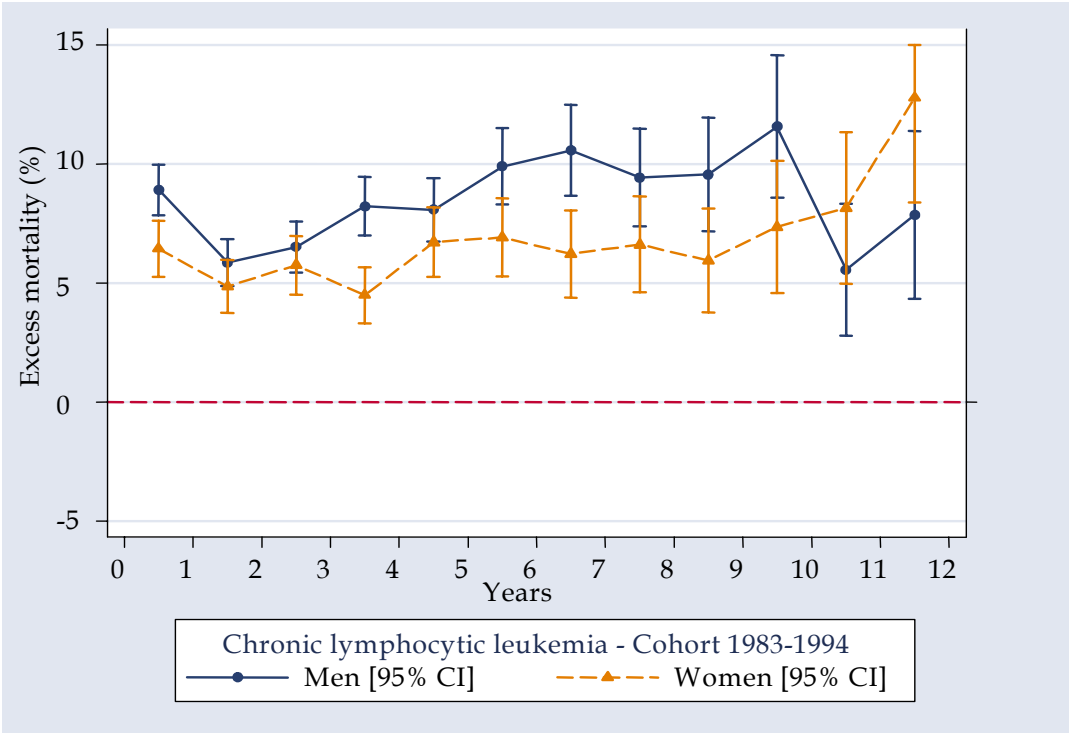

Figure 22.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 22.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 15-44 years (N = 151)	Cohort 45-54 years (N = 637)	Cohort 55-64 years (N = 1,672)	Cohort 65-74 years (N = 3,020)
0-1	2.46 [-0.11-5.03]	2.21 [0.95-3.46]	7.28 [5.93-8.62]	9.96 [8.75-11.17]
1-2	0.47 [-0.86-1.81]	4.36 [2.66-6.06]	5.07 [3.84-6.31]	6.31 [5.18-7.44]
2-3	3.90 [0.67-7.12]	4.25 [2.52-5.99]	4.72 [3.47-5.97]	7.80 [6.52-9.08]
3-4	5.49 [1.63-9.34]	4.11 [2.35-5.87]	5.72 [4.33-7.12]	8.26 [6.86-9.65]
4-5	3.67 [0.30-7.03]	6.98 [4.65-9.30]	7.07 [5.45-8.68]	8.30 [6.76-9.84]
5-6	4.92 [0.88-8.96]	6.85 [4.30-9.41]	8.71 [6.77-10.65]	9.50 [7.68-11.32]
6-7	7.18 [1.85-12.50]	9.11 [5.86-12.35]	7.68 [5.54-9.82]	9.66 [7.50-11.83]
7-8	-0.32 [-5.64-5.01]	6.09 [3.10-9.08]	7.04 [4.79-9.29]	10.56 [8.07-13.05]
8-9	10.81 [3.53-18.10]	5.64 [2.45-8.83]	6.56 [4.11-9.02]	9.65 [6.77-12.54]
9-10	8.93 [1.17-16.69]	6.49 [2.59-10.39]	9.84 [6.50-13.17]	10.92 [7.32-14.52]
10-11	4.02 [-1.96-10.00]	1.64 [-0.96-4.25]	5.56 [2.48-8.65]	10.78 [6.62-14.94]
11-12	-0.42 [-6.40-5.56]	11.05 [5.27-16.83]	11.35 [6.92-15.79]	9.56 [4.54-14.58]

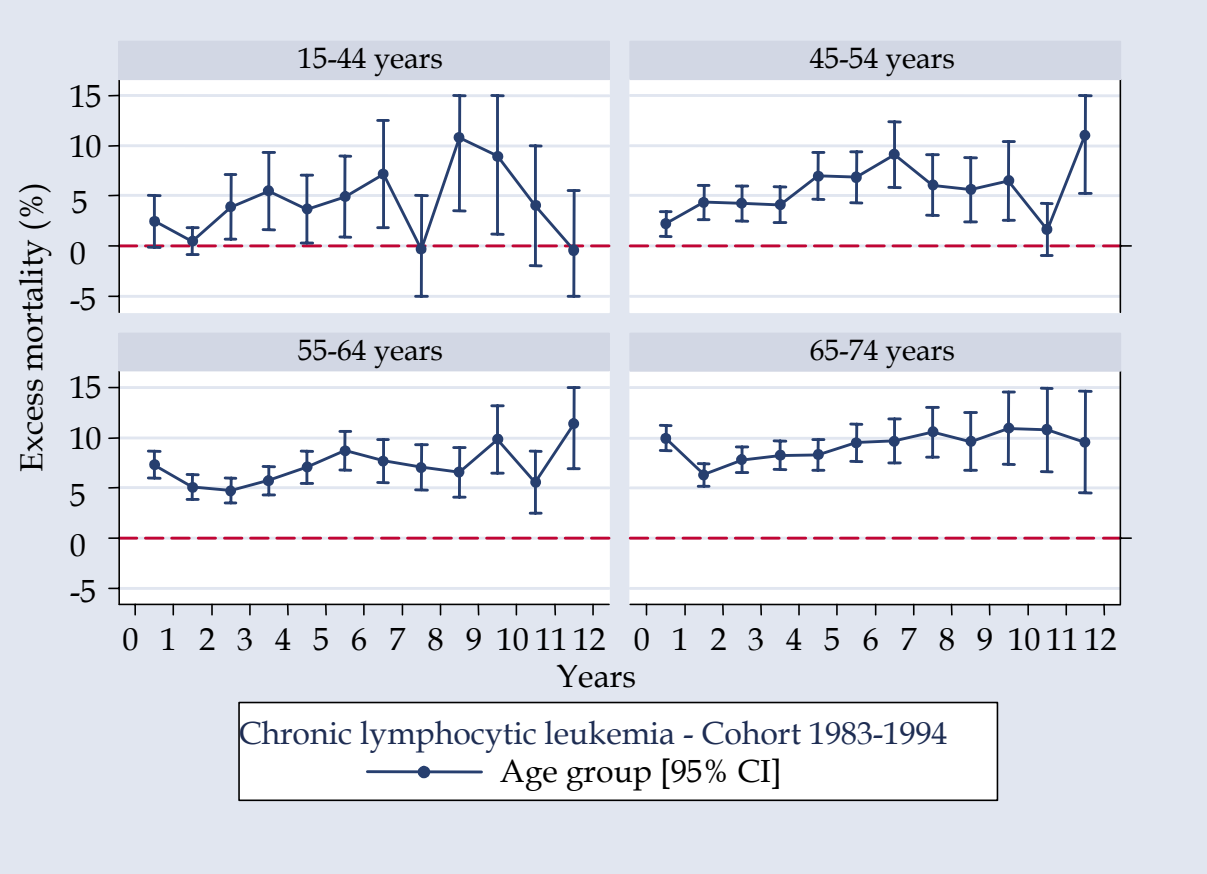

Figure 22.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 22.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 1983-1985 (N = 1,426)	Cohort 1986-1988 (N = 1,410)	Cohort 1989-1991 (N = 1,244)	Cohort 1992-1994 (N = 1,400)
0-1	10.07 [8.34-11.79]	8.53 [6.91-10.15]	6.85 [5.27-8.44]	6.43 [4.98-7.88]
1-2	5.52 [4.01-7.02]	6.59 [5.01-8.16]	5.80 [4.22-7.38]	4.15 [2.83-5.46]
2-3	6.10 [4.46-7.73]	6.67 [5.00-8.34]	6.33 [4.62-8.04]	5.87 [4.34-7.41]
3-4	7.21 [5.39-9.04]	6.16 [4.44-7.87]	7.44 [5.54-9.34]	6.39 [4.72-8.05]
4-5	7.48 [5.52-9.44]	7.84 [5.88-9.80]	6.78 [4.83-8.74]	8.00 [5.92-10.07]
5-6	9.08 [6.86-11.29]	9.69 [7.46-11.93]	7.32 [5.20-9.44]	8.21 [5.28-11.14]
6-7	9.03 [6.66-11.40]	8.16 [5.89-10.43]	9.25 [6.81-11.68]	-
7-8	7.27 [4.89-9.65]	8.57 [6.11-11.03]	8.76 [5.94-11.58]	-
8-9	6.63 [4.16-9.10]	9.28 [6.58-11.98]	7.79 [3.97-11.62]	-
9-10	10.69 [7.66-13.72]	8.63 [5.78-11.48]	-	-
10-11	6.18 [3.38-8.98]	7.55 [4.33-10.77]	-	-
11-12	12.12 [8.51-15.72]	5.92 [1.88-9.96]	-	-

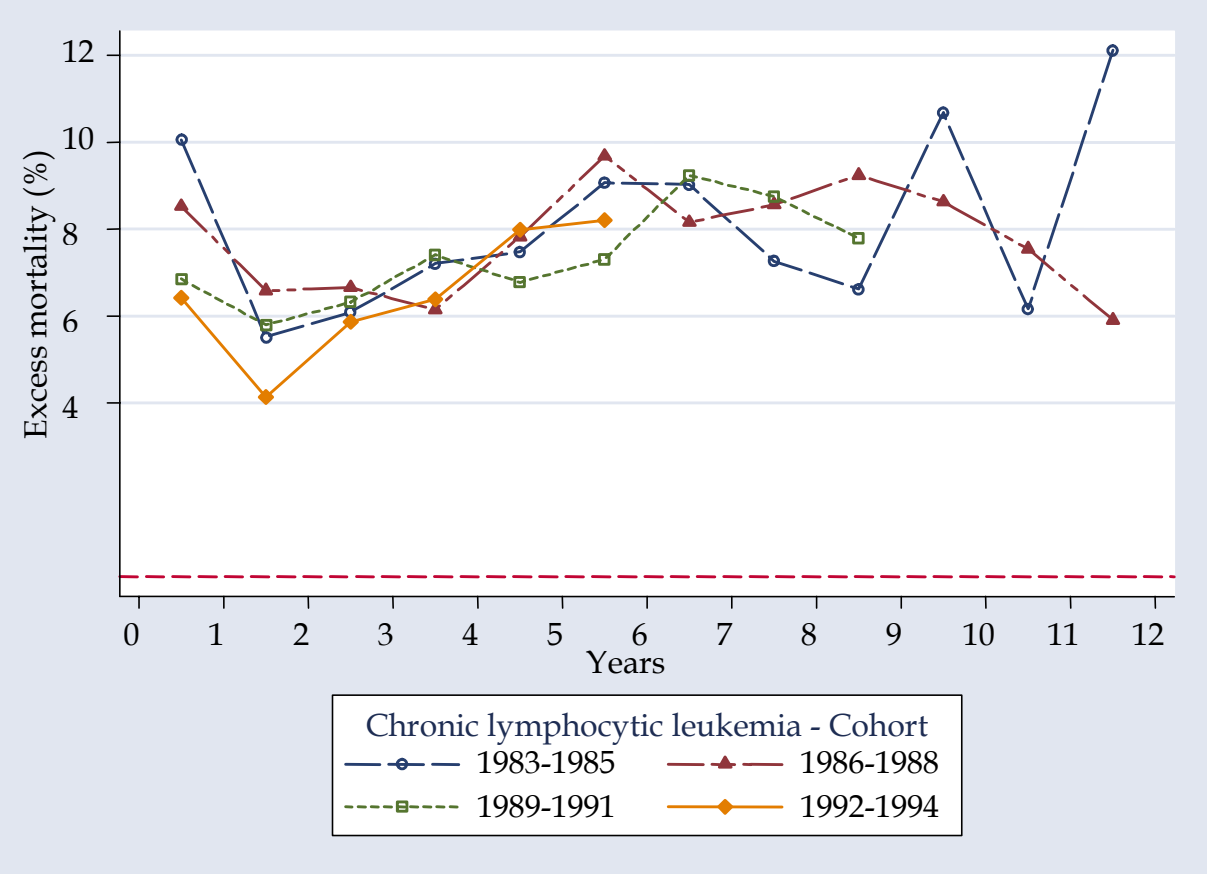

Figure 22.4: Time course of annual excess mortality by cohort

23

Chronic myeloid leukemia

The French Côte d'Or malignant blood disease registry has reported an age-standardized incidence rate for chronic myeloid leukemia (CML) of 0.9/100,000 for the period 1980-2001. Frequency rises with age and the median age is 53 years. The sex ratio is 1.1 - 1.2.

The Côte d'Or registry also reports the relative survival for the period 1980-1997: 52% (95% CI [42-63]) and 29% (95% CI [18-40]) at 10 years.

According to the Eurocare data, the 5-year relative survival of patients in the most recent cohort (1992-1994) for the 8 countries selected was 43.9%.

Annual excess mortality (all stages considered): Eurocare data

Table 23.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates take into account all the cases of CML diagnosed between 1983 and 1994 in Europe (8 countries). Annual excess mortality fell regularly but remained about 10% between year 7 and 12 post-diagnosis (figure 23.1).

Table 23.II shows the annual excess mortality data by gender. The mortality rates were higher for men in the first years post-diagnosis. After year 4 post-diagnosis, the time courses of the annual excess mortalities for men and women were similar (figure 23.2).

Table 23.III shows the annual excess mortality results obtained for various age groups. The age group 15-44 years showed the lowest excess mortality rates. For that age group, a regular fall in mortality rates was observed. The mortality rate reached about 5% between year 8 and 12 post-diagnosis (figure 23.3). For the other age groups, the annual excess mortality rates were higher during the first years post-diagnosis (from 15 to 30%). The confidence intervals became very large remotely from the diagnosis.

The analysis by cohort (table 23.IV and figure 23.4) shows a reduction in annual excess mortality for the most recent diagnostic cohorts, particularly over the period 0-5 years.

Impact of new treatments on excess mortality

The decrease in the annual excess mortalities observed for the Eurocare cohort, 1992-1994, relative to the older cohorts, illustrates the impact of therapeutic progress. Even more recent progress will fundamentally change the prognosis of CML. Currently the annual excess mortality remains high remotely from diagnosis due to the transformation of CML to acute leukemia.

The new drugs of the tyrosine kinase inhibitor series for the treatment of CML appear to have considerably improved survival. The first drug of the new series is Glivec (imatinib). At time point 27 months, the progression-free survivals were 90% with imatinib and 75% with

combined interferon and cytarabine therapy (O'Brien, 2003). However, some patients do not respond to that treatment.

Other treatments currently under development will doubtless enable an increase in the number of responders and an improvement in the quality of the response.

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Excess mortality data from the Eurocare study

Table 23.I: Annual excess mortality: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Overall (N = 2,526)
0-1	20.83 [19.20-22.46]
1-2	19.06 [17.26-20.85]
2-3	16.84 [14.91-18.76]
3-4	16.20 [14.10-18.30]
4-5	16.53 [14.14-18.92]
5-6	15.76 [13.00-18.52]
6-7	18.57 [15.02-22.11]
7-8	12.08 [8.57-15.58]
8-9	10.27 [6.38-14.17]
9-10	9.32 [4.57-14.07]
10-11	12.02 [6.01-18.04]
11-12	8.66 [1.83-15.48]

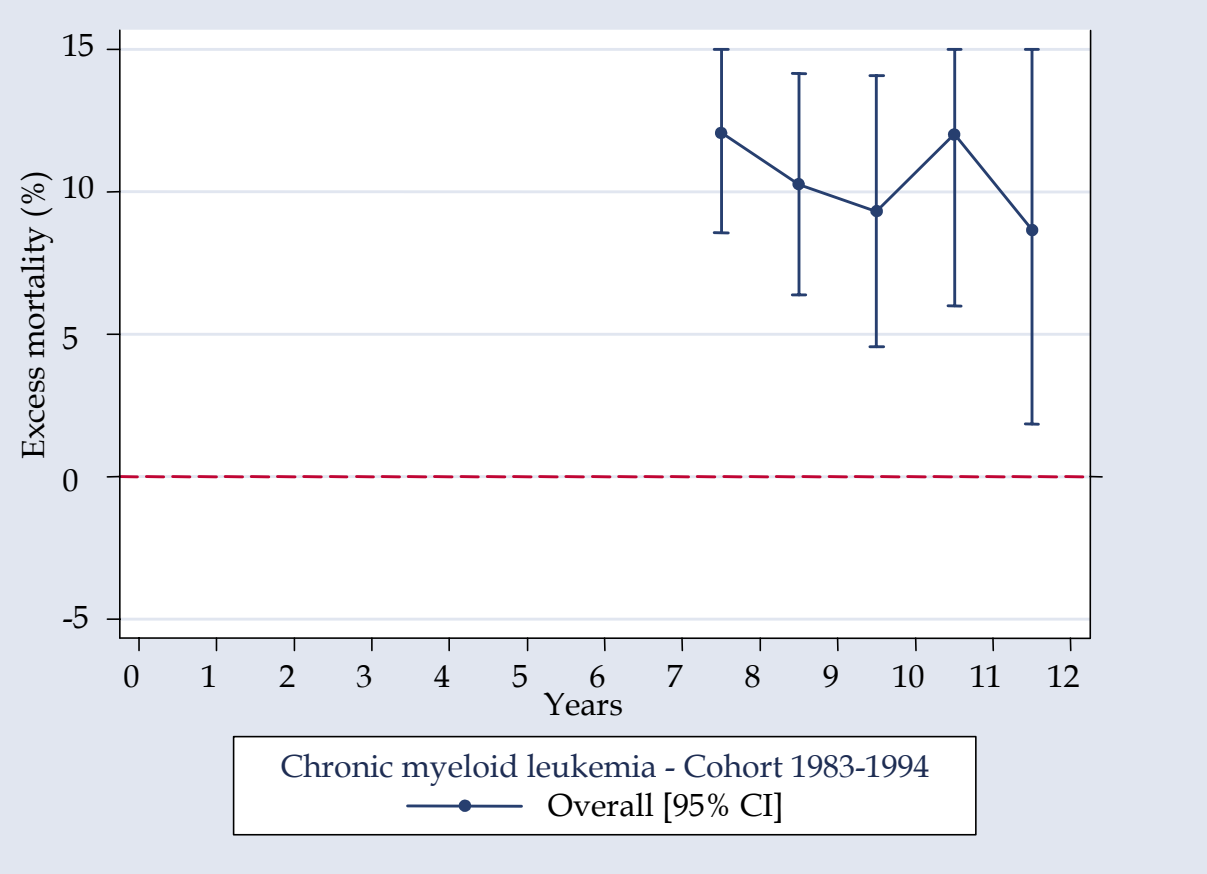

Figure 23.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 23.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 1,014)	Men (N = 1,509)
0-1	16.52 [14.18-18.86]	23.60 [21.38-25.82]
1-2	16.32 [13.75-18.88]	20.86 [18.40-23.33]
2-3	14.02 [11.36-16.68]	18.88 [16.17-21.59]
3-4	15.11 [12.11-18.11]	16.14 [13.26-19.01]
4-5	17.09 [13.56-20.62]	14.98 [11.80-18.16]
5-6	16.63 [12.52-20.75]	14.01 [10.37-17.66]
6-7	14.74 [10.07-19.41]	17.55 [12.60-22.51]
7-8	10.11 [5.51-14.71]	11.07 [6.20-15.95]
8-9	7.98 [3.09-12.87]	6.75 [1.89-11.60]
9-10	10.50 [3.81-17.20]	4.43 [-0.93-9.78]
10-11	10.59 [2.65-18.53]	11.37 [2.67-20.06]
11-12	6.87 [-1.25-14.98]	6.04 [-4.18-16.26]

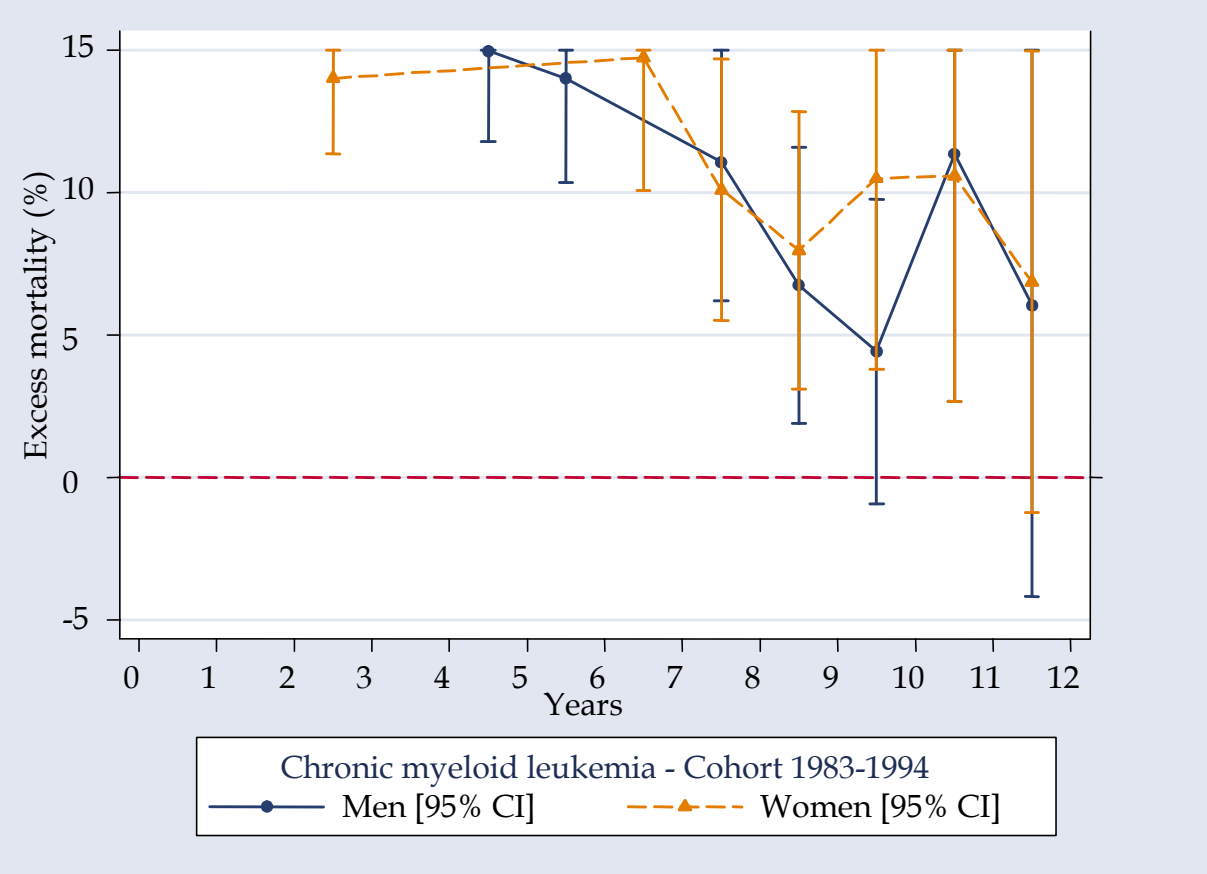

Figure 23.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 23.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 15-44 years (N = 656)	Cohort 45-54 years (N = 426)	Cohort 55-64 years (N = 607)	Cohort 65-74 years (N = 837)
0-1	14.67 [11.95-17.39]	15.64 [12.14-19.13]	19.23 [16.01-22.45]	29.68 [26.44-32.92]
1-2	17.80 [14.62-20.99]	15.38 [11.58-19.19]	18.02 [14.49-21.55]	23.58 [19.87-27.30]
2-3	13.00 [9.90-16.10]	15.01 [10.89-19.13]	16.88 [13.03-20.72]	22.42 [18.15-26.70]
3-4	11.99 [8.77-15.21]	11.11 [7.14-15.08]	18.89 [14.46-23.33]	23.08 [18.07-28.08]
4-5	9.61 [6.39-12.82]	16.87 [11.70-22.04]	20.50 [15.27-25.73]	22.26 [16.34-28.19]
5-6	9.95 [6.33-13.58]	15.90 [9.87-21.93]	20.54 [14.24-26.84]	21.03 [13.75-28.31]
6-7	12.64 [8.04-17.25]	17.96 [9.98-25.94]	23.61 [15.48-31.73]	26.70 [16.78-36.61]
7-8	7.16 [3.15-11.16]	12.56 [4.51-20.62]	14.53 [6.39-22.67]	22.72 [10.60-34.83]
8-9	4.49 [0.82-8.16]	7.49 [-0.23-15.22]	15.38 [5.07-25.68]	29.58 [12.60-46.57]
9-10	4.48 [-0.03-8.99]	12.62 [0.36-24.89]	18.91 [5.04-32.79]	8.80 [-10.71-28.30]
10-11	11.04 [3.66-18.41]	8.30 [-3.82-20.41]	25.57 [6.52-44.62]	-6.88 [-26.48-12.71]
11-12	4.17 [-1.86-10.21]	24.28 [2.86-45.70]	9.90 [-13.70-33.50]	-7.72 [-27.46-12.03]

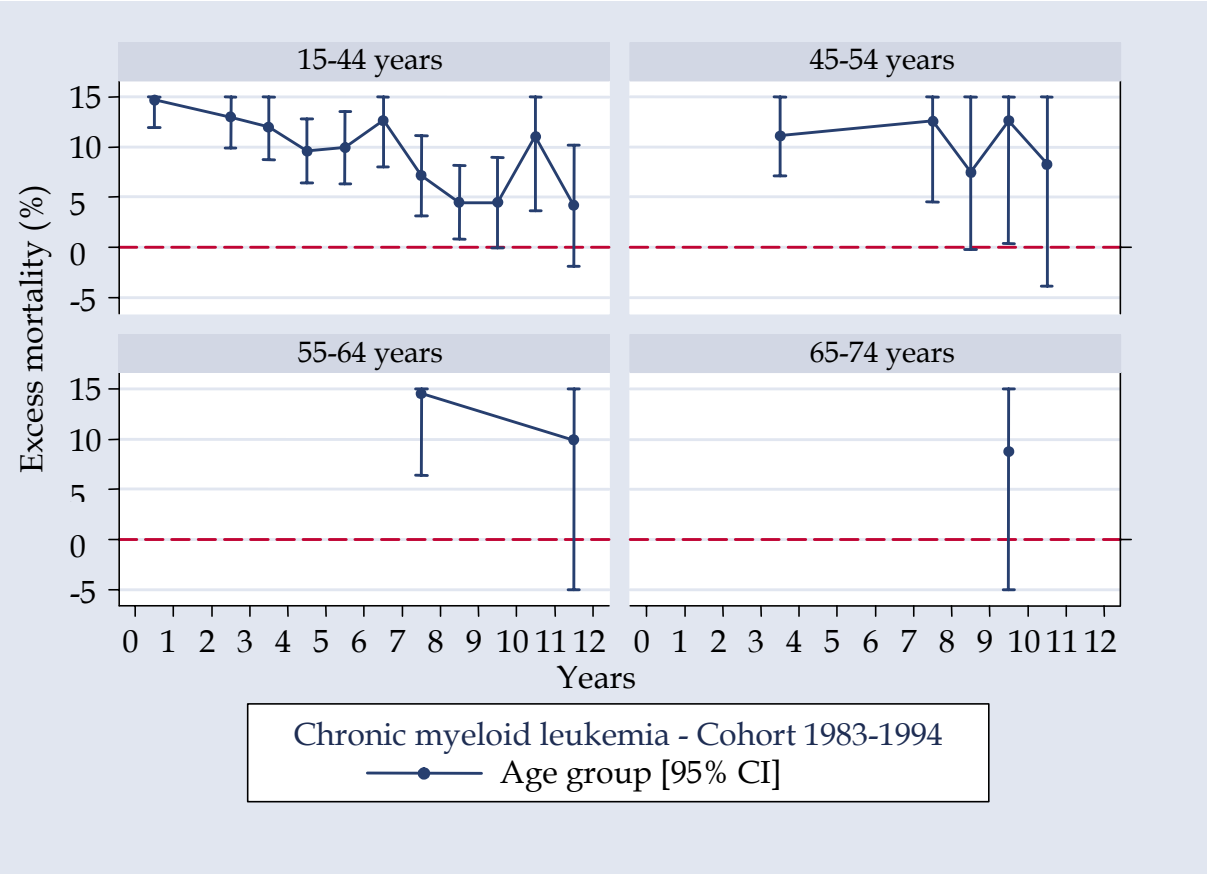

Figure 23.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 23.IV: Annual excess mortality for the four Eurocare cohorts

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 1983-1985 (N = 621)	Cohort 1986-1988 (N = 675)	Cohort 1989-1991 (N = 595)	Cohort 1992-1994 (N = 635)
0-1	24.32 [20.84-27.80]	20.15 [17.03-23.28]	21.96 [18.54-25.37]	17.09 [14.06-20.13]
1-2	23.01 [19.04-26.98]	16.25 [12.99-19.52]	18.84 [15.14-22.53]	18.63 [15.17-22.08]
2-3	18.93 [14.64-23.22]	18.54 [14.77-22.31]	14.38 [10.64-18.12]	15.47 [11.86-19.07]
3-4	21.62 [16.59-26.65]	17.03 [12.94-21.11]	14.20 [10.15-18.25]	12.82 [9.12-16.52]
4-5	24.66 [18.69-30.63]	17.65 [13.06-22.24]	13.11 [8.85-17.38]	11.74 [7.46-16.01]
5-6	24.10 [17.21-30.99]	19.46 [14.19-24.73]	9.37 [5.30-13.44]	9.18 [3.57-14.79]
6-7	19.33 [11.83-26.83]	22.11 [15.93-28.29]	14.80 [9.64-19.95]	-
7-8	11.54 [4.45-18.62]	15.99 [9.66-22.32]	8.44 [3.53-13.35]	-
8-9	12.83 [4.88-20.78]	8.87 [3.24-14.49]	9.70 [2.64-16.76]	-
9-10	14.09 [5.18-22.99]	6.18 [1.03-11.33]	-	-
10-11	10.54 [1.58-19.51]	13.04 [4.97-21.11]	-	-
11-12	8.27 [-0.73-17.27]	-	-	-

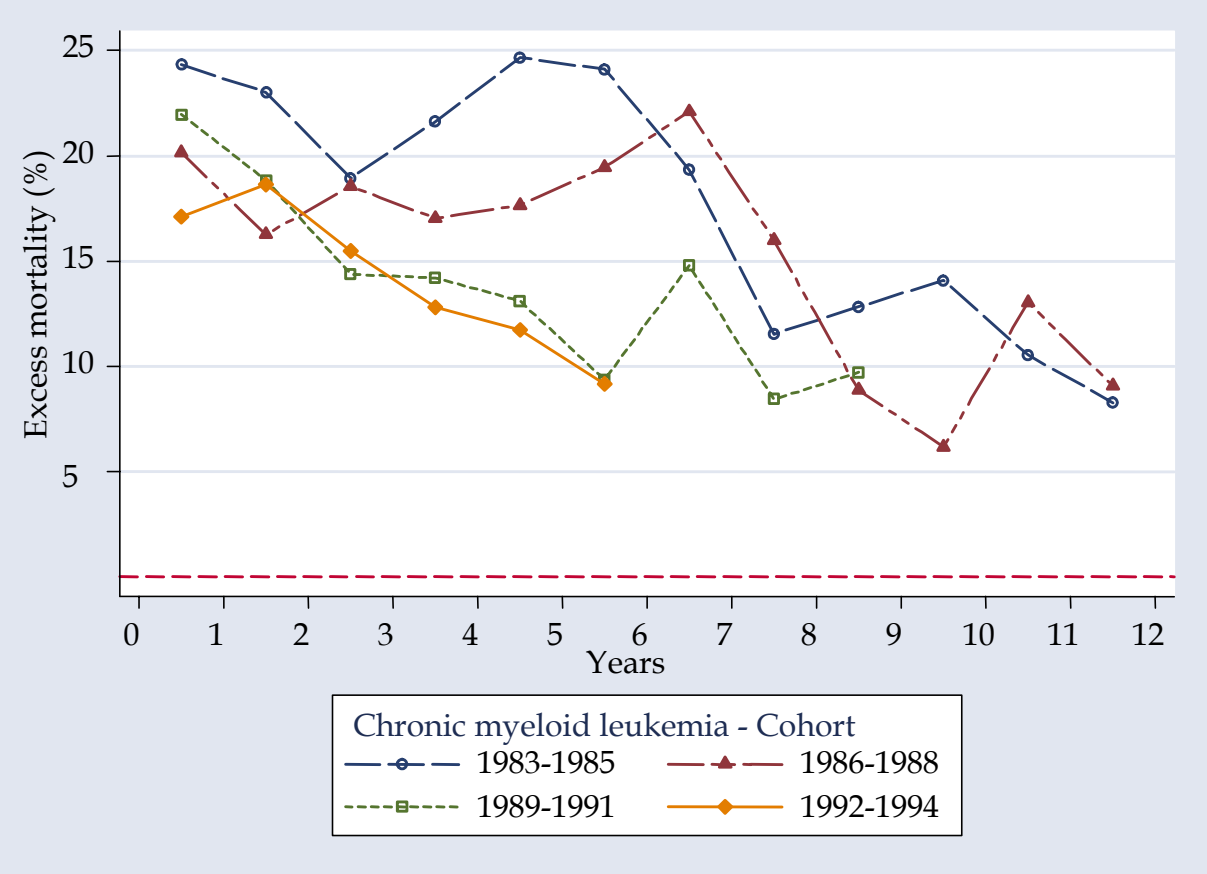

Figure 23.4: Time course of annual excess mortality by cohort

24

Hodgkin's disease

Hodgkin's disease accounted for 0.5% of all incident cases of cancer in 2000. In terms of frequency, Hodgkin's disease ranked 18th for men and 20th for women. The disease affects adults with two frequency peaks: one at about age 30 and the other at about age 60 years (Remontet *et al.*, 2003).

The disease ranks 23rd among the causes of cancer deaths and accounts for 0.1% of all deaths by cancer. The incidence rate has fallen slightly for men and women: the age-standardized incidence rate (world population) fell from 2.9/100,000 in 1980 to 2.0/100,000 in 2000 for men (mean annual rate = -1.37) and from 2.1/100,000 to 2.0/100,000 for women (mean annual rate = -0.50).

Mortality is falling regularly for both men and women. The fall is shown by a mean annual growth rate of -5.08 for men and -4.66 for women. Therapeutic progress related to the definition of a strategy adapted to the initial extent of the disease and combining radiotherapy and chemotherapy underlie the observed improvement in survival.

On the basis of the Eurocare data on the cohort 1992-1994, the 5-year survival for all stages of the disease taken together and for the 8 countries selected was 83.7%.

Annual excess mortality (all stages considered): Eurocare data

Table 24.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates take into account all the cases of Hodgkin's disease diagnosed between 1983 and 1994 in Europe (8 countries). The annual excess mortality, slightly greater than 5% at year 2 post-diagnosis, fell below 2% after year 6 (figure 24.1).

Table 24.II shows the annual excess mortality data by gender. The annual excess mortality was slightly higher for men in the first few years post-diagnosis but the difference disappeared after year 8 (figure 24.2).

Table 24.III shows the annual excess mortality results for various age groups. The age group 15-44 years showed the lowest annual excess mortality rates. The rates were less than 3% as of the first years post-diagnosis and fell to about 1% after 5-6 years. The age group 65-74 years had the highest annual excess mortality rate (figure 24.3).

The annual excess mortality data for the four Eurocare cohorts are shown in table 24.IV. A fall in annual excess mortality occurred for the most recent cohort (figure 24.4).

Very long-term annual excess mortality (all stages considered): other studies

Brenner (2002) evaluated the 5-, 10-, 15- and 20-year relative survivals of patients whose Hodgkin's disease was diagnosed between 1973 and 1998 using the data from the US Surveillance Epidemiology and End Results (SEER) program of the National Institute of

Cancer. The relative survival estimates were 81.0, 73.9, 66.2 and 57.4%, respectively. The mean annual excess mortality between 15 and 20 years was estimated to be of the order of 2.66%. With the period analysis method (which takes into account the survival observed during the first years post-diagnosis for the most recent periods), the estimates were 85.1, 79.8, 73.8 and 67.1%. In the latter case, the mean annual excess mortality between 15 and 20 years was estimated to be 1.9%.

Talbäck *et al*. (2004) evaluated the 5-, 10- and 15-year relative survivals of patients presenting with Hodgkin's disease diagnosed between 1965 and 1996 using the Swedish national cancer registry data. Using the period analysis method, the authors estimated the 5-, 10- and 15-year relative survivals to be 80.8, 72.7 and 56.3%, respectively. The data are similar to the 5-, 10- and 15-year relative survivals observed for the patients diagnosed during the most recent period. The figures were: 81, 73.3 and 67%. The mean annual excess mortality rate was estimated to be 1.7% for the period 10-15 years.

5-year relative survival by stage

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated 5-year relative survival data for three stages of Hodgkin's disease progression—localized, regional and metastatic (distant metastases)—and a non-determined stage (table 24.V). The distribution of the cases of Hodgkin's disease by stage (localized, regional and metastatic) was as follows: 25.7, 36.4 and 33.9%. The results are for men and women, all ages taken together, for the diagnostic period from 1988 to 2001.

Table 24.V: 5-year relative survival by stage at diagnosis taken from the SEER data (1988-2001)

Stage at diagnosis	5-year relative survival (%)
Localized disease	89.4
Regional disease	89.1
Metastatic disease	73.8
All stages	83.6

Impact of treatment on survival

The long-term risk of developing a second malignancy after Hodgkin's disease remains a problem for patients treated with radiotherapy with or without chemotherapy. Several studies have estimated the risk (Abrahamsen *et al*., 2002; Ng *et al*., 2002). After 15 and 20 years, the excess risk of a second malignancy is 2 and 4% (per person and per year), respectively. The risk continues to increase beyond 15-20 years.

The 5-year survival after development of a second malignancy is about 40%. The risk of death from the second malignancy or cardiovascular disease continues to increase after 10 years. Thirty years post-Hodgkin's disease diagnosis, the patients present with a higher risk of death due to adverse reactions to treatment.

The analyses of the cases of late deaths—essentially malignancies and coronary artery disease in the irradiated field—have enabled modification of the modalities of radiotherapy for the treatment of localized forms. The size of the field irradiated and the doses delivered have been reduced. Over the last 2 years, ongoing clinical trials have investigated abstention from radiotherapy for forms with a good prognosis.

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Excess mortality data from the Eurocare study

Table 24.I: Annual excess mortality: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Overall (N = 6,137)
0-1	8.26 [7.54-8.97]
1-2	5.29 [4.68 -5.91]
2-3	3.30 [2.78 -3.82]
3-4	3.68 [3.12 -4.23]
4-5	2.45 [1.95 -2.95]
5-6	2.35 [1.83 -2.88]
6-7	1.76 [1.23 -2.28]
7-8	1.46 [0.95 -1.98]
8-9	1.66 [1.07 -2.25]
9-10	1.03 [0.44 -1.63]
10-11	2.22 [1.41 -3.03]
11-12	1.41 [0.61 -2.20]

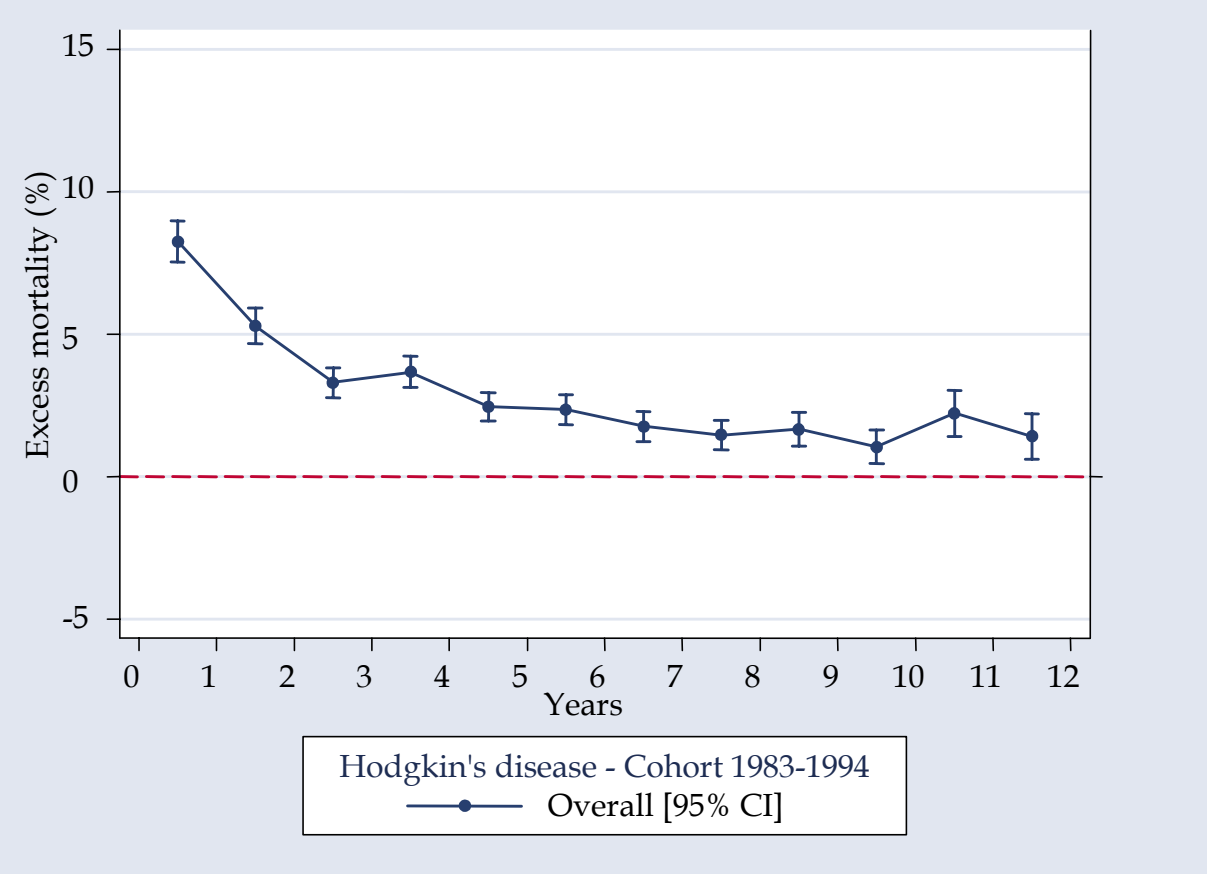

Figure 24.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 24.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 2,562)	Men (N = 3,569)
0-1	6.66 [5.67-7.65]	9.25 [8.26-10.24]
1-2	4.66 [3.78-5.54]	5.75 [4.89-6.60]
2-3	3.02 [2.27-3.76]	3.43 [2.71-4.14]
3-4	3.23 [2.45-4.01]	3.93 [3.15-4.70]
4-5	2.23 [1.53-2.93]	2.63 [1.94-3.32]
5-6	2.12 [1.39-2.86]	2.54 [1.81-3.28]
6-7	1.39 [0.70-2.08]	2.00 [1.25-2.75]
7-8	0.92 [0.29-1.55]	1.74 [0.99-2.49]
8-9	1.56 [0.73-2.39]	1.63 [0.82-2.44]
9-10	0.81 [0.03-1.59]	1.24 [0.39-2.10]
10-11	2.22 [1.03-3.40]	1.78 [0.76-2.80]
11-12	1.23 [0.13-2.32]	1.39 [0.33-2.45]

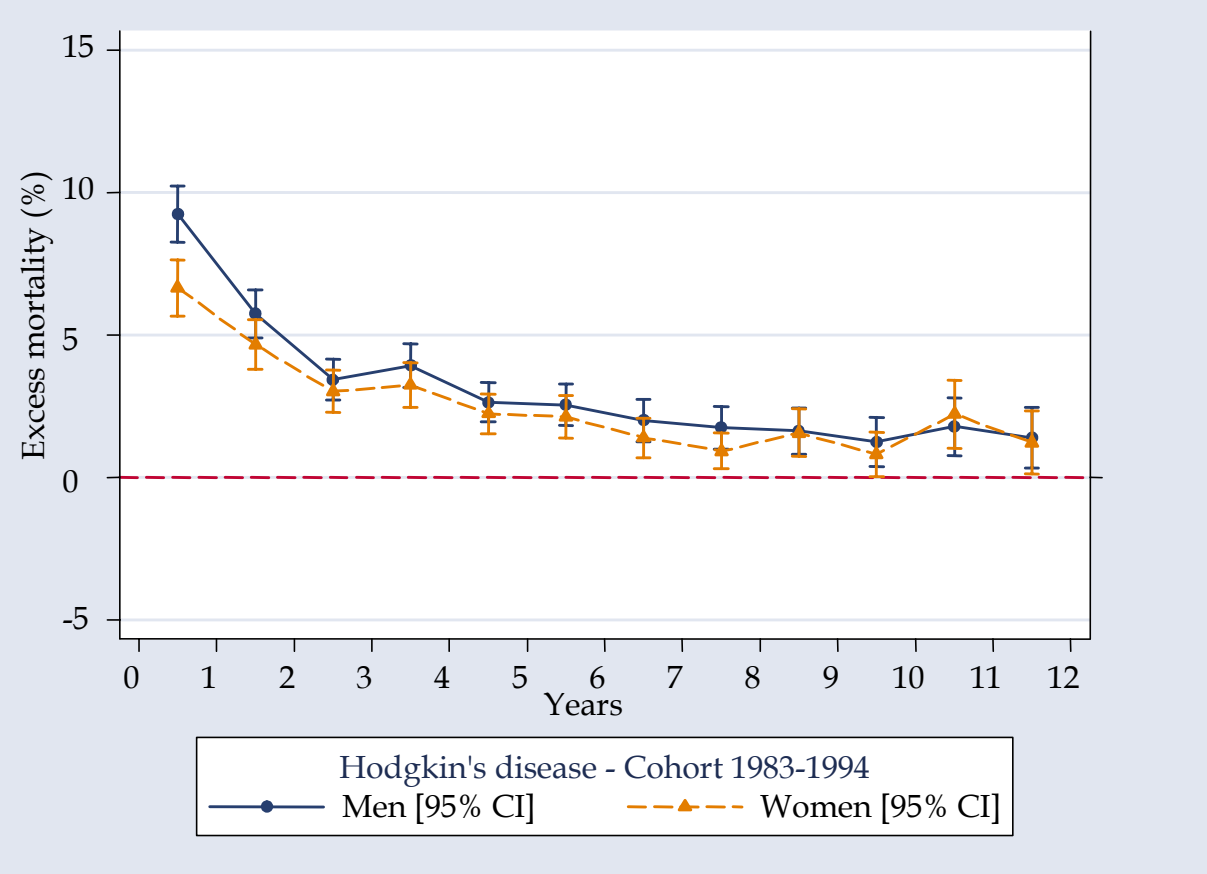

Figure 24.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 24.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

	Excess mortality [95% CI] (annual %)			
Interval (years)	Cohort 15-44 years (N = 3,887)	Cohort 45-54 years (N = 692)	Cohort 55-64 years (N = 752)	Cohort 65-74 years (N = 806)
0-1	2.32 [1.83-2.80]	7.41 [5.41-9.42]	16.89 [14.13-19.66]	30.19 [26.87-33.50]
1-2	2.83 [2.29-3.37]	7.28 [5.20-9.36]	9.76 [7.28-12.24]	15.35 [12.04-18.65]
2-3	2.13 [1.65-2.61]	3.44 [1.87-5.02]	5.69 [3.55-7.83]	9.97 [6.78-13.16]
3-4	2.49 [1.97-3.02]	4.12 [2.38-5.87]	7.10 [4.67-9.53]	9.57 [6.16-12.97]
4-5	1.66 [1.21-2.12]	2.02 [0.63-3.41]	4.74 [2.50-6.98]	8.03 [4.46-11.59]
5-6	1.58 [1.11-2.06]	2.59 [0.94-4.24]	3.74 [1.50-5.98]	8.51 [4.42-12.59]
6-7	1.11 [0.66-1.55]	2.46 [0.64-4.29]	3.81 [1.30-6.33]	5.22 [0.92-9.52]
7-8	0.94 [0.50-1.37]	2.47 [0.52-4.42]	2.25 [-0.07-4.57]	5.38 [0.57-10.19]
8-9	1.01 [0.52-1.49]	3.51 [1.02-6.00]	2.10 [-0.44-4.64]	6.78 [0.95-12.62]
9-10	0.44 [0.03-0.85]	3.67 [0.77-6.58]	0.17 [-2.17-2.50]	6.28 [-0.54-13.10]
10-11	1.29 [0.63-1.95]	4.80 [1.34-8.26]	3.90 [-0.11-7.91]	9.86 [0.95-18.77]
11-12	1.10 [0.39-1.80]	0.52 [-1.61-2.66]	2.16 [-2.00-6.32]	10.11 [-1.59-21.81]

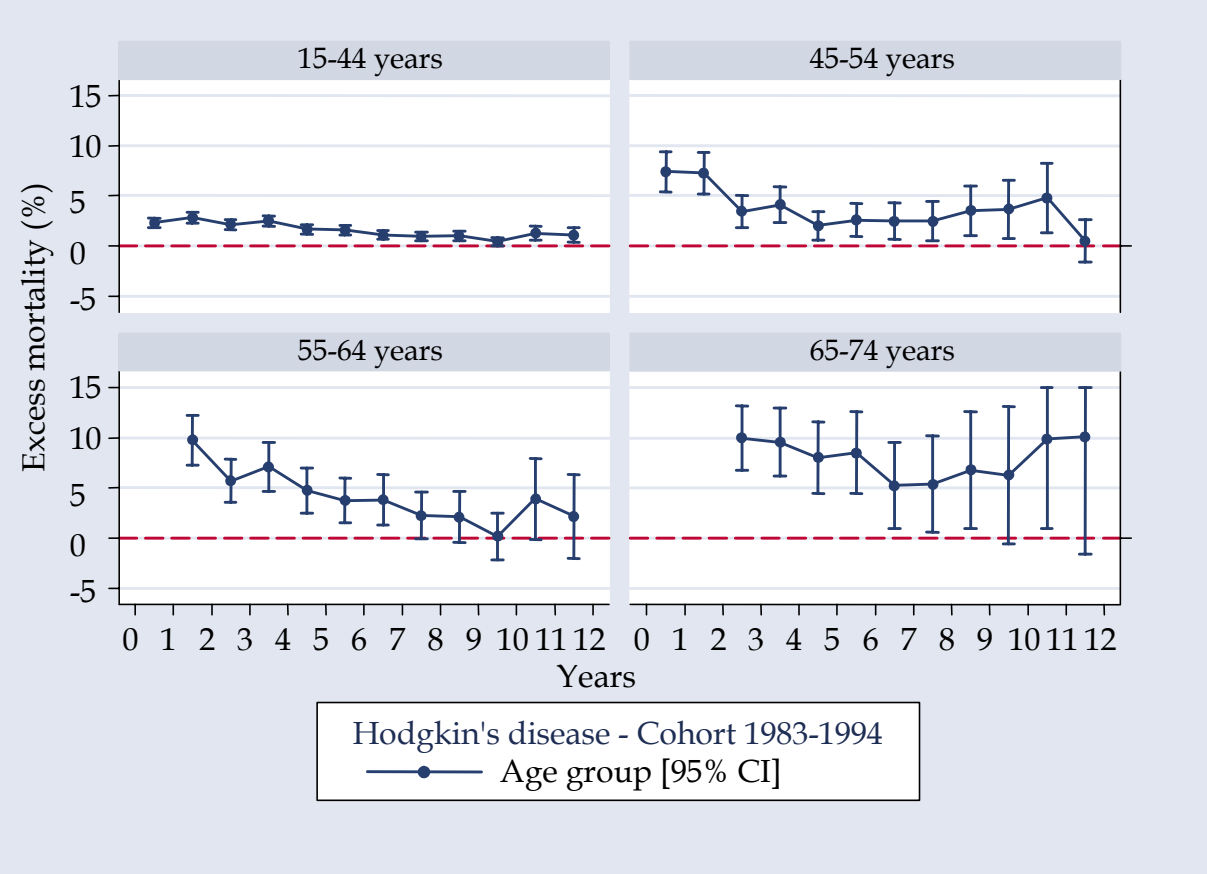

Figure 24.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 24.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 1983-1985 (N = 1,366)	Cohort 1986-1988 (N = 1,654)	Cohort 1989-1991 (N = 1,556)	Cohort 1992-1994 (N = 1,561)
0-1	11.43 [9.69-13.17]	8.91 [7.48-10.33]	7.79 [6.41-9.16]	5.27 [4.11-6.42]
1-2	6.91 [5.41-8.42]	5.41 [4.20-6.63]	4.01 [2.93-5.09]	5.10 [3.92-6.27]
2-3	4.64 [3.32-5.96]	3.89 [2.80-4.98]	2.60 [1.68-3.53]	2.32 [1.45-3.18]
3-4	4.85 [3.46-6.24]	3.73 [2.63-4.82]	3.47 [2.41-4.53]	2.92 [1.95-3.88]
4-5	2.92 [1.76-4.09]	2.96 [1.93-3.98]	2.05 [1.17-2.92]	1.87 [0.97-2.78]
5-6	3.71 [2.41-5.02]	3.24 [2.15-4.33]	1.03 [0.33-1.72]	1.12 [0.13-2.11]
6-7	1.92 [0.88-2.95]	2.10 [1.16-3.04]	1.30 [0.53-2.07]	-
7-8	2.08 [0.99-3.17]	1.28 [0.47-2.08]	1.11 [0.29-1.92]	-
8-9	1.56 [0.56-2.56]	2.11 [1.14-3.09]	0.87 [-0.14-1.88]	-
9-10	0.87 [0.02-1.72]	1.16 [0.35-1.98]	-	-
10-11	2.24 [1.07-3.41]	2.20 [1.07-3.32]	-	-
11-12	1.45 [0.43-2.47]	1.33 [0.08-2.59]	-	-

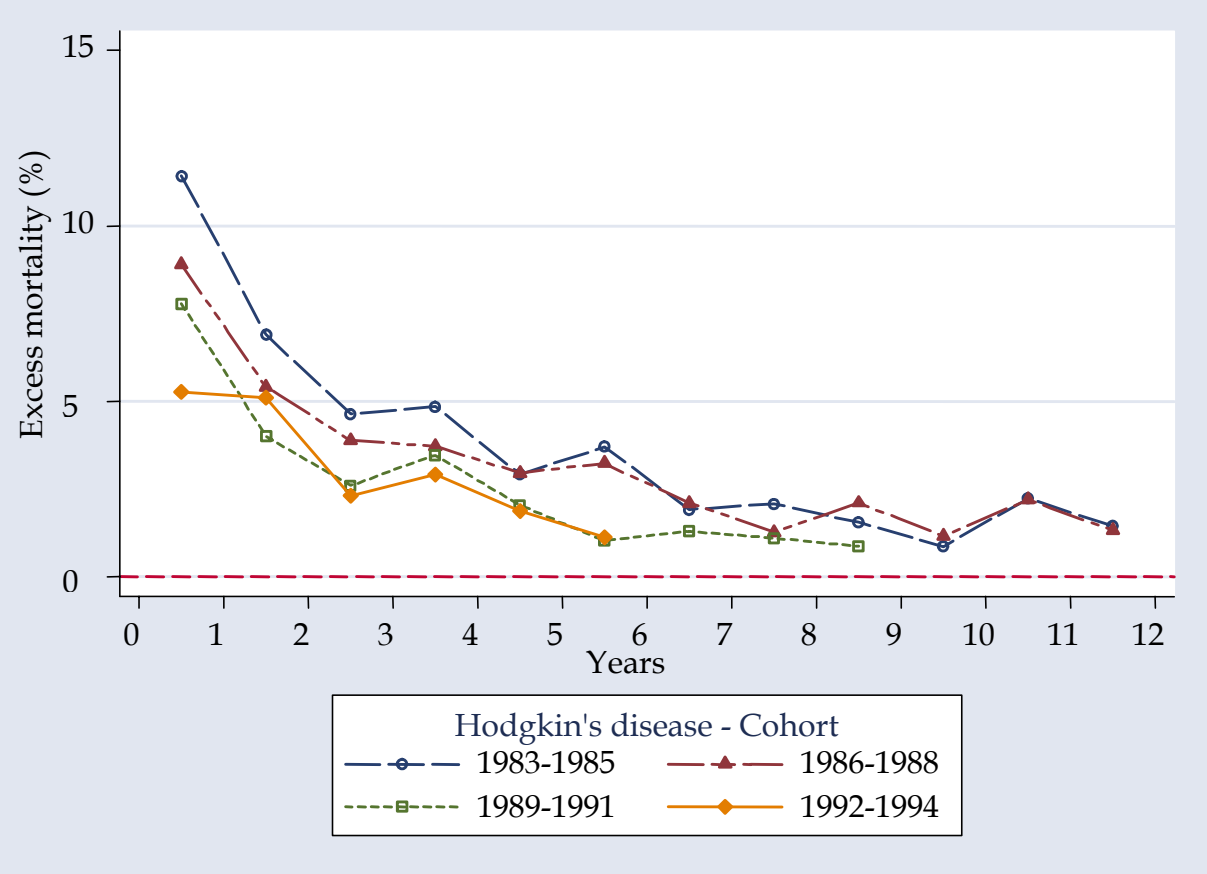

Figure 24.4: Time course of annual excess mortality by cohort

25

Malignant non-Hodgkin's lymphoma

With 9,908 new cases in 2000, malignant non-Hodgkin's lymphoma accounted for 3.6% of all cases of cancer and ranked 6th in terms of frequency for men and women. The age-standardized incidence rate (world population) was 13.3/100,000 for men and 7.8/100,000 for women. The median age of diagnosis was 64 years for men and 70 years for women. Over the last two decades, the incidence has increased (5% per year) for both men and women: this phenomenon has only been observed in this type of malignant blood disease.

Malignant non-Hodgkin's lymphoma ranks 7th among the causes of cancer deaths and accounts for 3.5% of all cancer deaths. The age-standardized mortality rates were 5.3/100,000 for men and 3.4/100,000 for women.

Using the Eurocare data for the most recent cohort (1992-1994), the 5-year relative survival was estimated to be 58.1% for all stages taken together and in the eight countries selected.

Annual excess mortality (all stages considered): Eurocare data

Table 25.I shows the annual excess mortality estimates with their 95% confidence intervals. The estimates take into account all patients whose malignant non-Hodgkin's lymphoma was diagnosed in Europe (8 countries) between 1983 and 1994. The annual excess mortality, greater than 20% for the first year post-diagnosis, fell off sharply over the first years. The annual excess mortality reached a value of the order of 5% at year 5 post-diagnosis and fell below 4% in year 10 (figure 25.1).

Table 25.II shows the annual excess mortality estimates by gender. The annual excess mortality was slightly lower for women than for men. The difference was more marked over the first few years post-diagnosis (figure 25.2).

Table 25.III shows the annual excess mortality for the age groups: 15-44, 45-54, 55-64 and 65-74 years. The annual excess mortality increases from age group 15-44 years to age group 65-74 years (for all years post-diagnosis). For age group 15-44 years, the annual excess mortality ranged from more than 17% for 0-1 year post-diagnosis to less than 2% for 11-12 years post-diagnosis. For age group, 65-74 years, the annual excess mortality varied from over 30% for 0-1 year to less than 5% at 10 years. For age group, 65-74 years, the annual excess mortality is less than 5% from year 7 post-diagnosis while it was less than 5% from year 3 post-diagnosis for age group 15-44 years. Figure 25.3 clearly showed the increase in annual excess mortality from the youngest age groups to the oldest age groups.

Table 25.IV showed the annual excess mortality data for the 4 diagnostic cohorts: 1983-1985, 1986-1988, 1989-1991 and 1992-1994. The data showed that the annual excess mortality decreased from the oldest cohort to the most recent cohort. Figure 25.4 illustrates the phenomenon, which was mainly observed in the first years post-diagnosis.

Long-term annual excess mortality (all stages considered): other studies

Brenner (2002) evaluated the 5-, 10-, 15- and 20-year relative survivals of patients whose malignant non-Hodgkin's lymphoma was diagnosed between 1973 and 1998 using the data from the US Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer. The relative survival estimates were 53.4, 43.4, 37.0 and 30.8%, respectively. The annual excess mortality rate between 15 and 20 years was estimated to be of the order of 3.6%. Using the period analysis method (which takes into account the survivals observed over the first years following diagnosis for the most recent periods), the estimates were 57.8, 46.3, 38.3 and 34.3%. In the latter case, the annual excess mortality rate between 15 and 20 years was estimated to be of the order of 2.2%.

Talbäck *et al*. (2004) evaluated the 5-, 10- and 15-year relative survivals of patients whose malignant non-Hodgkin's lymphoma was diagnosed between 1965 and 1996 using the data of the Swedish national cancer registry. Using the period analysis method, the authors estimated the 5-, 10- and 15-year relative survivals to be 54.6, 40.5 and 32.5%, respectively. The data were similar to the 5-, 10- and 15-year relative survivals observed for patients whose disease was diagnosed in the most recent period. The relative survivals were 54.8, 42 and 33.5%. The mean annual excess mortality rate was estimated to be of the order of 4.3% for the period 10-15 years.

5- and 10-year relative survivals by stage or grade

In France, the Côte d'Or registry has generated 5- and 10-year relative survival data (table 25.V) for patients whose various grades of malignant non-Hodgkin's lymphoma were diagnosed. The 5- and 10-year relative survivals for all grades were 60 and 49%. For low-grade lymphoma, the 5- and 10-year relative survivals were 80 and 74%. The results are for men and women, all ages taken together, and for the diagnostic period 1980-1997.

Table 25.V: 5- and 10-year relative survivals by grade: Côte d'Or registry (1980-1997)

Grade	5-year relative survival (%)	10-year relative survival (%)
Low grade (34%)	80 [74-86]	74 [66-82]
Intermediate and high grade (55%)	52 [47-58]	41 [35-47]
Other (11%)	40 [28-50]	28 [17-39]
All grades	60 [56-65]	49 [44-55]

In the United States, the Surveillance Epidemiology and End Results (SEER) program of the National Institute of Cancer has generated 5-year relative survival data for three stages of malignant non-Hodgkin's lymphoma progression—localized, regional and metastatic (distant metastases)—and a non-determined stage (table 25.VI). The distribution of the non-Hodgkin malignant lymphoma by stage (localized, regional and metastatic) was as follows: 31, 13.2 and 45.7%. The results are for men and women, all ages taken together, and the diagnostic period from 1988 to 2001.

Table 25.VI: 5-year relative survivals by diagnostic stage: SEER program data (1988-2001)

Diagnostic stage	5-year relative survival (%)
Localized disease	68.8
Regional disease	61.7
Metastatic disease (16%)	44.9
All stages	56.3

5- and 10-year relative survivals by lymphoma type and other prognostic factors

There are several types of lymphoma (E to H as per the WHO classification). The distribution of the various types is shown in table 25.VII.

Table 25.VII: Distribution of the various types of malignant non-Hodgkin's lymphoma (taken from The Non-Hodgkin's Lymphoma Classification Project, 1997)

Malignant non-Hodgkin's lymphoma type	Case distribution (%)
Diffuse large B-cell lymphomas	30.6
Follicular lymphomas	22.1
Marginal-zone B-cell lymphomas, Malt	7.6
Peripheral T-cell lymphomas	7.0
Small B lymphocytic lymphomas (CLL)	6.7
Mantle-cell lymphomas	6.0
Primary mediastinal large B-cell lymphomas	2.4
Anaplastic large T/nul-cell lymphomas	2.4
High-grade B-cell lymphomas, Burkitt-like	2.1
Marginal-zone B-cell lymphomas, nodal	1.8
Precursor T lymphoblastic lymphomas	1.7
Lymphoplasmocytoid lymphomas	1.2
Marginal-zone B-cell lymphomas, splenic	< 1
Burkitt's lymphomas	< 1
All other types	7.0

Aggressive non-Hodgkin's B-cell lymphoma

Aggressive non-Hodgkin's B-cell lymphoma accounts for one third of non-Hodgkin's lymphomas. Among the aggressive lymphomas, the most frequent is the diffuse large-cell lymphoma (which accounts for 35% of non-Hodgkin's lymphomas).

The international prognostic index (IPI) consists of 5 factors: age (greater than 60 years), clinical stage (III or IV), performance index (greater than or equal to 2), elevated LDH and involvement of at least 2 extranodal sites. This index constitutes a predictive model that is particularly significant in the short term for the outcome of patients presenting with aggressive lymphoma. Four IPI groups have been defined: low risk (0 factor); low risk, intermediate (1 factor); high risk, intermediate (2 factors); and high risk (3 or more factors)

with 5-year overall survivals of 73, 51, 43 and 26%, respectively (Shipp *et al*., 1993). In practice, the simplified age-adjusted IPI is used. The latter consists of 3 risk factors: clinical stage, general condition and LDH.

In France, for subjects aged less than 60 years with no age-adjusted IPI risk factor, the 5-year overall survival is 80% (Reyes *et al*., 2005). For patients aged less than 60 years with 2 or 3 factors of the age-adjusted IPI, the 8-year overall survival is 64% (Haioun *et al*., 2000).

The advent of new drugs (Rituximab®) in combination with chemotherapy has enhanced short-term survival (Coiffier *et al*., 2002). In subjects aged over 60 years with one or more age-adjusted IPI factor, the 4-year overall survival was 59% vs. 47% for the control group that did not receive Rituximab® ($p = 0.01$).

Burkitt's lymphoma

Burkitt's lymphoma accounts for 2% of adult lymphomas. The overall 5-year survival in patients free from neurological involvement and leukemic presentation was 81% (van Imhoff *et al*., 2005). The 3-year overall survival fell to 52% in a cohort of patients including those with neurological involvement and/or a leukemic presentation (Rizzieri *et al*., 2004).

In Burkitt's lymphoma, recurrences occur early, generally during the 3 years post-completion of treatment (Kasamon and Swinnen, 2004; Rizzieri *et al*., 2004). After that period, the annual excess mortality is negligible.

Indolent B-cell lymphoma

Indolent B-cell lymphoma is a small-cell lymphoma that is more frequent than follicular lymphoma (22% of all lymphomas). The disease mainly affects the elderly. The 5- and 10-year overall survivals for follicular lymphoma are 70% (Solal-Celigny *et al*., 2004). The survival rates by Follicular Lymphoma International Prognostic Index (FLIPI) are shown below. The prognostic factors considered are: age (greater than 60 years), stage (3-4), elevated LDH, lymph node involvement (greater than 4) and hemoglobin (less than 12 g/dL).

Table 25.VIII: 10-year survival as a function of FLIPI prognostic factors

	Low risk 0 or 1 factor	Intermediate risk 2 factors	High risk 3 factors or more
Observed survival	70.7%	50.9%	35.5%

The survival rates stated above were calculated prior to the advent of therapeutic monoclonal antibodies.

T-cell lymphomas

T-cell lymphomas account for 7% of non-Hodgkin's lymphomas in France. With the exception of anaplastic lymphomas, they are associated with a worse prognosis than B-cell lymphomas. The 5-year survival is of the order of 30% approximately (table 25.IX) versus over 60% for anaplastic lymphomas (Gisselbrecht *et al*., 1998).

Table 25.IX: Observed survival for patients presenting with non-anaplastic T-cell lymphoma (taken from Gisselbrecht *et al.*, 1998; Lopes-Guillermo *et al.*, 1998; Rûdiger *et al.*, 2002)

Type of treatment	5-year observed survival (%)
CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) 96 patients; 144 patients	26.32
ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) 228 patients	35
COPADEM* CYVE (etoposide/cytarabine (high dose) 77 patients	40
ESHAP (etoposide, cisplatin, cytarabine (high dose), methylprednisolone) 58 patients	36 (at 2 years)

* Treatment described by Blay *et al.*, 1995

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Excess mortality data from the Eurocare study

Table 25.I: Annual excess mortality: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Overall (N = 25,002)
0-1	22.61 [22.08-23.15]
1-2	12.05 [11.56-12.54]
2-3	7.71 [7.27-8.16]
3-4	6.40 [5.96-6.83]
4-5	6.24 [5.77-6.70]
5-6	5.15 [4.66; 5.63]
6-7	5.13 [4.57-5.70]
7-8	4.27 [3.69-4.84]
8-9	4.39 [3.73-5.05]
9-10	4.18 [3.39-4.98]
10-11	3.57 [2.73-4.41]
11-12	3.97 [2.94-5.01]

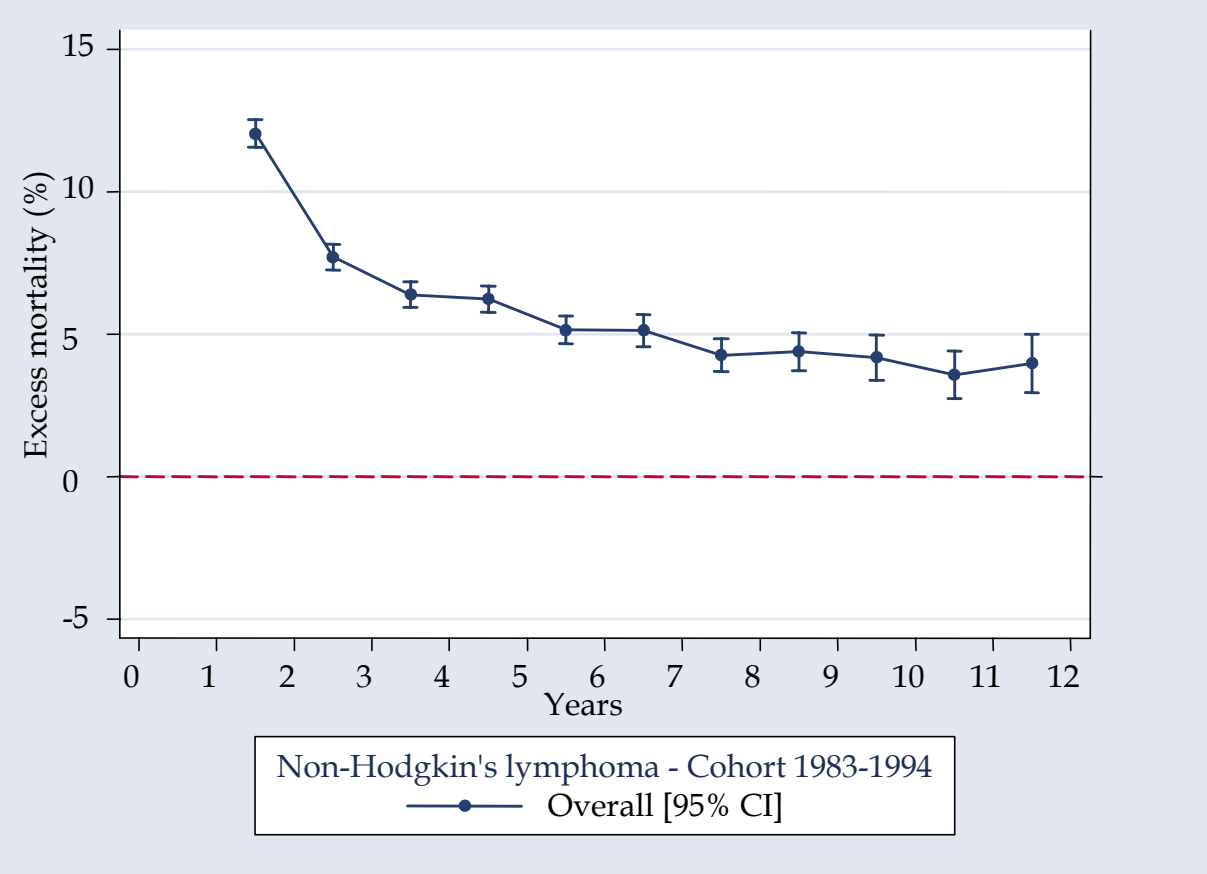

Figure 25.1: Annual excess mortality: diagnostic cohort 1983-1994

Table 25.II: Annual excess mortality by gender: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Women (N = 10,880)	Men (N = 14,122)
0-1	20.89 [20.11-21.67]	23.95 [23.22-24.67]
1-2	11.01 [10.32-11.71]	12.91 [12.23-13.59]
2-3	7.16 [6.54-7.78]	8.20 [7.58-8.83]
3-4	5.61 [5.02-6.21]	7.11 [6.48-7.74]
4-5	5.83 [5.19-6.48]	6.62 [5.95-7.28]
5-6	4.64 [3.98-5.30]	5.67 [4.96-6.37]
6-7	4.99 [4.21-5.77]	5.35 [4.54-6.15]
7-8	3.98 [3.20-4.77]	4.62 [3.78-5.46]
8-9	3.75 [2.88-4.62]	5.08 [4.09-6.07]
9-10	4.20 [3.10-5.30]	4.28 [3.13-5.42]
10-11	3.80 [2.62-4.97]	3.50 [2.30-4.69]
11-12	4.24 [2.77-5.71]	3.80 [2.34-5.26]

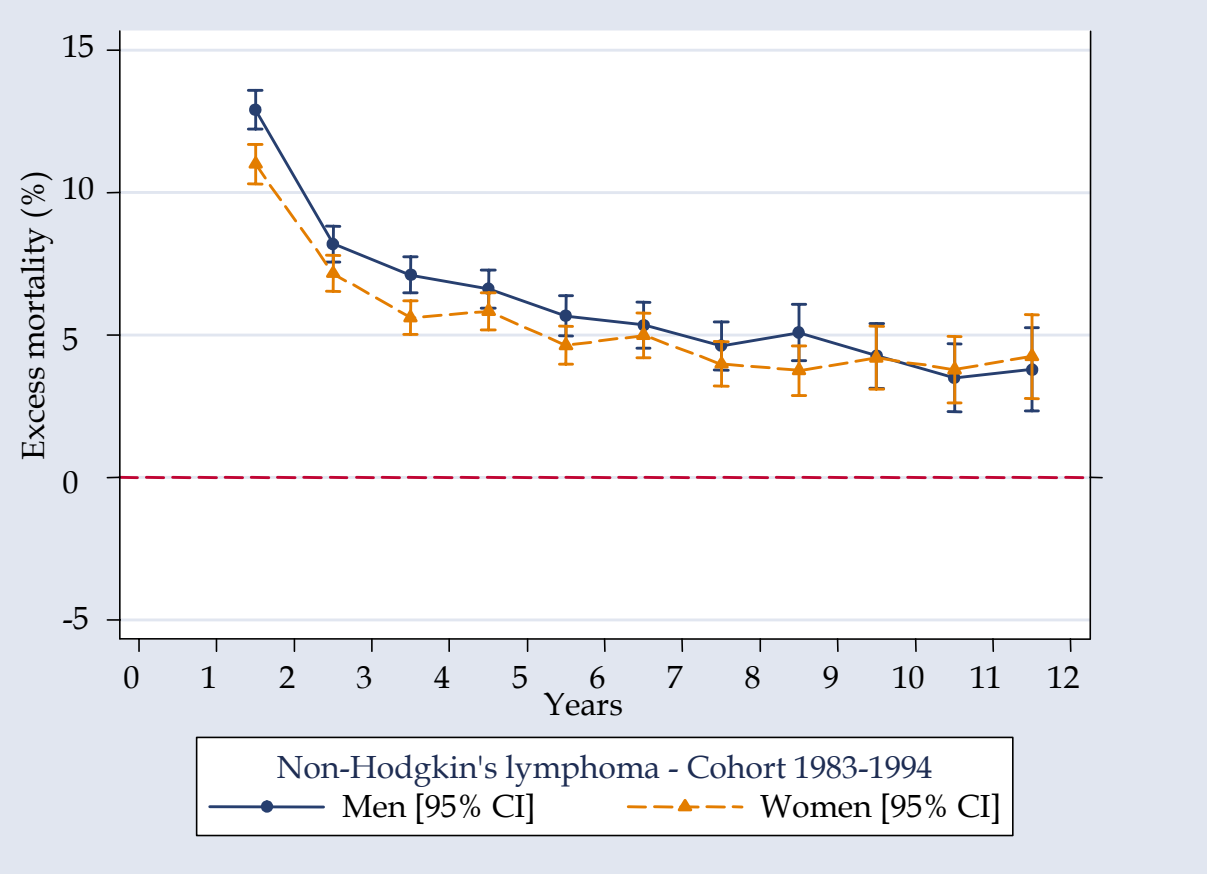

Figure 25.2: Annual excess mortality by gender: diagnostic cohort 1983-1994

Table 25.III: Annual excess mortality by age group: diagnostic cohort 1983-1994

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 15-44 years (N = 4,439)	Cohort 45-54 years (N = 4,253)	Cohort 55-64 years (N = 6,789)	Cohort 65-74 years (N = 9,521)
0-1	17.31 [16.19-18.43]	15.48 [14.38-16.59]	20.39 [19.40-21.37]	30.01 [29.05-30.97]
1-2	10.40 [9.40-11.39]	10.38 [9.36-11.40]	11.49 [10.59-12.39]	14.42 [13.48-15.35]
2-3	4.29 [3.58-5.00]	6.09 [5.23-6.96]	8.41 [7.55-9.26]	10.21 [9.29-11.14]
3-4	3.99 [3.29-4.69]	4.47 [3.68-5.25]	7.27 [6.42-8.12]	8.50 [7.56-9.45]
4-5	3.34 [2.66-4.02]	5.45 [4.55-6.36]	6.97 [6.06-7.88]	8.23 [7.20-9.26]
5-6	2.54 [1.89-3.20]	4.39 [3.48-5.31]	5.93 [4.98-6.88]	7.03 [5.90-8.16]
6-7	2.67 [1.92-3.42]	4.06 [3.03-5.08]	5.63 [4.54-6.71]	7.68 [6.28-9.08]
7-8	2.35 [1.60-3.09]	4.18 [3.06-5.29]	5.49 [4.32-6.66]	4.90 [3.49-6.31]
8-9	2.47 [1.62-3.32]	4.62 [3.30-5.93]	5.62 [4.27-6.97]	4.82 [3.16-6.48]
9-10	2.24 [1.27-3.21]	3.83 [2.36-5.31]	6.19 [4.49-7.88]	4.34 [2.28-6.40]
10-11	2.14 [1.12-3.17]	2.37 [1.02-3.73]	4.96 [3.19-6.72]	4.78 [2.39-7.17]
11-12	1.72 [0.64-2.81]	2.60 [0.96-4.24]	5.47 [3.25-7.69]	6.76 [3.57-9.94]

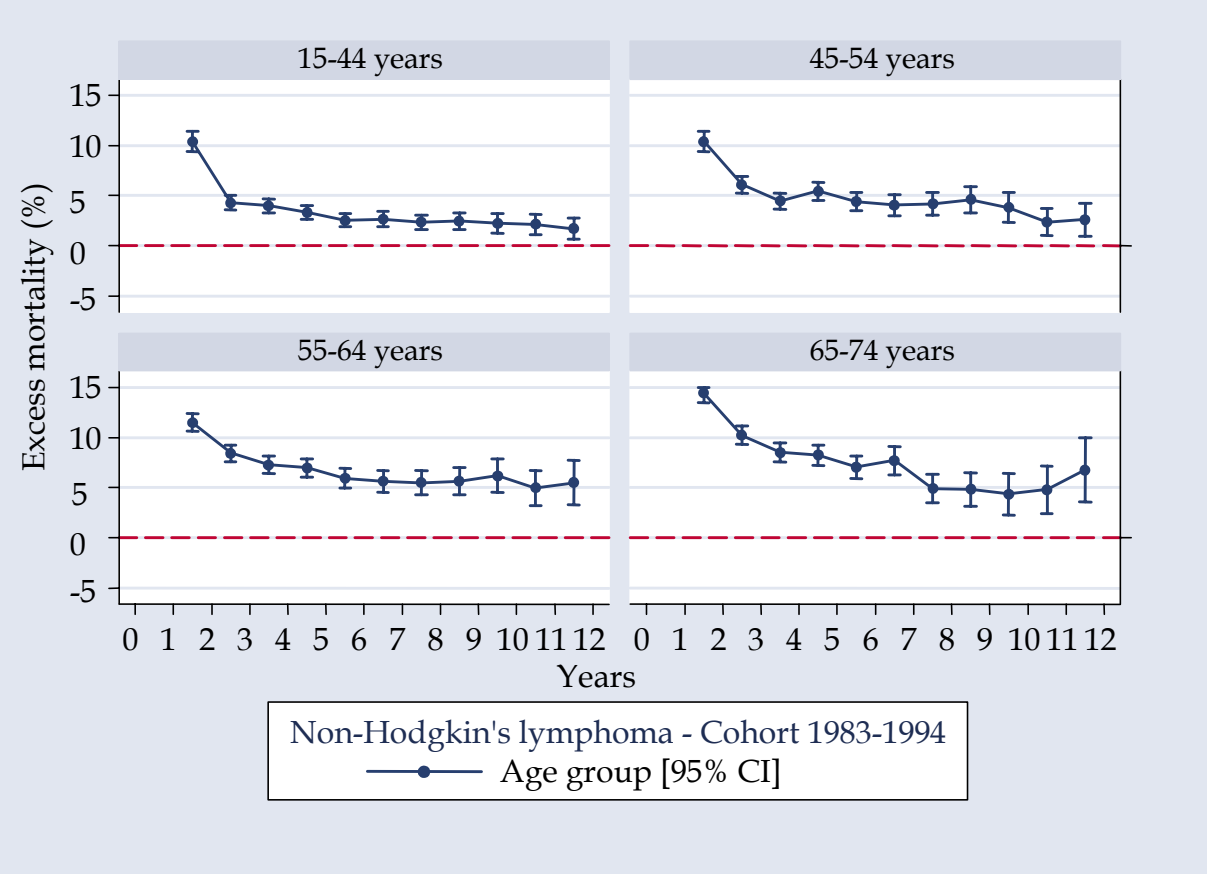

Figure 25.3: Annual excess mortality by age group: diagnostic cohort 1983-1994

Table 25.IV: Annual excess mortality for the four Eurocare cohorts

Interval (years)	Excess mortality [95% CI] (annual %) Cohort 1983-1985 (N = 4,371)	Cohort 1986-1988 (N = 6,100)	Cohort 1989-1991 (N = 7,001)	Cohort 1992-1994 (N = 7,530)
0-1	25.98 [24.64-27.32]	23.26 [22.17-24.35]	21.64 [20.64-22.63]	21.04 [20.09-21.99]
1-2	13.10 [11.85-14.34]	12.45 [11.44-13.46]	12.57 [11.64-13.50]	10.70 [9.86-11.53]
2-3	8.28 [7.14-9.43]	8.38 [7.44-9.32]	6.78 [5.99-7.58]	7.73 [6.94-8.53]
3-4	6.64 [5.52-7.75]	7.35 [6.41-8.30]	6.59 [5.77-7.42]	5.36 [4.64-6.09]
4-5	7.01 [5.82-8.21]	6.61 [5.66-7.57]	6.01 [5.17-6.84]	5.65 [4.81-6.50]
5-6	6.69 [5.45-7.93]	5.31 [4.38-6.24]	4.58 [3.78-5.37]	4.34 [3.31-5.38]
6-7	5.75 [4.51-6.98]	5.04 [4.08-5.99]	4.88 [4.03-5.72]	-
7-8	4.66 [3.45-5.87]	4.21 [3.27-5.15]	4.04 [3.13-4.96]	-
8-9	4.09 [2.88-5.30]	3.97 [3.01-4.93]	5.39 [4.02-6.77]	-
9-10	4.40 [3.10-5.69]	4.04 [3.03-5.05]	-	-
10-11	3.83 [2.53-5.13]	3.35 [2.25-4.45]	-	-
11-12	4.56 [3.14-5.98]	3.14 [1.64-4.63]	-	-

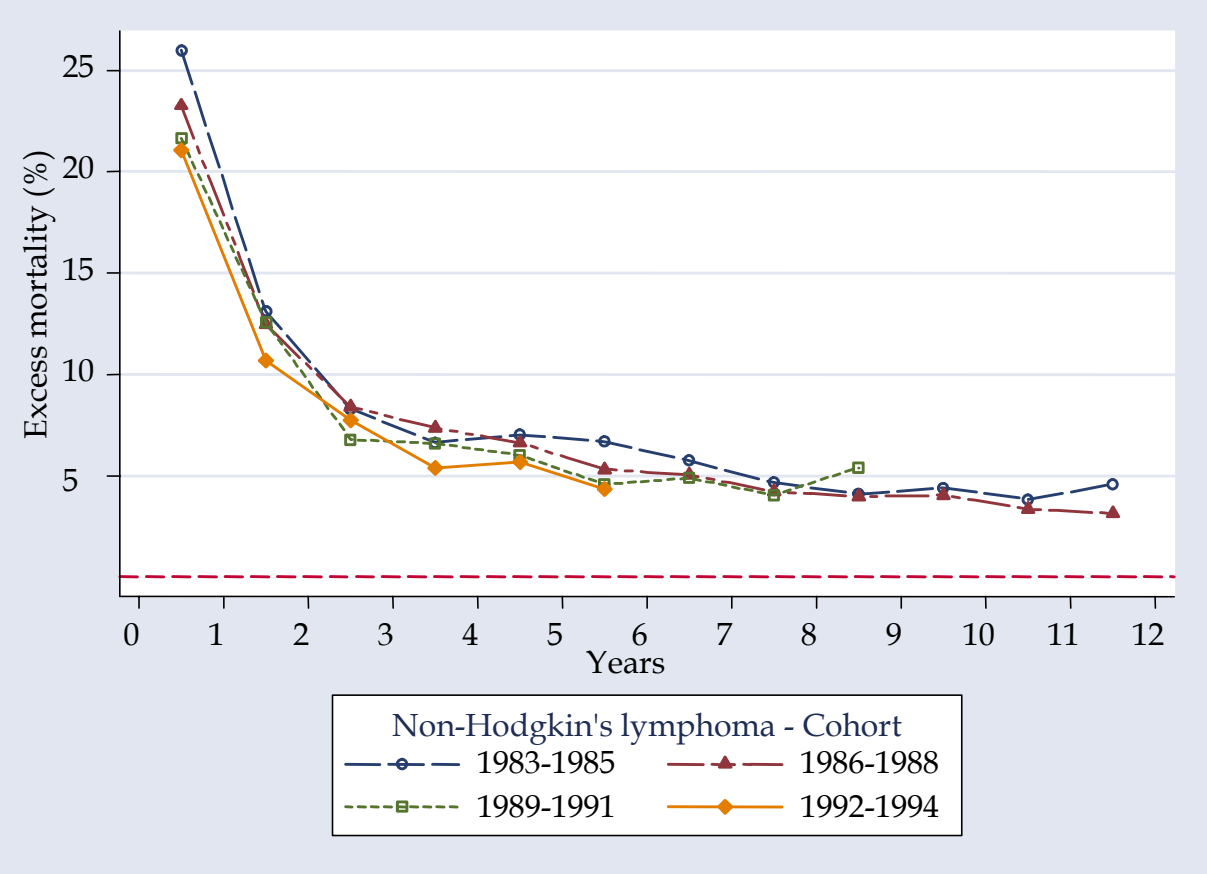

Figure 25.4: Time course of annual excess mortality by cohort

II

Childhood cancers

26

All childhood cancers

Childhood cancer is rare (less than 1% of all cancers). The standardized annual incident rate is estimated to be $132/10^6$ children aged from 0 to 14 years (Désandes *et al*., 2004). This means that almost 1,500 new cases of childhood cancer occur in France each year. In half of the cases, the disease occurs before age 6 years and 1 child out of 500 develops a cancer before age 15 years. Nonetheless, therapeutic progress over the last 30 years now enables recovery in over two thirds of cases. Thus, in France, it may be currently considered that one person out of 850 aged from 20 to 45 years has survived a childhood cancer. The total is over 25,000 people.

Unlike cancer in adults, which mainly consists in carcinoma, the histological types of childhood cancers are very heterogeneous.

The most frequent childhood neoplastic disease is leukemia: 450 incident cases are reported each year. In contrast to what is observed in adults, chronic lymphocytic leukemia does not occur in children. Most of the cases (80%) consist in acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) only accounts for 17% of cases. The remaining 3% of the cases consist in chronic myeloid leukemia and subacute myelomonocytic leukemia. The age distribution shows a peak incidence of ALL between the ages of 2 and 3 years (Clavel *et al*., 2004).

Brain tumor ranks second in frequency with about 300 new cases per year. The tumors mainly consist in astrocytomas, primary neuroectodermal tumors, ependymomas and infratentorial tumors that tend to be well differentiated in contrast to what is observed in adults, for whom high-grade gliomas and meningiomas predominate.

Lymphoma ranks 3rd with about 190 cases per year. Non-Hodgkin's lymphoma accounts for 56% of those cases and affects children toward the age of 2-3 years while Hodgkin's disease emerges later, with increasing incidence, particularly after the age of 10 years.

Among the solid tumors, embryonal tumors predominate: neuroblastoma, nephroblastoma, retinoblastoma and hepatoblastoma which occur in the first years of life. Bone and soft tissue sarcomas are rarer and occur in older children.

Table 26.I, derived from the data of 6 regional pediatric registries (Désandes *et al*., 2004), shows the distribution of those neoplastic diseases and their incidences.

Table 26.I: Raw, age-standardized (world population) and cumulative incidence rates for children aged 0-14 years (1990-1999)

	No. of cases	%	Incidence rate (/10^6/year)			Sex ratio
			raw	standardized	cumulative	
I. Leukemia	**1 277**	**30.2**	**39.9**	**42.3**	**604.5**	**1.1**
Acute lymphoblastic leukemia	995	23.5	31.1	33.1	471.0	1.2
Acute myeloid leukemia	227	5.4	7.1	7.5	107.5	0.8
Chronic myeloid leukemia	30	0.7	0.9	0.9	14.1	1.1
Other types of leukemia	11	0.3	0.3	0.4	5.2	0.6
Leukemia, unspecified	14	0.3	0.4	0.4	6.6	1.0
II. Lymphoma and reticulohistiocytic tumors	**525**	**12.4**	**16.4**	**15.6**	**244.3**	**2.2**
Hodgkin's disease	187	4.4	5.8	5.3	86.5	1.8
Malignant non-Hodgkin's lymphoma	155	3.7	4.8	4.7	72.2	2.0
Burkitt's lymphoma	151	3.6	4.7	4.6	70.5	3.3
Miscellaneous lymphoreticular tumors	19	0.4	0.6	0.7	9.1	1.7
Unspecified lymphomas	13	0.3	0.4	0.4	6.1	1.2
III. Central nervous system tumors	**922**	**21.8**	**28.8**	**29.1**	**433.3**	**1.1**
Ependymoma	127	3.0	4.0	4.3	60.5	0.8
Astrocytoma	384	9.1	12.0	11.9	179.9	1.1
Primary neuroectodermal tumors	176	4.2	5.5	5.6	82.8	1.8
Other gliomas	109	2.6	3.4	3.4	51.0	1.0
Other types of central nervous system tumors	103	2.4	3.2	3.2	48.3	1.1
Unspecified central nervous system tumors	23	0.5	0.7	0.7	10.8	0.4
IV. Sympathetic nervous system tumors	**385**	**9.1**	**12.0**	**14.1**	**186.1**	**1.2**
Neuroblastomas and ganglioneuroblastomas	377	8.9	11.8	13.9	182.3	1.2
Other types of sympathetic nervous system tumors	8	0.2	0.3	0.2	3.7	1.7
V. Retinoblastoma	**99**	**2.3**	**3.1**	**3.7**	**48.0**	**1.3**
VI. Renal tumors	**256**	**6.0**	**8.0**	**9.1**	**122.6**	**0.7**
Wilms' tumor, rhabdoid sarcoma	248	5.9	7.8	8.8	118.9	0.6
Renal carcinoma	8	0.2	0.3	0.2	3.7	1.7
Unspecified renal tumors	0	0.0	0.0	0.0	0.0	-
VII. Hepatic tumor	**42**	**1.0**	**1.3**	**1.5**	**20.2**	**2.2**
Hepatoblastoma	35	0.8	1.1	1.3	16.9	2.2
Hepatic carcinoma	7	0.2	0.2	0.2	3.2	2.5
Unspecified hepatic tumors	0	0.0	0.0	0.0	0.0	-
VIII. Malignant bone tumors	**233**	**5.5**	**7.3**	**6.6**	**107.8**	**1.3**
Osteosarcoma	114	2.7	3.6	3.1	52.5	1.7
Chondrosarcoma	4	0.1	0.1	0.1	1.8	1.0
Ewing's sarcoma	103	2.4	3.2	3.0	47.9	0.9
Other types of malignant bone tumor	7	0.2	0.2	0.2	3.2	1.3
Unspecified malignant bone tumors	5	0.1	0.2	0.1	2.3	1.5
IX. Soft tissue sarcoma	**230**	**5.4**	**7.2**	**7.4**	**108.4**	**1.6**
Rhabdomyosarcoma and embryonal sarcoma	130	3.1	4.1	4.3	61.4	1.7
Fibrosarcoma and neurofibrosarcoma	21	0.5	0.7	0.7	9.9	1.1
Kaposi's sarcoma	1	0.0	0.0	0.0	0.5	0.0
Other types of soft tissue sarcoma	53	1.3	1.7	1.7	25.0	1.8
Unspecified soft tissue sarcoma	25	0.6	0.8	0.7	11.6	1.8
X. Germ-cell, trophoblastic and gonadal tumors	**142**	**3.4**	**4.4**	**4.5**	**66.9**	**0.9**
Germ-cell tumors of the central nervous system	51	1.2	1.6	1.5	23.7	1.7
Other types of non-gonadal germ-cell tumors	29	0.7	0.9	1.1	14.1	0.6
Gonadal germ-cell tumors	49	1.2	1.5	1.5	22.9	0.8
Gonadal carcinomas	5	0.1	0.2	0.1	2.3	0.0
Other types of malignant gonadal tumors	8	0.2	0.3	0.3	3.8	0.6
XI. Carcinomas and malignant squamous-cell tumors	**116**	**2.7**	**3.6**	**3.3**	**53.6**	**1.0**
Adrenal carcinoma	6	0.1	0.2	0.2	2.9	2.0
Thyroid carcinoma	40	0.9	1.3	1.1	18.5	0.8
Nasopharyngeal carcinoma	12	0.3	0.4	0.3	5.5	3.0
Malignant melanoma	13	0.3	0.4	0.4	6.0	0.4
Skin carcinoma	11	0.3	0.3	0.3	5.1	1.2
Other types of carcinoma	34	0.8	1.1	1.0	15.7	1.1
XII. Other types of malignant tumor	**7**	**0.2**	**0.2**	**0.2**	**3.3**	**1.3**
Other malignant tumors	5	0.1	0.2	0.2	2.4	1.5
Unspecified malignant tumors	2	0.0	0.1	0.1	0.9	1.0
All cancers	4 234	100.0	132.4	137.5	1 998.8	1.2

5-year survival

On the basis of the Eurocare 3 data on the period 1990-1994, the 5-year age-standardized survival rate for childhood cancer of all types is 71.8% (Gatta *et al*., 2003). However, there are marked differences between countries: from 45% for Estonia to 90% for Iceland. In general, the survival is 60-70% in Eastern European countries while it is greater than 75% in Switzerland, German and Northern European countries (excluding Denmark). France is in an intermediate position in Europe with a 5-year survival of 72.8%.

Childhood cancer survival has considerably improved over the last 30 years, rising from 44% in the 1970s to 74% in the 1990s (Steliarova *et al*., 2004). The progress has been observed for all types of cancer but is nonetheless less marked for solid tumors than for malignant blood diseases. The recent Eurocare 3 publication on the time course of childhood cancer survival from 1983 to 1994 (Gatta *et al*., 2005) confirms the data and shows that the risk of death has fallen by about 5% per year on average. The improvement in the results is the consequence of centralized organization of multicenter clinical research including over 70% of patients in clinical trials and observational studies (Bleyer *et al*., 2002).

Table 26.II shows the 5-year survival rates calculated from the Eurocare 3 data for all European countries for the period 1990-1994 for the most frequent types of childhood cancer.

Table 26.II: 5-year survival of diagnostic cohort 1990-1994 calculated from the Eurocare 3 data for the whole of the European countries

Type of cancer	5-year survival (%)
All cancers	73.24
Acute lymphoblastic leukemia	81.60
Acute non-lymphoblastic leukemia	47.50
Hodgkin's disease	95.30
Burkitt's lymphoma	83.10
Malignant non-Hodgkin's lymphoma	80.00
Central nervous system tumor	63.90
Neuroblastoma	58.20
Nephroblastoma	83.70
Bone tumor	64.80
Soft tissues tumor	65.40

Excess mortality for all types of cancer and all Eurocare study countries

The Eurocare data on childhood cancer show survivals with a maximum follow-up duration of 7 years. As was the case for cancer in adults, the excess mortality by 1-year interval over the 7 years of follow-up was calculated for the types of cancer cited above. The mortality is termed 'excess mortality', as was the case for adult cancer, but in fact is not an excess mortality since the observed and not the relative survival is used. In fact, for children, the two indicators are very close since the mortality in the overall population is very small.

Table 26.III shows the annual excess mortality estimates with their 95% confidence intervals. The estimates were made taking into account the childhood cancer cases diagnosed between 1990 and 1994 in Europe. The annual excess mortality fell from over 10% to about 1% 7 years

post-diagnosis. As early as the 4th year, the annual excess mortality was 2%. Figure 26.1 clearly shows the fast falloff in annual excess mortality.

Long-term survival

The Eurocare 3 study did not generate long-term survival data on childhood cancer. However, two large-scale studies have addressed the survivors 5 years post-childhood cancer diagnosis (before the age of 20 years): the US Childhood cancer survivor study (Mertens *et al*., 2001), which included 20,227 patients, and a Scandinavian study (Möller *et al*., 2001), which included 13,711 patients. Both studies are of great interest. In addition, a recent Dutch study (Cardous-Ubbink *et al*., 2004) of a smaller patient population (1,378 patients treated in the same hospital center between 1966 and 1996) is available.

Long-term mortality risk

The above three studies have quantified the long-term mortality risk (up to 25 years post-diagnosis) for their patient cohorts by calculating two indicators.

The absolute excess mortality risk is obtained by subtracting the expected number of deaths from the observed number and dividing by the number of person-years at risk. This indicator has the advantage of reflecting an annual excess risk (and not a cumulative excess) and is thus similar to the indicator calculated from the Eurocare data. The three studies report similar figures for the indicator:

- US study: 0.88 deaths per 100 person-years ;
- Scandinavian study: 0.77 deaths per 100 person-years ;
- Dutch study: 0.70 deaths per 100 person-years.

Thus, for those three studies addressing late mortality (up to 25 years) post-childhood cancer diagnosis, the excess mortality is less than 1% per year after 5 years. The excess is very small. The results have also to be weighted by the fact that the studies addressed old cohorts (diagnosis between 1960 and 1989) and by the fact that considerable progress in the treatment of childhood cancer has been achieved in the last 30 years.

The standardized mortality ratio (SMR) is the number of deaths occurring before year's end (December 31, 1996) over the expected number of deaths (calculated from specific mortality rates by age and gender for the overall population). The ratio is an indicator of cumulative risk. The SMR was 10.8 for the US and Scandinavian study. It was higher for the Dutch study (17.2 with median follow-up of 16 years). The authors of the latter study explained the higher SMR by the fact that their study includes more recent diagnostic years and, in consequence, they have a higher percentage of patients with follow-up of less than 10 years. The mortality is higher in the years closest to diagnosis and this tends to increase the overall SMR. This relatively high figure for excess mortality is explained by the risk, which remains very low, of mortality in the overall population for the age groups in question (adolescents, young adults).

Causes of death

In the three studies, the deaths were due to:

- a recurrence of the initial cancer in 70% of cases (particularly in settings of leukemia, and brain or bone tumor);

- a second malignancy in 10 to 12% of cases;
- sequelae of treatment in 10% of cases;
- other causes unrelated to cancer in 10% of cases.

Given the therapeutic progress achieved in recent years and demonstrated by the improvement in 5-year survival, it is likely that the late relapse rate is also falling for patients treated most recently. With regard to the occurrence of a second malignancy, several studies show that the risk is mainly related to radiotherapy (Bhatia *et al*., 2002; Pui *et al*., 2003). However, in leukemia, for instance, the systematic cerebral radiotherapy used to prevent meningeal relapses is no longer practiced. In Hodgkin's disease, radiotherapy is increasingly less used and the irradiated fields are becoming smaller and smaller. This should decrease the risk of a second malignancy in recently treated patients.

Factors influencing the SMR

Several different factors are liable to influence the SMR:

- gender: the SMR is higher for women; this is explained by the fact that the basic overall mortality is lower for women than for men;
- age at diagnosis: the SMR is higher for the youngest children at the time of diagnosis;
- type of malignancy: the SMR is higher after leukemia (15.5) or brain tumor (15.7). Conversely, it is lower for non-Hodgkin's lymphoma (5.1) and nephroblastoma (6.2);
- type of treatment: chemotherapy and radiotherapy increase the risk while patients who have undergone surgery only have no excess mortality;
- relapse: particularly if it occurs after 5 years;
- follow-up duration: the SMR is particularly high between 5 and 9 years post-diagnosis; it then falls, stabilizing at 3-4 after 20 years;
- period: the risk of death is smaller for patients treated in the most recent period. It is 40% lower for patients whose malignancy was diagnosed between 1980 and 1989, compared to the two preceding decades. The decrease is most marked for patients having had leukemia (hazard ratio (HR) = 0.34) or Hodgkin's disease (HR = 0.28) (Möller et al., 2001). Given the therapeutic progress achieved in recent years, a further significant reduction in the risk of death is to be expected for the pediatric cohorts treated in the most recent years;
- age: the risk of death decreases markedly as the patient's age increases; the SMR of subjects aged over 30 years is only 1.56, which is not significant (Cardous-Ubbink et al., 2004).

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Observed survival and excess mortality data from the Eurocare study

Table 26.III: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	All cancers (N = 24,620)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	88.18 [87.34-89.02]	11.82 [11.39-12.25]
1-2	80.68 [79.66-81.7]	8.51 [7.99-9.03]
2-3	76.87 [75.77-77.97]	4.72 [4.16-5.28]
3-4	74.76 [73.62-75.9]	2.74 [2.16-3.32]
4-5	73.24 [72.08-74.4]	2.03 [1.44-2.62]
5-6	72.38 [71.2-73.56]	1.17 [0.57-1.77]
6-7	71.48 [70.25-72.71]	1.24 [0.61-1.87]

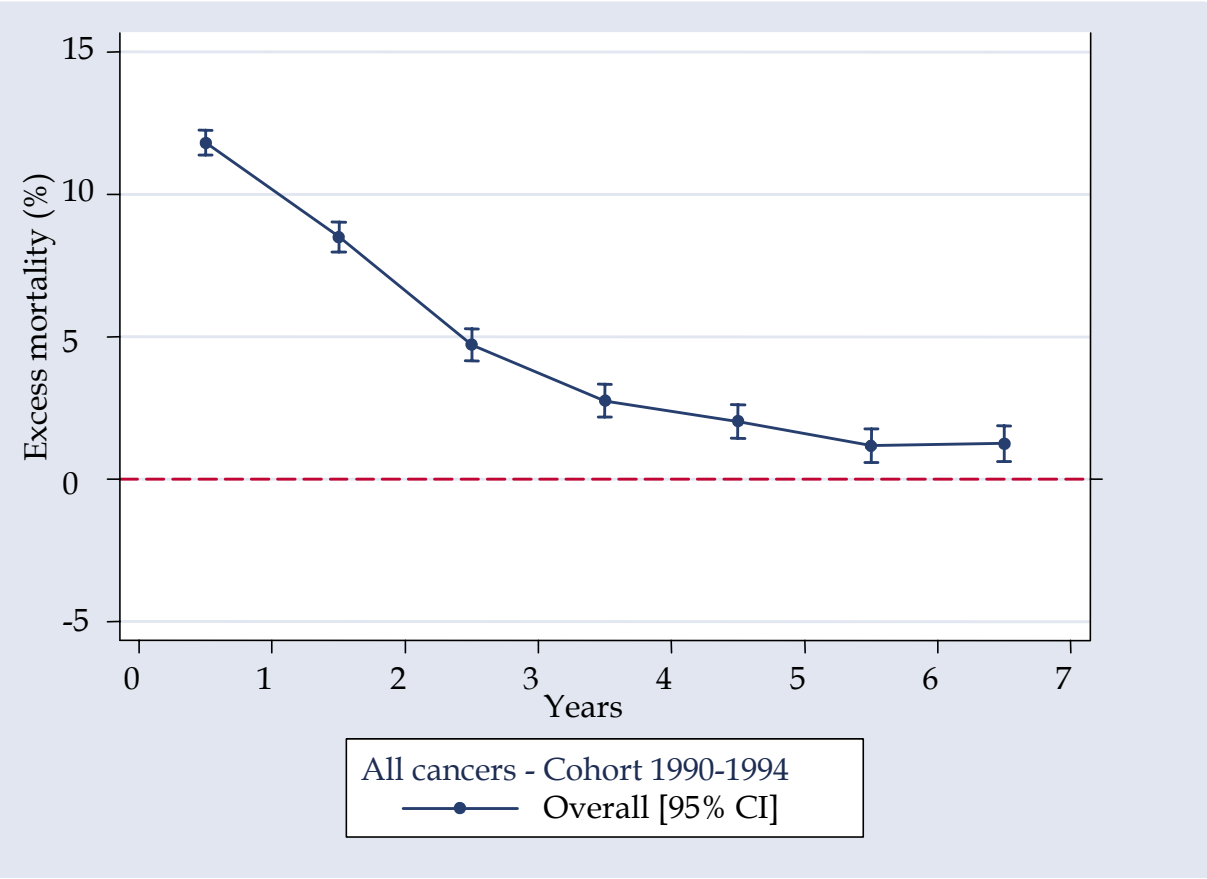

Figure 26.1: Annual excess mortality: diagnostic cohort 1990-1994

27

Acute lymphoblastic leukemia

On the basis of the data from six French pediatric registries, acute lymphoblastic leukemia (ALL) accounts for 23.5% of the malignancies diagnosed in children aged 0 to 14 years for the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was 34.3/10^6 per year and the sex ratio is 1.4 (Clavel *et al*., 2004).

On the basis of the Eurocare data for the period 1990-1994, the 5-year survival for ALL is 81.6% (95% CI: [79.7-83.5]) for all European countries. France ranks a little below average with survival of 77.9% (95% CI: [68.7-87.0]).

Progress has been achieved in recent years in the treatment of pediatric ALL as shown by the French data from the national registry of pediatric malignant blood diseases (RNHE) (Goubin *et al*., 2006) with a 5-year survival which increased from 77% for the period 1990-1992 to 85% for the period 1997-2000.

Annual excess mortality: Eurocare data

Table 27.I shows the annual excess mortality estimates with their 95% confidence intervals. Annual excess mortality fell from 6% the first year post-diagnosis to about 1% 7 years post-diagnosis. Figure 27.1 illustrates the gradual fall over time.

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Observed survival and excess mortality data from the Eurocare study

Table 27.I: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	Acute lymphoblastic leukemia (N = 6,650)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	94.01 [92.87-95.15]	5.99 [5.41-6.57]
1-2	89.60 [88.13-91.07]	4.69 [3.94-5.44]
2-3	85.82 [84.13-87.51]	4.22 [3.36-5.08]
3-4	83.46 [81.66-85.26]	2.75 [1.83-3.67]
4-5	81.60 [79.72-83.48]	2.23 [1.27-3.19]
5-6	80.46 [78.50-82.42]	1.40 [0.40-2.40]
6-7	79.50 [77.44-81.56]	1.19 [0.14-2.24]

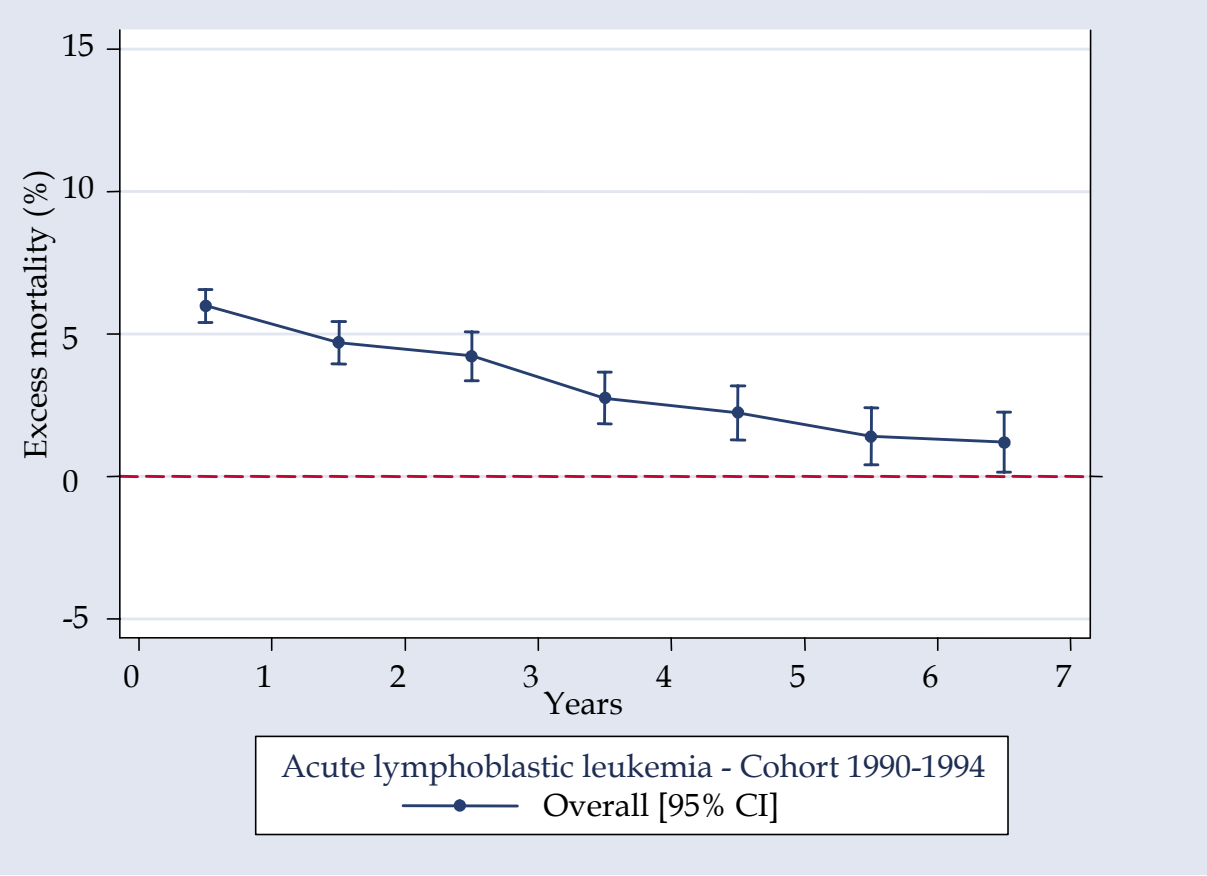

Figure 27.1: Annual excess mortality: diagnostic cohort 1990-1994

28

Acute myeloblastic leukemia

On the basis of the data from six French pediatric registries, acute myeloblastic leukemia (AML) accounted for 5.4% of the malignancies diagnosed in children aged 0 to 14 years over the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was $7.1/10^6$ per year and the sex ratio 1.0 (Clavel *et al*., 2004).

AML has a markedly more pejorative prognosis than ALL since the 5-year survival was 47.5% (95% CI: [41.7-53.3]) for all European countries over the period 1990-1994 (table 28.I). With a 5-year survival of 45.4% (95% CI: [21.0- 69.9]), France is situated slightly below the average. The Nordic countries obtained better results (5-year survival: 61.8%).

The data from the French National registry of childhood malignant blood diseases (RNHE) (Goubin *et al*., 2006) also show progress in the treatment of AML in recent years, since the 5-year survival increased from 47% for the period 1990-1992 to 61% for the period 1997-2000, equivalent to the survival reported by Nordic countries in Eurocare 3.

Annual excess mortality: Eurocare data

Table 28.I shows the annual excess mortality estimates with their 95% confidence intervals. For years 1 and 2 post-diagnosis, the annual excess mortality was 30 and 20%, respectively. Excess mortality subsequently fell to below 1% 5 years post-diagnosis. Figure 28.1 illustrates the fast decrease in annual excess mortality.

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Observed survival and excess mortality data from the Eurocare study

Table 28.I: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	Acute myeloblastic leukemia (N = 1,169)	
Interval (year)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	69.45 [64.14-74.76]	30.55 [27.84-33.26]
1-2	55.51 [49.77-61.25]	20.07 [17.14-23]
2-3	50.43 [44.65-56.21]	9.15 [6.20-12.10]
3-4	48.22 [42.44-54.00]	4.38 [1.43-7.33]
4-5	47.52 [41.74-53.30]	1.45 [-1.50-4.40]
5-6	47.25 [41.45-53.05]	0.57 [-2.39-3.53]
6-7	46.23 [40.27-52.19]	2.16 [-0.88-5.20]

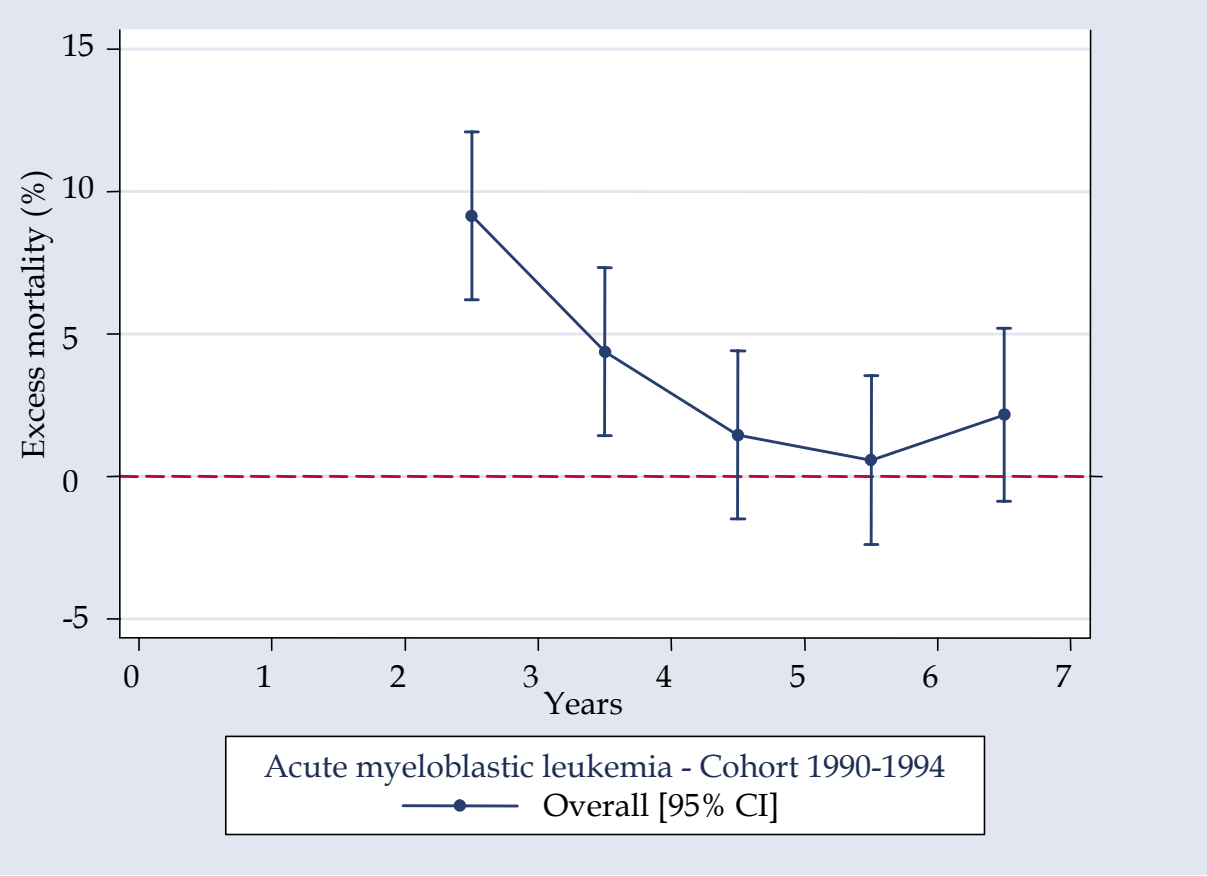

Figure 28.1: Annual excess mortality: diagnostic cohort 1990-1994

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Hodgkin's disease

On the basis of the data from six French pediatric registries, Hodgkin's disease accounted for 4.4% of the cancers diagnosed in children aged 0 to 14 years for the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was $5.3/10^6$ per year and the sex ratio was 1.8.

On the basis of the Eurocare 3 data for the period 1990-1994, the 5-year survival for Hodgkin's disease was 95.3% (95% CI [92.7-97.9]) for all European countries (table 29.I). France was average with survival of 96.2% (95% CI [85.7-100.0]).

Annual excess mortality: Eurocare data

Table 29.I shows the annual excess mortality estimates with their 95% confidence intervals. The annual excess mortality is very low (less than 2%) as of year 1 post-diagnosis and subsequently falls to zero. Figure 29.1 shows the low annual excess mortality associated with pediatric Hodgkin's disease.

Impact of stage and therapeutic progress on survival

The very good prognosis for Hodgkin's disease (over 90% 5-year survival in subjects aged less than 20 years) is the result of progress in therapeutic strategy. Chemotherapy now predominates with radiotherapy restricted to targeting bulky lymph node masses.

Ann Arbor staging of the disease enables setup of an appropriate therapeutic strategy since the stage is the most decisive prognostic factor. The current strategy consists in further improving survival for severe forms (stage IV in particular) and decreasing the aggressiveness of treatment (particularly radiotherapy), without compromising survival in localized forms of the disease (stages I and II).

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Observed survival and excess mortality data from the Eurocare study

Table 29.I: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	Hodgkin's disease (N = 1,039)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	98.64 [97.23-100.05]	1.36 [0.64-2.08]
1-2	97.56 [95.68-99.44]	1.09 [0.13-2.05]
2-3	96.57 [94.34-98.80]	1.01 [-0.13-2.15]
3-4	95.86 [93.41-98.31]	0.74 [-0.51-1.99]
4-5	95.30 [92.67-97.93]	0.58 [-0.76-1.92]
5-6	94.73 [91.89-97.57]	0.60 [-0.85-2.05]
6-7	94.08 [90.90-97.26]	0.69 [-0.93-2.31]

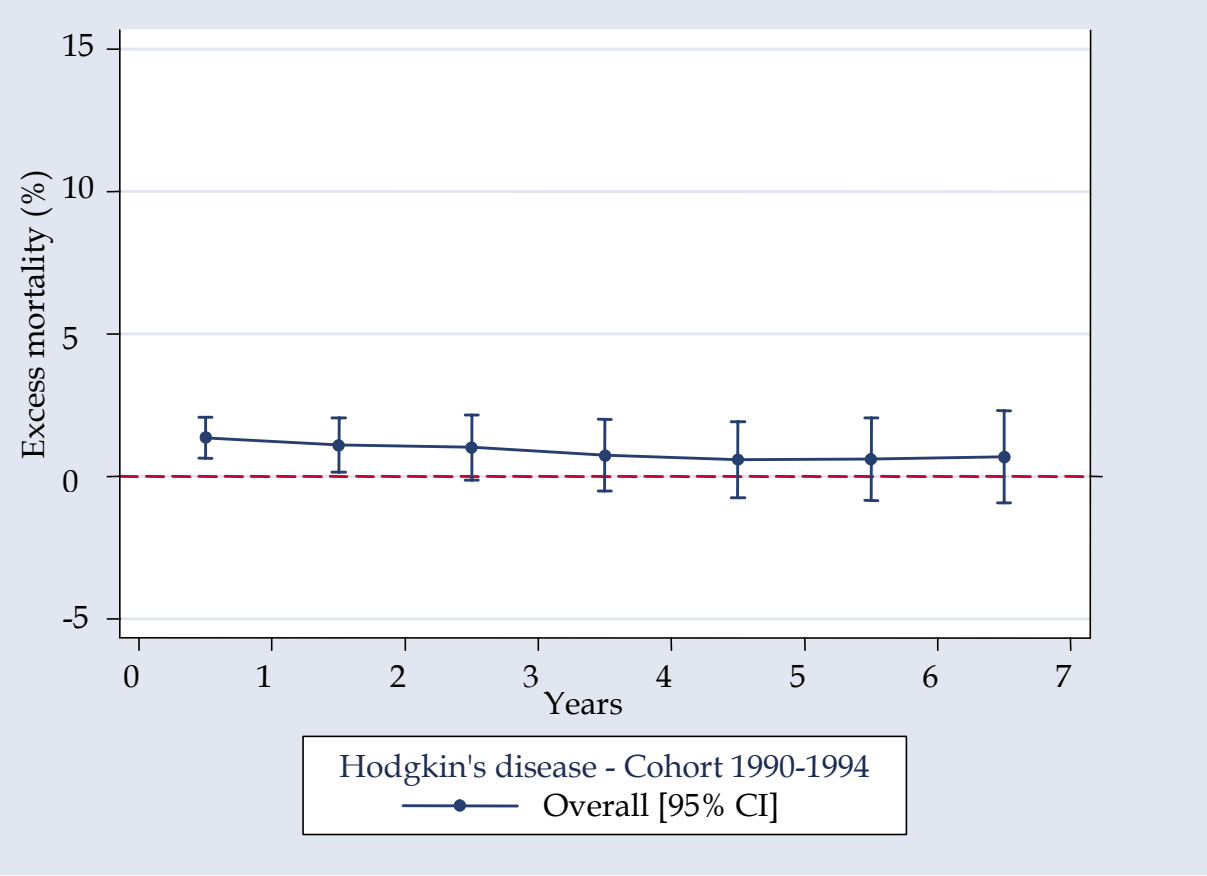

Figure 29.1: Annual excess mortality: diagnostic cohort 1990-1994

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Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) consists in a group of diseases of which the two main malignancies are non-Burkitt's NHL and Burkitt's lymphoma. On the basis of the data from six French pediatric registries, non-Burkitt's NHL accounted for 3.7% of the malignancies diagnosed in children aged 0 to 14 years for the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was $4.9/10^6$ per year and the sex ratio was 1.8. Burkitt's lymphoma accounts for a similar share (3.6%) of pediatric malignancies and its standardized incidence ratio was 4.1 with, however, a higher sex ratio (3.3) (Clavel *et al*., 2004).

The prognosis for pediatric non-Hodgkin's lymphoma is good with 5-year survival of 80.0% (95% CI: [75.6-84.4]) for all European countries (table 30.I). France is above average with a 5-year survival of 86.3% (95% CI: [68.7-100.0]).

Annual excess mortality: Eurocare data

Tables 30.I and 30.II show the annual excess mortality estimates for NHL (non-Burkitt's and Burkitt's) with their 95% confidence intervals. For non-Burkitt's NHL, the annual excess mortality ranges from 12% the first year post-diagnosis to less than 1% as of year 4 post-diagnosis. For Burkitt's lymphoma, the annual excess mortality ranges from 13% to less than 1% as of year 3 post-diagnosis. Figures 30.1 and 30.2 show that a plateau is very rapidly achieved with an annual excess mortality rate of close to zero for both Burkitt's and non-Burkitt's lymphomas.

Impact of lymphoma type and treatment on survival

The most detailed analysis conducted by the French National registry of malignant blood diseases of childhood (RNHE) (Goubin *et al*., 2006) shows that the 5-year survival for phenotype B NHL was 91% for 1990-1995 and remained stable for 1995-2000. In contrast, a significant improvement in prognosis was observed with T-cell lymphoblastic lymphoma for which the 5-year survival increased from 72 to 85%. Similarly, for anaplastic lymphoma, the 5-year survival increased from 82 to 91%.

With regard to therapy, NHL is very sensitive to chemotherapy, which is the primary therapeutic instrument. Surgery has no role and radiotherapy is only used for exceptional indications (irradiation of a persistent mass in the mediastinum, irradiation of the central nervous system in the event of initial meningeal involvement).

Due to the major therapeutic progress achieved over the last 30 years and the now very favorable prognosis for those tumors, the current strategy consists in reducing the duration and intensity of therapy in order to reduce the risk of complications or long-term sequelae.

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Observed survival and excess mortality data from the Eurocare study

Table 30.I: Annual observed survival and excess mortality in patients presenting with non-Burkitt's NHL diagnosed between 1990 and 1994

	Non-Burkitt's NHL (N = 1,292)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	87.93 [84.36-91.50]	12.07 [10.25-13.89]
1-2	82.98 [78.86-87.10]	5.63 [3.53-7.73]
2-3	81.32 [77.05-85.59]	2.00 [-0.18-4.18]
3-4	80.53 [76.18-84.88]	0.97 [-1.25-3.19]
4-5	79.99 [75.60-84.38]	0.67 [-1.57-2.91]
5-6	79.64 [75.19-84.09]	0.44 [-1.83-2.71]
6-7	79.28 [74.73-83.83]	0.45 [-1.87-2.77]

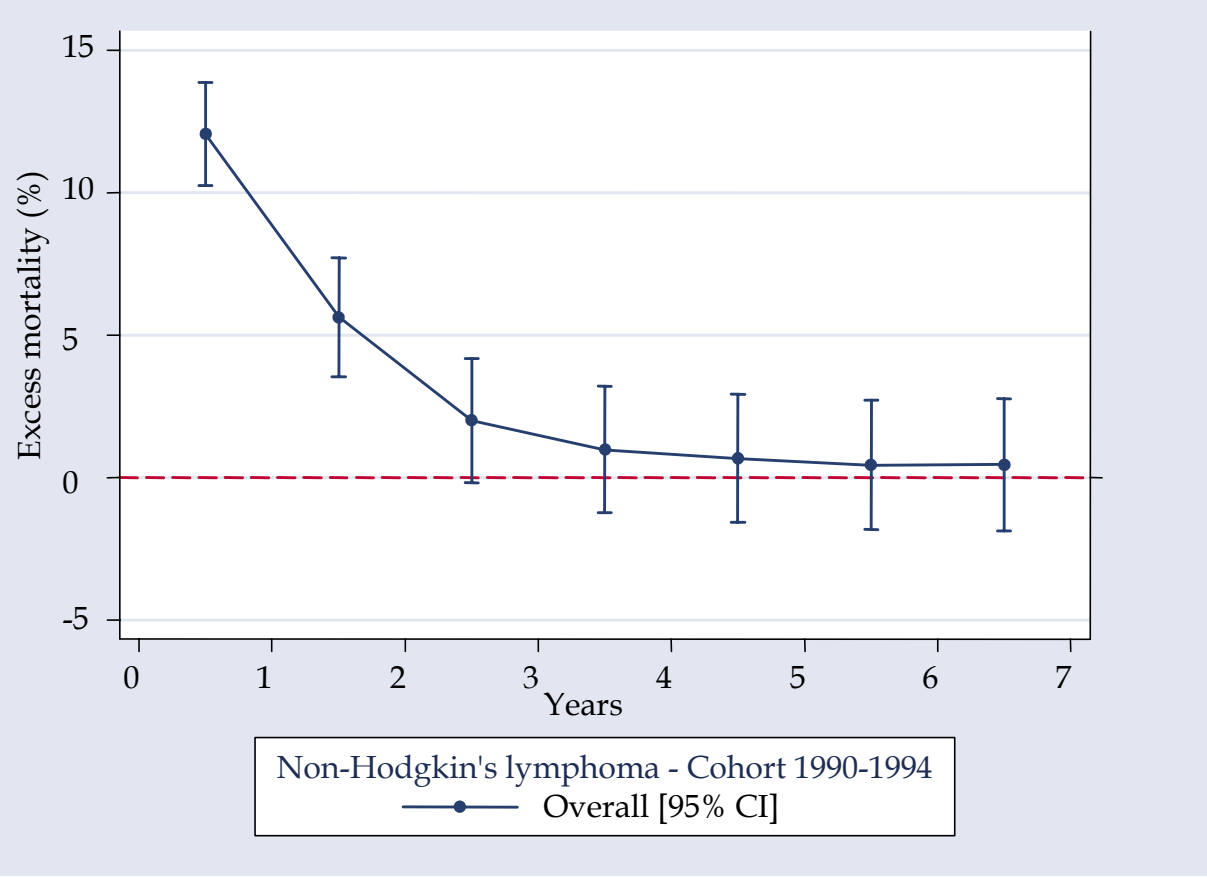

Figure 30.1: Annual excess mortality: diagnostic cohort 1990-1994

Table 30.II: Annual observed survival and excess mortality for patients Burkitt's lymphoma diagnosed between 1990 and 1994

	Burkitt's lymphoma (N = 283)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	86.84 [78.94-94.74]	13.16 [9.13-17.19]
1-2	84.34 [75.83-92.85]	2.88 [-1.46-7.22]
2-3	83.98 [75.40-92.56]	0.43 [-3.95-4.81]
3-4	83.98 [75.40-92.56]	0.00 [-4.38-4.38]
4-5	83.12 [74.30-91.94]	1.02 [-3.48-5.52]
5-6	83.12 [74.30-91.94]	0.00 [-4.50-4.50]
6-7	83.12 [74.30-91.94]	0.00 [-4.50-4.50]

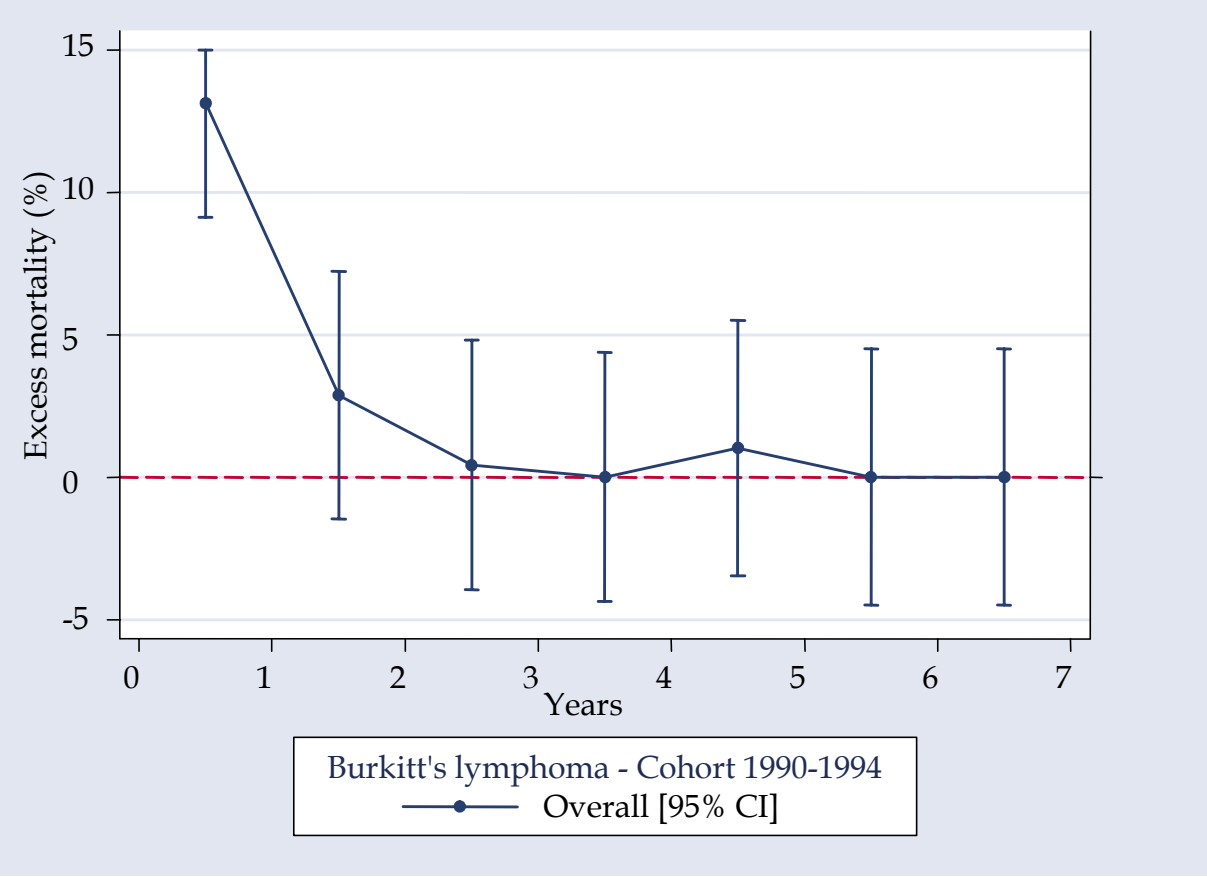

Figure 30.2: Annual excess mortality: diagnostic cohort 1990-1994

31

Central nervous system tumors

On the basis of the data from six French pediatric registries, central nervous system tumors accounted for 21.8% of the malignancies diagnosed in children aged 0 to 14 years for the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was 29.1/10^6 per year and the sex ratio was 1.1.

On the basis of the Eurocare 3 data for the period 1990-1994, the 5-year survival for central nervous system tumors was 63.9% (95% CI [61.1-66.8]) for all European countries (table 31.I). France was average with a 5-year survival of 58.8% (95% CI [46.8-70.9]).

Annual excess mortality (all types considered): Eurocare data

Table 31.I shows the annual excess mortality estimates with their 95% confidence intervals. The annual excess mortality was less than 20% the first year post-diagnosis and subsequently fell rapidly. The annual excess mortality was between 1 and 2% after year 5. Figure 31.1 illustrates the fast decrease in annual excess mortality.

Impact of histological type on survival

The prognosis depends markedly on the histological type. For ependymomas and primary neuroectodermal tumors (PNET), the 5-year survival was less than 60%. In contrast, the survival rate for astrocytoma was high: 79% (Gatta *et al*., 2003). The prognosis was most pejorative for very young infants (Magnani *et al*., 2001), in part because they present with the most pejorative type of malignancies (PNET, brain stem tumors) but also because the therapeutic options are more limited (radiotherapy to the developing brain is contra-indicated).

Impact of diagnostic instruments and treatment on survival

The survival rate for central nervous system tumors has improved over the last 20 years with a fall in the risk of death of 3% per year (Gatta *et al*., 2005). The introduction of CT scanners and MRI has, in particular, enabled enhanced disease staging and precise assessment of the conditions for excision. The latter remains the primary treatment for the type of tumor in question. Chemotherapy has slightly improved the vital and, above all, functional prognosis, by restricting the indications for radiotherapy and thus reducing the risk of sequelae.

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Observed survival and excess mortality data from the Eurocare study

Table 31.I: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	Central nervous system (N = 4,622)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	80.92 [78.63-83.21]	19.08 [17.91-20.25]
1-2	71.96 [69.33-74.59]	11.07 [9.73-12.41]
2-3	68.12 [65.40-70.84]	5.34 [3.95-6.73]
3-4	65.81 [63.03-68.59]	3.39 [1.97-4.81]
4-5	63.93 [61.09-66.77]	2.86 [1.41-4.31]
5-6	62.83 [59.95-65.71]	1.72 [0.25-3.19]
6-7	61.73 [58.75-64.71]	1.75 [0.23-3.27]

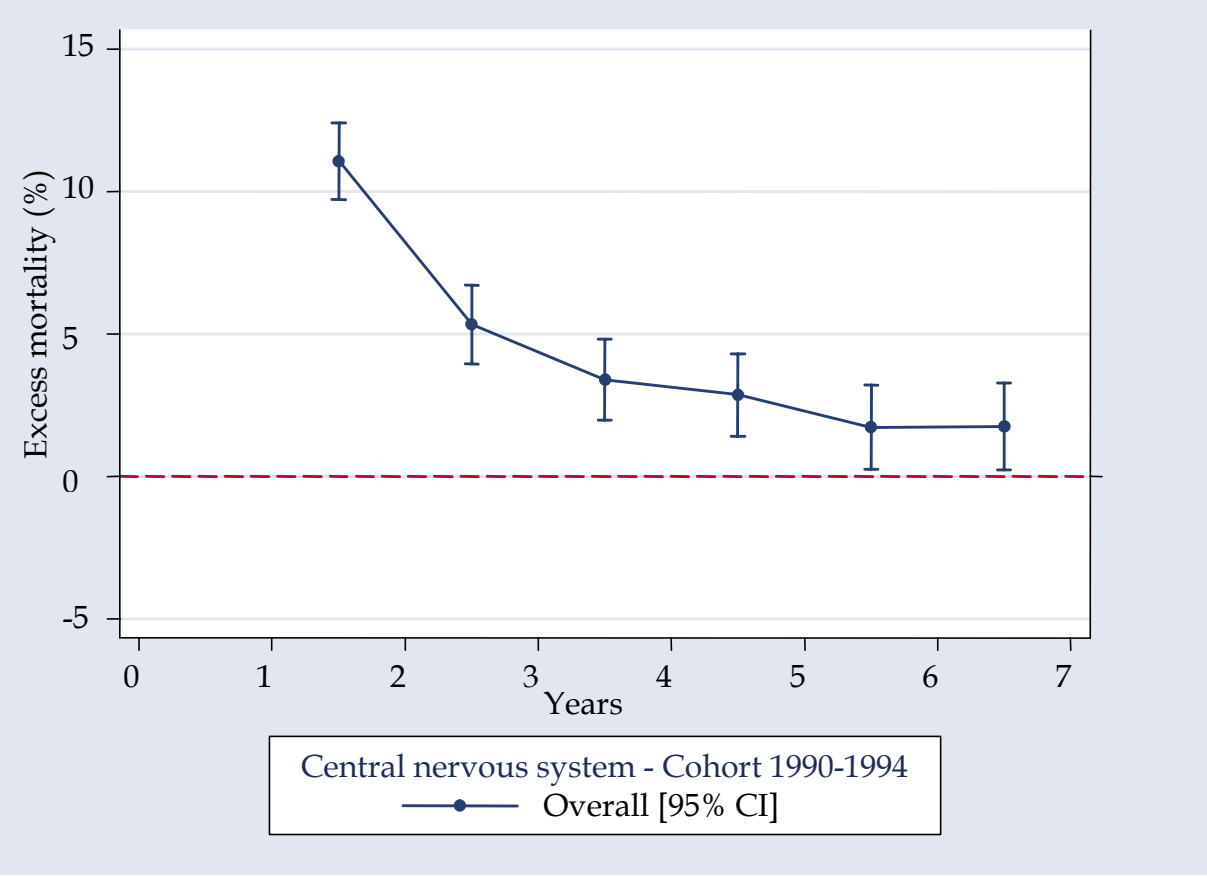

Figure 31.1: Annual excess mortality: diagnostic cohort 1990-1994

32

Neuroblastoma

On the basis of the data from six French pediatric registries, neuroblastoma accounted for 8.9% of the malignancies diagnosed in children aged 0 to 14 years for the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was $13.9/10^6$ per year and the sex ratio 1.2.

On the basis of the Eurocare 3 data for the period 1990-1994, the 5-year survival for neuroblastoma was 58.2% (95% CI: [53.5-62.9]) for all the European countries (table 32.I). France was above average with a 5-year survival of 68.9% (95% CI: [52.9-84.7]).

Annual excess mortality: Eurocare data

Table 32.I shows the annual excess mortality estimates with their 95% confidence intervals. The annual excess mortality was less than 20% for the first 2 years post-diagnosis. It then fell off rapidly to less than 2% after year 5 post-diagnosis. Figure 32.1 illustrates the decrease in annual mortality and its stabilization at between 1 and 2% a few years post-diagnosis.

Impact of prognostic factors on survival

The prognosis of neuroblastoma depends on patient age and disease stage at the time of diagnosis, but also on other factors such as the presence of amplification of the N-*myc* gene or a chromosomal aberration. The forms observed in infants have a superior prognosis to those observed in older children. The latter are frequently disseminated forms with strong progressive potential at the time of diagnosis.

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Observed survival and excess mortality data from the Eurocare study

Table 32.I: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	Neuroblastoma (N = 1,731)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	81.89 [78.24-85.54]	18.11 [16.25-19.97]
1-2	68.48 [64.09-72.87]	16.38 [14.14-18.62]
2-3	62.89 [58.30-67.48]	8.16 [5.82-10.50]
3-4	59.28 [54.62-63.94]	5.74 [3.36-8.12]
4-5	58.22 [53.54-62.90]	1.79 [-0.60-4.18]
5-6	57.54 [52.80-62.28]	1.17 [-1.25-3.59]
6-7	56.7 [51.88-61.52]	1.46 [-1.00-3.92]

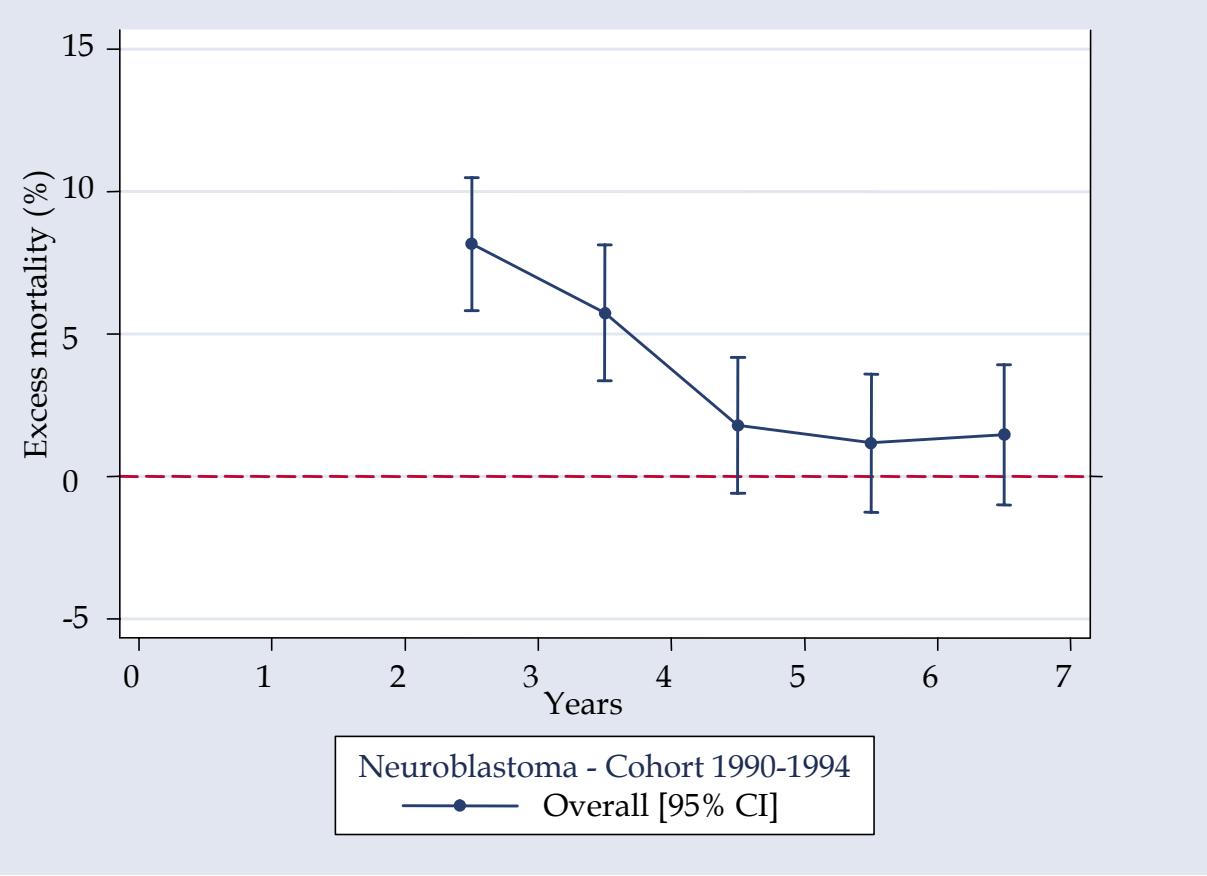

Figure 32.1: Annual excess mortality: diagnostic cohort 1990-1994

33

Nephroblastoma

On the basis of the data from six French pediatric registries, nephroblastoma (renal tumor) accounted for 6.0% of the malignancies diagnosed in children aged 0 to 14 years for the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was $9.1/10^6$ per year and the sex ratio was 0.7.

On the basis of the Eurocare 3 data for the period 1990-1994, the 5-year survival for nephroblastoma was 83.7% (95% CI: [79.9-87.6]) for all European countries (table 33.I). France was average with a 5-year survival of 84.7% (95% CI [69.6-99.5]).

Annual excess mortality: Eurocare data

Table 33.I shows the annual excess mortality estimates with their 95% confidence intervals. The annual excess mortality was about 6% for the first 2 years post-diagnosis, then fell rapidly to below 1% as of year 5 post-diagnosis. Figure 33.1 illustrates the rapid fall.

The very good survival of children having presented with nephroblastoma results from almost all patients being included in multicenter studies. The current problem mainly consists in limiting the sequelae related to radiotherapy or the toxicity of chemotherapy.

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Observed survival and excess mortality data from the Eurocare study

Table 33.I: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	Nephroblastoma (N=1,440)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	93.28 [90.69-95.87]	6.72 [5.40-8.04]
1-2	87.44 [83.99-90.89]	6.26 [4.50-8.02]
2-3	85.45 [81.78-89.12]	2.28 [0.41-4.15]
3-4	84.24 [80.46-88.02]	1.42 [-0.51-3.35]
4-5	83.74 [79.90-87.58]	0.59 [-1.37-2.55]
5-6	83.52 [79.64-87.40]	0.26 [-1.72-2.24]
6-7	83.19 [79.21-87.17]	0.40 [-1.63-2.43]

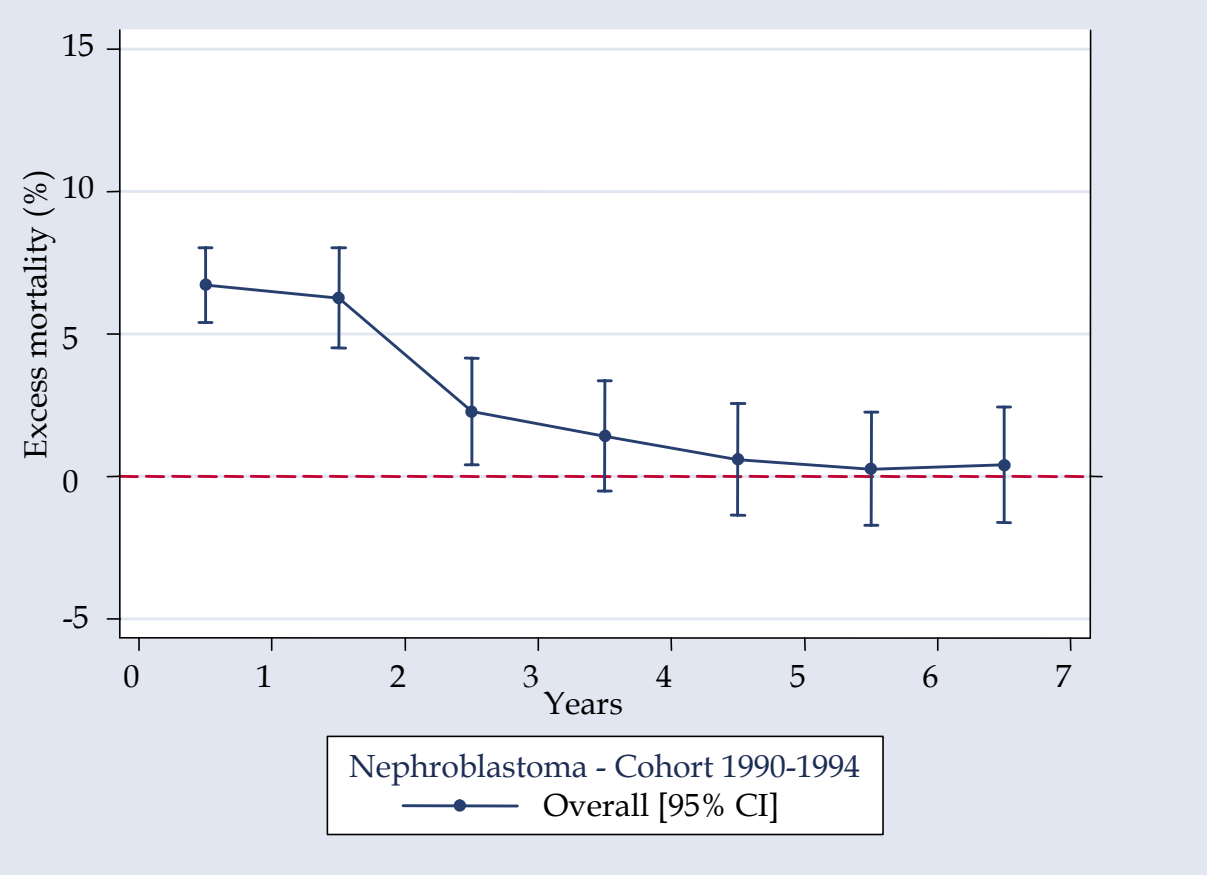

Figure 33.1: Annual excess mortality: diagnostic cohort 1990-1994

34

Soft tissues tumors

On the basis of the data from six French pediatric registries, soft tissues tumors accounted for 5.4% of the malignancies diagnosed in children aged 0 to 14 years for the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was $7.4/10^6$ per year and the sex ratio was 1.6.

On the basis of the Eurocare 3 data for the period 1990-1994, the 5-year survival for soft tissues tumors was 65.4% (95% CI: [60.5-70.2]) for all European countries (table 34.I). The results were superior for France with a 5-year survival of 72.8% (95% CI: [51.4-94.3]).

Annual excess mortality: Eurocare data

Table 34.I shows the annual excess mortality estimates with their 95% confidence intervals. The annual excess mortality was greater than 10% for the first 2 years post-diagnosis. The annual excess mortality was between 1 and 2% after year 6 post-diagnosis. Figure 34.1 illustrates the rapid fall in annual excess mortality over the first years post-diagnosis.

Impact of tumor type and treatment on survival

Rhabdomyosarcoma, the most frequent soft tissue tumor in children, has an inferior prognosis. The 5-year survival was 65.4% (95% CI: [59.1–71.8]) while 'non-rhabdomyosarcoma' tumors had a 5-year survival of 76.5% (95% CI: [63.0–90.2]). Irrespective of whether the malignancy is a rhabdomyosarcoma or not, the metastatic forms have a highly pejorative prognosis with survival of less than 30%.

Current therapeutic progress is increasingly incorporating chemotherapy enabling conservative surgery and restricting the indications for radiotherapy and the tissue volumes irradiated.

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Observed survival and excess mortality data from the Eurocare study

Table 34.I: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	Soft tissues tumor (N = 1,536)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	88.79 [85.61-91.97]	11.21 [9.59-12.83]
1-2	76.58 [72.33-80.83]	13.75 [11.58-15.92]
2-3	70.21 [65.60-74.82]	8.32 [5.97-10.67]
3-4	67.24 [62.50-71.98]	4.23 [1.81-6.65]
4-5	65.35 [60.53-70.17]	2.81 [0.35-5.27]
5-6	64.75 [59.87-69.63]	0.92 [-1.57-3.41]
6-7	63.65 [58.59-68.71]	1.70 [-0.88-4.28]

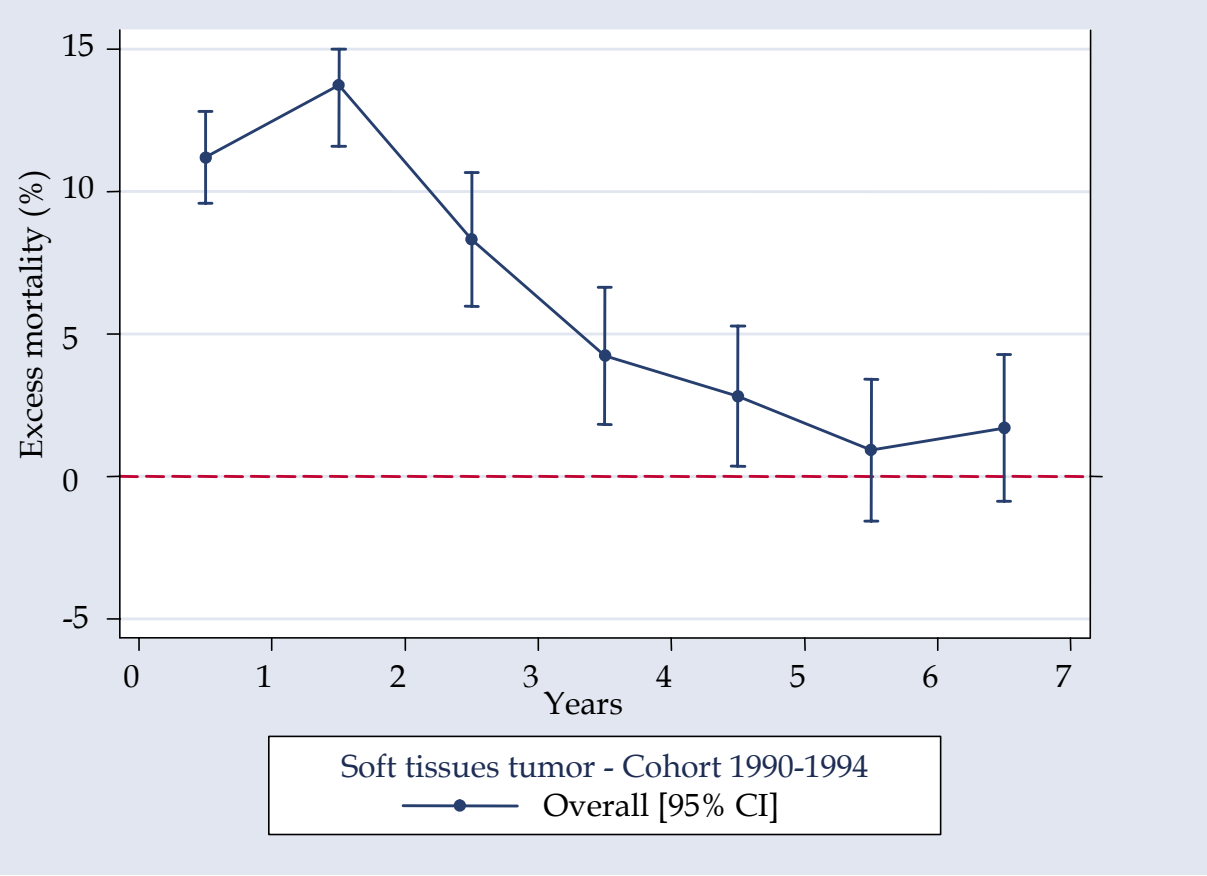

Figure 34.1: Annual excess mortality: diagnostic cohort 1990-1994

35

Bone tumors

On the basis of the data from six French pediatric registries, bone tumors accounted for 5.5% of the malignancies diagnosed in children aged 0 to 14 years over the period from 1990 to 1999 (Désandes *et al*., 2004). The age-standardized incidence rate (world population) was $6.6/10^6$ per year and the sex ratio was 1.3.

On the basis of the Eurocare 3 data for the period 1990-1994, the 5-year survival for bone tumor was 64.8% (95% CI [58.9-70.1]) for all the European countries (table 35.I). France was average with a 5-year survival of 62.7% (95% CI [39.9-85.5]).

Annual excess mortality: Eurocare data

Table 35.I shows the annual excess mortality estimates with their 95% confidence intervals. The annual excess mortality, which was about 10% over the first 3 years post-diagnosis, fell to between 2 and 3% after year 6 post-diagnosis. Figure 35.1 shows that the annual excess mortality plot remains above 5% over the first years.

Impact of tumor type and treatment on survival

The bone tumors mainly consisted in osteosarcoma and Ewing's sarcoma. The 5-year survival was somewhat lower for osteosarcoma: 62.4% (95% CI: [53.9-70.9]) compared to 66.9% (95% CI: [57.6-76.2]) for Ewing's sarcoma. Pre- and post-operative chemotherapy combined, if feasible, with conservative surgery, has limited the indications for radiotherapy.

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Observed survival and excess mortality data from the Eurocare study

Table 35.I: Annual observed survival and excess mortality: diagnostic cohort 1990-1994

	Bone tumor (N = 1,041)	
Interval (years)	Observed survival [95% CI] (annual %)	Excess mortality [95% CI] (annual %)
0-1	93.05 [89.95-96.15]	6.95 [5.37-8.53]
1-2	79.93 [75.03-84.83]	14.10 [11.60-16.6]
2-3	72.01 [66.52-77.50]	9.91 [7.11-12.71]
3-4	68.07 [62.37-73.77]	5.47 [2.56-8.38]
4-5	64.77 [58.87-70.67]	4.85 [1.84-7.86]
5-6	63.24 [57.20-69.28]	2.36 [-0.72-5.44]
6-7	61.38 [55.05-67.71]	2.94 [-0.29-6.17]

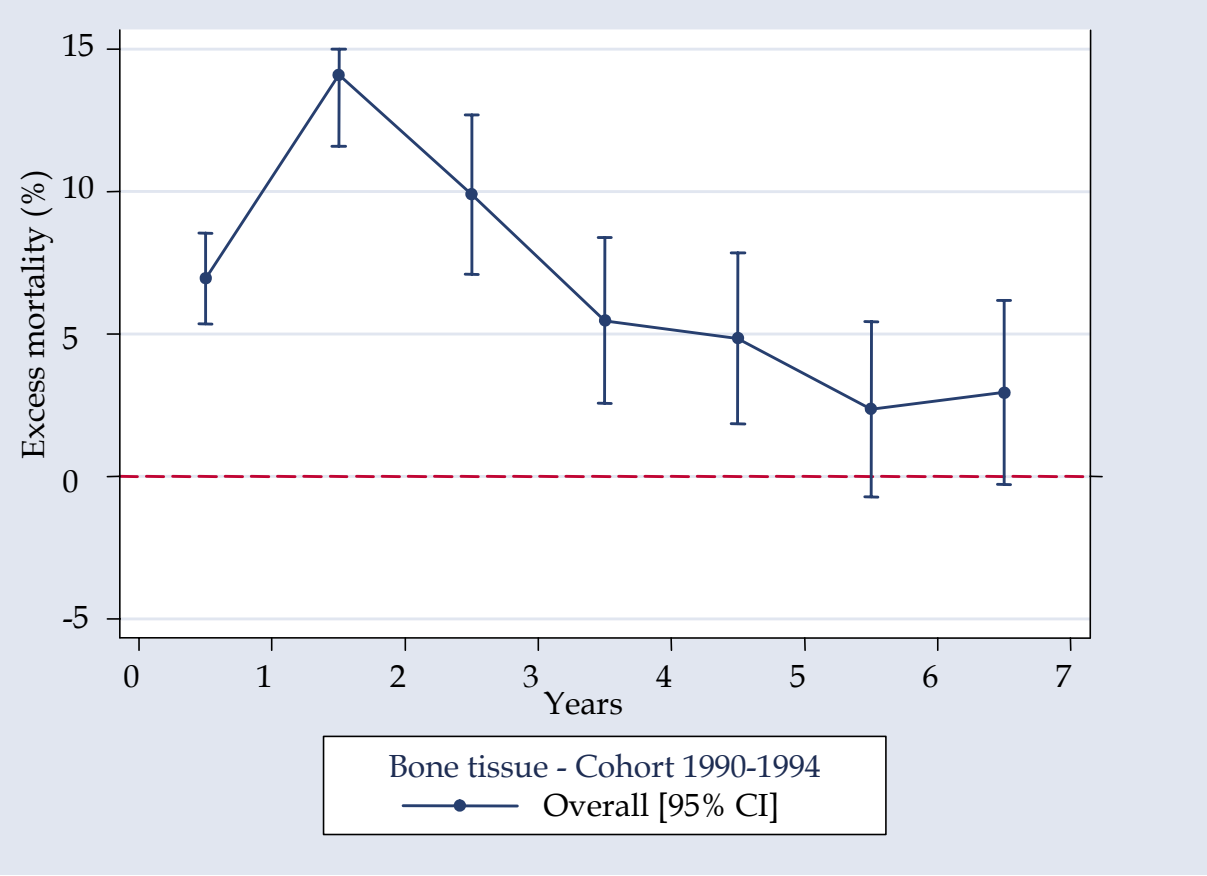


Figure 35.1: Annual excess mortality: diagnostic cohort 1990-1994

Synthesis

Estimating the excess mortality risk of people having had cancer is an issue that is pertinent to both patients and the professionals of the insurance industry when a loan is negotiated or when the premium for a contract is to be calculated. The degree of excess risk may be calculated as a function of the patient's age and gender and, sometimes, the characteristics of the tumor. The recent European data on the life expectancy of cancer patients enable calculation of the excess risk or excess mortality associated with the various neoplastic disease sites.

Data sources

In the context of this collective expert report, the excess risk was calculated using the mean survival data for cancer patients. The data were collected by the European cancer registries and published as the results of the Eurocare study. In 2005, the Eurocare data consisted in those of 67 registries (including 4 to 6 French registries) spanning some 20 countries. The survival rates reported for those countries were updated as at January 1, 2000, and cover the cases of neoplastic disease diagnosed during the periods: 1978-1985, 1985-1989 and 1990-1994. The rates were analyzed by gender and age at the time of diagnosis.

With a view to establishing a firm basis for the survival estimates, the group of experts enriched the French data published in the context of the Eurocare study with those of 7 other countries (Spain, Italy, the Netherlands, Switzerland, Sweden, Finland and Norway) selected for the quality of their data and the similarity of that data to the French data.

The Eurocare study has not presented the data by cancer stage. The people responsible for the European cancer registries consider that the staging data routinely collected are not sufficiently reliable and standardized for use in survival studies. Staging is, in fact, the resultant of a set of information on the various dimensions of neoplastic disease spread. The evaluation of those dimensions is highly dependent on the investigations conducted.

In the United States, the Surveillance Epidemiology and End Results program (SEER program) has been collecting data from 11 population registries and 3 hospital registries covering about 14% of the US population since 1973. The program has generated survival data as a function of disease stage.

For certain disease sites, the data derived from the hospital series, although subject to selection bias, have been cited, several times, with a view to refining the evaluation of prognostic factors with respect to survival. Clinical trials yield detailed information on the survival gains associated with more recently developed therapies.

In the near future, survival data on all the cases of cancer collected by the French registries will be available and constitute a valuable addition to the results presented in this expert report. Information on long-term survival for the main neoplastic diseases, as a function of initial stage, will also be available in the form of the data specifically collected by the registries. In addition, the hospital data generated by the Étude Permanente Cancer (EPC, ongoing cancer study, hospital registry of the cancer centers) will also be available.

The various neoplastic diseases were defined in accordance with the International Classification of Diseases (ICD-10). In the context of this expert report, 22 disease sites in adults and 9 sites in children were selected.

Adult disease sites studied

Gynecology
Breasts (women)
Ovaries
Cervix
Corpus uteri
Urology
Prostate
Testes
Kidneys
Gastrointestinal
Colon
Rectum
Lungs
ENT
Larynx
Hypopharynx
Oropharynx
Nasopharynx
Thyroid
Melanoma
Malignant blood diseases
Acute lymphoblastic leukemia
Acute myeloid leukemia
Chronic lymphocytic leukemia
Chronic myeloid leukemia
Hodgkin's disease
Non-Hodgkin's lymphoma

Principle of the method of evaluating excess mortality

The net survival, for instance at 10 years, of a group of patients is the 'net' probability of being alive 10 years after the diagnosis of cancer with the hypothesis that all other causes of death are eliminated. The complement to 1 of the net probability of survival is the net probability of dying due to the cancer 'alone' within 10 years. This probability therefore reflects the excess mortality, i.e. the excess mortality to which the patient group is subject.

The difficulty of estimating post-cancer net survival (which is related to the difficulty involved in ruling out other causes of death) has led to relative survival estimates being considered preferable. The relative survival estimate does not require knowledge of the cause of death, which may be impossible to determine in the context of a cancer registry.

The relative survival rate is the ratio, in a given time t, between the observed survival probability in a population of subjects presenting with cancer and the expected survival probability in a general population of subjects not presenting with cancer, of the same gender, in the same age group, in the same region and at the same time. The excess mortality, the complement to 1 of the net survival estimate, is then deduced.

The Eurocare study uses that approach to calculate the relative survival. The approach has also been used to conduct new analyses of the Eurocare data in the context of the present expert report.

The excess mortality, expressed as a percentage, was determined on an annual basis. It is to be interpreted as follows: 1% annual excess mortality between years 9 and 10 means that at time point t = 9 years post-diagnosis, the probability of dying of cancer or its consequences in the following year (10th year) is 0.01. The indicator was considered pertinent to the objective of this expert report.

It should be noted that the probability of dying of cancer takes into account all the cofactors that contributed to disease emergence. By way of an example, consider lung cancer in a smoker. The observed survival in a patient population presenting with lung cancer results from having had cancer but also from the morbidity induced by smoking. If the observed survival is corrected by the expected survival in order to obtain the relative survival, all the factors (cancer and the comorbidity induced by smoking) are taken into account. Thus, in any evaluation of the excess risk of death, smoking is not to be incorporated again in order not to take account of the same risk factor twice.

Application of the method to the Eurocare study data for this expert report

The Eurocare 3 study generated grouped data and not individual data. The expected survival estimates by interval are thus only available for certain groups defined by the diagnostic cohort, gender or age group.

The diagnostic period mainly influences the survival in the first years and very little the excess annual risk remotely from the diagnosis, as has been confirmed by most of the Eurocare study data. The data for all the periods available were thus pooled in order to more precisely estimate the excess mortality remote from the diagnosis.

For the pooled data for the eight countries (including France) and for each disease site selected, all the annual excess mortality estimates were calculated for the following pools:

- both genders: any age and any cohort;
- by gender: any age and any cohort;
- by age group: any gender and any cohort;
- by diagnostic cohort: any gender and any age.

The annual excess mortality estimates based on the Eurocare data for the eight countries were first implemented for all forms of cancer taken together and then for each of the disease sites considered.

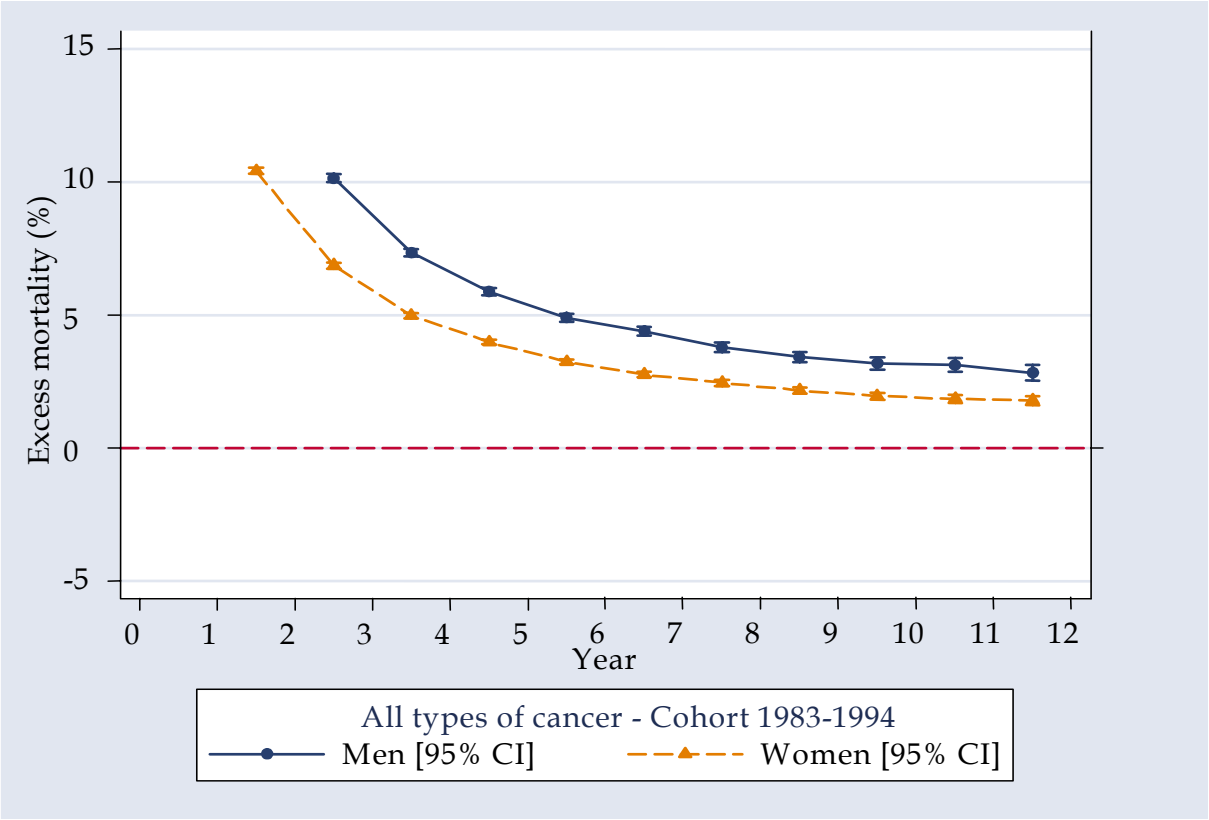
Annual excess mortality for all forms of cancer

The annual excess mortality estimates for all disease sites taken together were obtained by taking into account all the cases diagnosed between 1983 and 1994 in the Eurocare study and in the eight countries selected for this expert report.

Annual excess mortality decreased over time. It ranged from more than 27% 0-1 year post-diagnosis to less than 2% 11-12 years post-diagnosis. The annual excess mortality was less than 15% as of year 2 post-diagnosis, then less than 5% as of year 5 post-diagnosis, falling to about 2% for year 12.

The annual excess mortality was lower in women than in men. It ranged from about 20% for 0-1 year post-diagnosis to less than 2% for 11-12 years post-diagnosis for women. For men, the annual excess mortality ranged from about 33% for 0-1 year to a little more than 2% for

11-12 years post-diagnosis. The difference between men and women was more marked in the first years post-diagnosis.



Annual excess mortality by gender, cohort 1983-1994, all forms of cancer

The annual excess mortality increased from age group 15-44 years to age group 65-74 years (for all years post-diagnosis). For age group 15-44 years, the annual excess mortality ranged from 12% for 0-1 year post-diagnosis to a little more than 1% for 11-12 years post-diagnosis. It was less than 5% as of year 4. For age group 65-74 years, the annual excess mortality ranged from more than 33% for 0-1 year post-diagnosis to more than 3% for 11-12 years post-diagnosis.

The annual excess mortality decreased from the oldest to the most recent cohort, mainly during the first years post-diagnosis.

Annual excess mortality (%) as of year 10 post-diagnosis, all forms of cancer (taken from the Eurocare data)

	Annual excess mortality (%) [95%CI] Year 10 post-diagnosis
Overall	2.27 [2.14 ; 2.39]
Women	1.95 [1.82 ; 2.08]
Men	3.18 [2.94 ; 3.41]
Age group 15-44 years	1.24 [1.09 ; 1.38]
Age group 45-54 years	2.06 [1.85 ; 2.27]
Age group 55-64 years	2.42 [2.21 ; 2.64]
Age group 65-74 years	3.03 [2.72 ; 3.34]

Annual excess mortality by disease site, all stages taken together and remotely from diagnosis

Using the Eurocare data, the excess mortality estimates for the various disease sites and for year 10 post-diagnosis were analyzed. The overall excess mortality for all forms of adult cancer taken together was 2.27%. Out of the 22 adult disease sites addressed herein, 10 had an excess mortality of less than 2% at year 10. Six sites were associated with excess mortality of between 2 and 5%. For five sites, the excess mortality was greater than 5%.

For female tumors (breast, ovary, cervix and *corpus uteri*), the excess mortality in year 10 ranged from 0.28% (*corpus uteri*) to 2.57% (breast). For men, the annual excess mortality was 0.03% for testicular germ-cell tumors and 6.67% for prostatic tumors (in older patients: the diagnostic age limit was extended to 84 years). For disease sites common to men and women, the annual excess mortality ranged from 0.33% for acute lymphoblastic leukemia to 10.27% for chronic myeloid leukemia.

In general, the excess mortalities for the various disease sites in year 10 post-diagnosis were lower for the youngest diagnostic age group (15-44 years). They were also generally lower for women.

Thus, 10 years post-diagnosis, the excess risk may be considered stable and of limited amplitude for most disease sites. For certain sites, the excess risk was practically nil.

Annual excess mortality (%) in year 10 post-diagnosis (taken from the Eurocare data)

Site	Annual excess mortality (%) [95%CI] (year 10 post-diagnosis)
All adult neoplastic diseases	2.27 [2.14 ; 2.39]
Breast cancer	2.57 [2.35 ; 2.80]
Ovarian cancer	1.80 [1.22 ; 2.38]
Cervical cancer	1.13 [0.69 ; 1.57]
Corpus uteri cancer	0.28 [- 0.04 ; 0.61]
Prostatic cancer	6.67 [5.93 ; 7.42]
Testicular germ-cell tumor	0.03 [- 0.24 ; 0.31]
Kidney cancer	3.13 [2.38 ; 3.88]
Colon cancer	0.91 [0.49 ; 1.34]
Rectal cancer	1.44 [0.87 ; 2.02]
Lung cancer	5.64 [4.54 ; 6.74]
Laryngeal cancer	2.74 [1.73 ; 3.76]
Hypopharyngeal cancer	9.11 [4.22 ; 13.99]
Oropharyngeal cancer	2.76 [0.31 ; 5.21]
Nasopharyngeal cancer	2.96 [- 0.30 ; 6.22]
Thyroid cancer	0.49 [0.08 ; 0.90]
Cuteaneous melanoma	0.91 [0.58 ; 1.24]
Acute lymphoblastic leukemia	0.33 [- 1.03 ; 1.69]
Acute myeloblastic leukemia	2.75 [0.33 ; 5.17]
Chronic lymphoid leukemia	9.67 [7.59 ; 11.76]
Chronic myeloid leukemia	10.27 [6.38 ; 14.17]
Hodgkin's disease	1.03 [0.44 ; 1.63]

Non-Hodgkin's malignant lymphoma	4.18 [3.39 ; 4.98]

For certain disease sites, the very long-term survival data (10, 15 and 20 years) reported in the literature confirm the time course of the annual excess mortality remotely from diagnosis that was demonstrated, up to year 12, by the Eurocare data.

Annual excess mortality by stage soon after diagnosis

The annual excess mortality estimates for soon after diagnosis are highly dependent on tumor stage at the time of diagnosis. The data available by stage or for localized disease thus enable more precise annual excess mortality estimates for the first years post-diagnosis for certain disease sites.

Few French or European data are available for estimation of annual excess mortality by tumor stage. Using US data, the SEER program has estimated annual excess mortality up to year 10 post-diagnosis as a function of tumor stage at the time of diagnosis. Tumor stage was defined as follows: localized tumor; tumor with regional disease spread (lymph node involvement); tumor with distant metastases.

SEER program data are available for four specifically-female disease sites (breast, ovary, cervix and *corpus uteri*), two male-specific sites (testicular germ-cell and prostatic tumors) and five sites common to both genders (kidney, lung, larynx, thyroid and melanoma). In general, the differences in the annual excess mortalities associated with the three stages fall over the time from diagnosis for each of the disease sites. However, in the first years post-diagnosis, the annual excess mortality is greatly influenced by tumor stage at the time of diagnosis.

It is thus of interest to have annual excess mortality data for the localized disease stage for the first years post-diagnosis. For localized disease and for all the disease sites cited, the annual excess mortality in year 5 post-diagnosis ranges from 0 to 7%. For eight disease sites (breast, ovary, cervix, *corpus uteri*, prostate, testis, thyroid, melanoma), the annual excess mortality was nil, less than 1% or close to 1%. For two sites (kidney, larynx), the annual excess mortality was less than 3%. The lungs constitute the only site for which the excess mortality in year 5 post-diagnosis was greater than 5%.

Annual excess mortality (%) for year 5 post-diagnosis and for localized disease (taken from the SEER data)

Site	Annual excess mortality (%) (Year 5; localized disease)	Localized disease (%)
Breast cancer	1.02	62.10
Ovarian cancer	0.86	19.60
Cervical cancer	0.90	53.80
Corpus uteri cancer	0.50	72.40
Prostatic cancer	0.00	84.30
Testicular germ-cell tumor	0.00	69.10
Kidney cancer	1.80	50.30
Lung cancer	7.20	15.90
Laryngeal cancer	2.90	50.00
Thyroid cancer	0.00	55.10
Cuteaneous melanoma	0.61	82.00

Some fragmentary French data from hospital registers and series confirm the estimates for localized disease.

Prognostic factors for female-specific tumors

Recent data sometimes enable evaluation of survival as a function of various prognostic factors (other than age at the time of diagnosis, gender and disease stage) for certain disease sites. The annual excess mortality during the first years post diagnosis may be influenced by various disease characteristics (histologic type, etc.) or treatment modalities. However, no population data taking those factors into account are currently available.

For breast cancer, the clinical stage, pathological stage, grade and the presence of hormone receptors all constitute prognostic factors. The presence of hormone receptors determines the sensitivity to hormone treatment. Numerous other prognostic markers have been investigated in breast cancer but none has yet been validated for use in clinical practice. Early attempts to control metastatic disease spread is based on adjuvant treatment. Progress has been made with respect to adjuvant chemotherapy with the advent of new cytotoxic agents, the anthracyclines in the nineteen-eighties then, more recently, the taxanes, which have just been approved for adjuvant indications. Adjuvant hormone therapy, which was long restricted to tamoxifen or castration, is currently progressing with the advent of new-generation aromatase inhibitors which block endogenous estrogen production.

The prognosis for ovarian tumor depends on clinical factors (staging, age), histologic factors (grade and type) and biological factors. The importance of the prognostic factors varies as a function of stage. Instruments such as tumor markers must therefore be developed in order to enable early diagnosis of ovarian cancer. Ovarian epithelial carcinomas are relatively chemotherapy-sensitive. The main drugs used in the treatment of ovarian cancer are platinum salts, anthracyclines, taxanes and alkylating agents.

Considerable progress has been made in the treatment of cervical cancer over the last decade. In particular, survival has increased. Disease stage, tumor volume, lymph-node involvement, bilateral lesions, histologic type and biological factors are all of prognostic value. The treatment depends on disease stage. In the early stage and in the event of a small tumor without lymph-node involvement, the treatment consists in surgery, radiotherapy or combined surgery and radiotherapy.

The prognosis of *corpus uteri* cancer is based on the following factors: stage, grade, histologic differentiation, involvement or non-involvement of the cervix, myometrial lesion depth, pelvic lymph node involvement, etc. The good prognostic factors mainly consist in low grade and limited myometrial invasion. Depending on certain prognostic factors, surgery may be followed by radiotherapy.

Prognostic factors for male-specific tumors

Currently, only the localized stages of prostatic cancer can be cured. The three principal prognostic factors determined by multifactorial analyses and liable to predict, pre-treatment, the risk of tumor recurrence and overall patient survival are: serum prostate specific antigen (PSA) level; tumor stage; and the degree of differentiation of the tumor. Several studies have attempted to define the practical conditions for use of those prognostic factors to orient everyday patient management. An initial approach was based on determining prognostic groups enabling prediction of the biological recurrence-free survival and overall survival. A

second approach consists in taking into account the weight of each prognostic factor and considering each prognostic factor in its continuity. A point score is thus allocated to each patient. The point score matches a recurrence-free survival probability.

Numerous studies have confirmed that the prognosis of localized seminomatous or non-seminomatous tumors is excellent. Localized disease is taken to mean the absence of detectable gross metastases on CT scan and the normality (or normalization subsequent to orchidectomy) of the serum tumor markers. For metastatic tumors, an international prognostic classification has been compiled and enables estimation of the expected 5-year survival post-appropriate treatment on the basis of two principal prognostic factors: the presence or absence of non-pulmonary visceral metastases (liver, bone or brain) and the degree of elevation of serum tumor markers. Orchidectomy is the reference treatment. The complementary treatments depend on the results of CT-scan staging and the assays of serum tumor markers (alpha-fetoprotein and human chorionic gonadotropin).

Prognostic factors for neoplastic diseases common to both genders

For the patients with a localized renal malignancy, the three main prognostic factors with respect to overall survival are disease stage, general condition and the degree of tumor differentiation. Those three independent prognostic factors were recently used to compile a nomogram concomitantly taking into account the weight of each prognostic factor in its continuity and a prognostic group classification. For localized disease, the reference treatment is surgery (radical nephrectomy or possibly partial nephrectomy as a function of tumor size and location). For already metastatic tumors, nephrectomy is considered for young patients in good general condition. Immunotherapy (interferon α and interleukin 2), which is of limited efficacy and toxic, is also restricted to patients in good general condition presenting with a limited number of metastatic sites. The recent development of drugs targeting neo-angiogenesis and certain intracellular molecules involved in carcinogenesis affords interesting prospects for patients who are not candidates for immunotherapy.

The prognoses of colon and rectal cancer have improved with the increasing use of colonoscopy. The investigation results in earlier diagnosis and, hence, treatment, and an increase in the proportion of resected tumors. Since 1990, the progress has, however, been modest. It remains too early to evaluate the benefits related to the emergence of effective adjuvant and palliative treatments. The risk of colorectal cancer is increased 2- or 3-fold for subjects presenting with a personal history of colorectal cancer or adenoma of dimension greater than 1 cm and for first degree relatives of subjects with colorectal cancer. The risk is also high in the event of ulcerative colitis or Crohn's disease that is extensive at the time of diagnosis. The risk is very high in the event of hereditary forms of the disease (familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC)). In such families, almost 1 person out of 2 will present with colorectal cancer.

There are various histologic types of lung cancer. However, the number of histologic types or subtypes is frequently simplified to two main prognostic groups for which different management strategies are applied: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). This simple classification is used by clinicians in everyday practice. For NSCLC, the 10-year survival of patients having survived 5 years post-complete resection is estimated to be 91%. The long-term residual annual excess mortality is related to the lung cancer itself but also to the effects of related factors on the emergence of other diseases.

With regard to laryngeal cancer, studies have demonstrated differences in survival as a function of the anatomic site of the lesion. Glottic tumors have a superior prognosis to other

forms of laryngeal cancer. The poor prognosis of tumors of the proximal larynx is to be compared to that of tumors of the hypopharynx and is related to the risk factors for those tumors (alcohol abuse and smoking), which give rise to substantial comorbidity. The poor prognosis of hypopharyngeal tumors is generally considered related to late diagnosis of the disease since the anatomical site is such that symptoms emerge late. For the same reasons, the prognoses of the various sub-sites differ. Post-cricoarytenoid region tumors have a more pejorative prognosis than other hypopharyngeal sites. With regard to the oropharynx, tumors of the tonsil and tonsillar fossa have a better prognosis than those of the other oropharyngeal sites. The differences are probably due to the earliness of diagnosis and the scope for surgical treatment. The survival of subjects presenting with nasopharyngeal tumors is a function of tumor morphology. The undifferentiated forms have the best prognosis since they have greater sensitivity to radiotherapy and chemotherapy, which constitute the standard treatments given that the topography of the tumors renders surgical treatment difficult.

The predominant group (over 80% of cases) of thyroid tumors consists in differentiated tumors: papillary tumors and follicular tumors. Little differentiated tumors (about 2% of cases) and undifferentiated or anaplastic tumors (4-5%) are rarer. In addition (7% of cases), C cell-derived (secreting calcitonin, CT) tumors or medullary tumors exist. One quarter of those cases are hereditary. Early screening for familial forms results in 100% recovery. Anaplastic tumors are more frequent in subjects aged over 60 years. The prognosis is based on histologic type, age at diagnosis (greater than or less than 45 years), tumor size (greater than or less than 3 cm), local/regional status (confined or not confined to the gland), the presence or absence of lymph node metastases and the presence or absence of distant metastases. For a subject aged less than 45 years presenting with a tumor measuring less than 3 cm and that is differentiated with no lymph node invasion, lymph node metastasis or remote metastasis, the 20-year survival is 100%.

The increase in the incidence of melanoma is essentially due to superficial melanomas of limited thickness. They thus constitute a markedly preponderant subgroup of 'thin' melanomas (< 0.75 mm) whose behavior is characterized by weak progression. The prognostic factors that intervene during the course of melanoma are essentially the prognostic factors for recurrence. The recurrence rate is estimated to be between 3.3 and 7.2%. The distribution of the recurrence sites is substantially the same for the 'thin' melanoma group. However, the 10- and 15-year survivals for melanoma < 0.75 mm and those from 0.75 to 1 mm are very slightly different but greater than 90%.

Therapeutic progress has strongly influenced the survival associated with malignant blood diseases. However, the results for acute lymphoblastic leukemia in adults are not as good as those obtained in pediatric settings. While the relapse-free survival rate is not satisfactory, a plateau is nonetheless observed. In young adults, no excess mortality is observed after 5 years of complete remission. Similarly, for acute myeloid leukemia, after year 3 post-diagnosis, the risk of death appears negligible irrespective of disease stage at the time of diagnosis. The impact of treatment on survival is a function of two factors: age (greater than 70 years, treatment is only symptomatic) and cytogenetic status A non-negligible contingent of patients presenting with chronic lymphocytic leukemia is characterized by a life expectancy equivalent to that of controls of comparable age. The immunoglobulin gene mutation rate and karyotype anomalies are now accepted as major prognostic criteria which predominate relative to the clinical stage of leukemia alone. Currently, the annual excess mortality associated with chronic myeloid leukemia remains high remotely from diagnosis due to the transformation of CML into acute leukemia. Recent therapeutic progress (tyrosine kinase inhibitors and other drugs) will markedly change the prognosis.

The long-term risk of developing a second malignancy after Hodgkin's disease for patients treated with radiotherapy with or without chemotherapy is taken into account in the new therapeutic strategies. The analyses of the cases of late deaths - essentially malignancies and coronary artery disease in the irradiated field - have enabled modification of the modalities of radiotherapy for the treatment of localized forms. The size of the field irradiated and the doses delivered have been reduced. Over the last 2 years, ongoing clinical trials have investigated abstention from radiotherapy for forms with a good prognosis.

The WHO classification recognizes several types of non-Hodgkin's lymphoma. The time courses of the lymphomas differ. A prognostic index defined in terms of three risk factors (clinical stage, general condition and lactate dehydrogenase level) constitutes a predictive model that is particularly significant in the short term for the outcome of patients presenting with aggressive lymphoma. The advent of new drugs in combination with chemotherapy has enhanced short-term survival. In Burkitt's lymphoma, recurrences occur early, generally during the 3 years post-completion of treatment. After that period, the annual excess mortality is negligible. In the treatment of indolent B-cell lymphoma, which frequently affects the elderly, the introduction of monoclonal antibodies will contribute to improving survival rates. T-cell lymphomas (with the exception of anaplastic lymphomas) are associated with a worse prognosis than B-cell lymphomas.

Repercussions of childhood cancer on adult survival

Childhood cancer is rare (less than 1% of all cancers). Therapeutic progress over the last 30 years now enables recovery in over two thirds of cases. Thus, in France, it may be currently considered that one person out of 850 aged from 20 to 45 years has survived a childhood cancer. The total is over 25,000 people. The most frequent childhood neoplastic disease is leukemia: 450 incident cases are reported each year. Brain tumor ranks second in frequency with about 300 new cases per year. Lymphoma ranks third with about 190 cases per year. Non-Hodgkin's lymphoma accounts for 56% of those cases and affects children toward the age of 2-3 years while Hodgkin's disease emerges later, with increasing incidence, particularly after the age of 10 years. Among the solid tumors, embryonal tumors predominate and occur in the first years of life. Bone and soft tissue sarcomas are rarer and occur in older children.

The Eurocare data on childhood cancer show survivals with a maximum follow-up duration of 7 years. The annual excess mortality fell from over 10% to about 1% 7 years post-diagnosis. As early as the 4th year, the annual excess mortality was 2%.

Three studies (American, Scandinavian and Dutch) have addressed late mortality up to 25 years post-childhood cancer diagnosis. The annual excess mortality was very low: less than 1% after 5 years.

In the 3 studies, the mortality was due to:

- recurrence of the initial cancer in 70% of cases (particularly in settings of leukemia, and brain or bone tumor);
- a second cancer, in 10 to 12% of cases;
- treatment sequelae, in 10% of cases;
- other causes unrelated to cancer, in 10% of cases.

Given the therapeutic progress achieved in recent years and demonstrated by the improvement in 5-year survival, it is likely that the late relapse rate is also falling for patients

treated most recently. With regard to the occurrence of a second malignancy, several studies show that the risk is mainly related to radiotherapy. However, in leukemia, for instance, the systematic cerebral radiotherapy used to prevent meningeal relapses is no longer practiced. In Hodgkin's disease, radiotherapy is increasingly less used and the irradiated fields are becoming smaller and smaller. This should decrease the risk of a second malignancy in recently treated patients.

In conclusion, the annual excess risk remote from diagnosis (10 years) was estimated to be close to 2% for all forms of cancer taken together. For certain neoplastic diseases diagnosed at the localized stage, the excess risk is nil as of the first years. Given therapeutic progress, the excess risk related to the long-term complications of old treatments should decrease further in coming years.

The regular updating of survival data by the French cancer registries and the incorporation of certain prognostic factors in the population studies are decisive with respect to further enhancing the survival estimates in response to the concerns of patients and healthcare professionals.

Communications

Insurability of ex-cancer patients

Among the difficulties confronting patients having received treatment for cancer, the problem of insurability is a particularly adverse experience. The person is the victim of a dual injustice: that of having been sick and that of being unable to resume social and professional life.

Insurance is indispensable in order to obtain a mortgage. The ideal is to be able to obtain group insurance, hitherto almost always refused, if the applicant has received cancer treatment.

Certain individual insurance policies particularly address the exacerbated risks, among them those due to health problems.

Even if the application is accepted, all the difficulties are not solved: higher premiums are usual and the differences between the amounts charged are striking, since each insurer is free to do as they wish.

The Belorgey Agreement was set up in order to attempt to overcome those difficulties.

The Belorgey Agreement

The Belorgey Agreement was signed in September 2002 after 4 years of preparatory work.

Follow-up commission

The follow-up commission is responsible for ensuring that the agreement progresses. The commission's work is based on the data supplied by the scientific section and mediation section.

Scientific section

The scientific section consists of 8 members of whom 4 represent the users and 4 physicians. The section collects and studies the data available on the mortality and morbidity associated with the various diseases. Those data are used to determine the additional premium rates for higher risks or to justify rejection.

The section's objectives consist in demonstrating the consequences of therapeutic progress with respect to the risk of mortality. The basis consists in the statistics on the duration of life after initial treatment. These are the basic tools of insurance physicians and, in particular, actuaries. However, the estimates are still too frequently based on statistics that are not up to date and do not take into account recent progress.

Moreover, while the higher premium rates are calculated using mortality tables (estimate of the number of people alive from birthday x to date x+n), there are marked differences between insurers with regard to the additional premium rates. Insurers are currently free to determine those rates themselves. However, the insurers only have old statistics available.

Thus, if the risk is considered too great (which is the case for metastatic cancer), the application will be rejected. However, in many cases, either the rejection is unjustified or the additional premium is disproportionate.

The objectives of the scientific section are thus to propose scientific arguments to the follow-up commission, enabling relaxation of the conditions of the current Agreement and harmonization of the additional premium rates imposed on treated patients free from signs of progression.

The Scientific Commission has devoted several sessions to the time course of risk for various cancers in order to stress the improvements achieved with regard to certain disease sites: testes, certain lymphomas, acute leukemia, thyroid and breast. To do so, it has called in the appropriate experts.

Progress targeted

One of the objectives is to ensure that 'any patient who has been treated for a cancer in the preceding 10 years, has been perfectly followed up as per the rules prescribed by the specialists and who presents with no sign suggesting recurrence can be considered exposed to the same risk as that to which a person never having had cancer is exposed'.

In order to do so, long-term recurrence-free survival statistics are indispensable. The frequency of cancer recurrence is at its highest in the first 5 years. Subsequently it falls gradually. After 10 years, the risk is, if not nil, at least minimal.

However, malignancies differ in their time courses. A few rare cases of late first relapse are known to exist, particularly in certain forms of breast cancer, follicular lymphoma or prostatic cancer. However, no statistics in other terms, statistics of the long-term relapse-free duration of life for the various cancers are available. In addition, if the insurer agrees to insure, an additional premium is generally imposed. The additional premium rates vary markedly between insurers.

Up-to-date and precise statistics would enable greater transparency in premium rates to be demanded.

The problem of the risk of invalidity

Hitherto, only the risk of death was considered. In this context, the follow-up Commission has been apprised of the strong demand from patient associations to enlarge the coverage of risks related to mortality to risks related to invalidity.

Before any discussion is possible, it is indispensable to procure objective data enabling evaluation of the feasibility or the conditions of application of such an enlargement.

For that reason, given the economic arguments advanced by insurers, we will initially restrict our work to third-level invalidity, i.e. with total loss of independence. The statistics forwarded by the health insurance organization (CNAM) are difficult to interpret. A group of scientific experts could also address the problem.

Dr. Françoise May-Levin
National league against cancer, Paris

About breast cancer

The title of this expert report expresses an essential issue for patients suffering from cancer of the breast or other organs. What time? How much time?

In what follows, we will attempt to describe: the image of the disease, cancer, the times of cancer and its psychological and social repercussions.

The aim of this expert report may be considered the elucidation of a temporal experience in the specific context of cancer. The specificity of breast cancer resides in the organ affected and its symbolism in female life: femininity, sexuality, maternity. Above all, however, breast cancer is a cancer.

The word cancer has a social meaning and image which take little account of the very great variability of the different diseases covered by the term. However, the symbolic value of the word is considerable.

A woman said: 'Do not call my tumor a cancer. I'm not scared of the cancer; it's the word that is horrible: unemployment is the cancer of society, gangs are the cancer of the suburbs, the word cancer is an evil metaphor.' As is often the case, the patient's words are highly enlightening. The connotation of the word will impregnate the patient's entire trajectory. It would appear that the word is little sensitive to therapeutic progress. The information on that point remains inadequate.

For all women, there is an immediate repercussion of the diagnosis of cancer on the person who is suffering from it. Despite the real therapeutic progress, the word cancer evokes fear of death, mutilation and suffering. Mastectomy, while only conducted in 30% of procedures, remains associated with breast cancer. The image is frightening. The fear of the treatments necessary to combat the disease may be as great as the fear of the disease itself. The consequences on sexual, genital, affective and professional life of the disease site are patent. The woman's very self-image is threatened. The woman frequently feels more altered in her own eyes than in those of her loved ones. This may increase relationship difficulties. A great deal could be said about certain affective breakups sometimes unconsciously provoked by a woman who can no longer stand herself and flees her partner: 'My husband wanted to make love; I can't stand the fact that he loves me the way I am; it means that he didn't love who I was before.' The feeling of self-betrayal exacerbated by the great significance of the organ affected, results in a feeling of betrayal by others and makes relationships more difficult.

The diagnosis of cancer constitutes a trauma, which each subject has to confront with her own psychological structure and history. This explains the variable individual responses to the same situation in terms of the disease. There is always a fracture in mental and psychological function. According to Norbert Bensaïd, recovering 'is becoming otherwise the same.'

Addressing the times of cancer

With a view to investigating the after-cancer, it would appear of value to address the times of cancer.

The cancer diagnosis moves the subject into a time that is no longer hers: the time of cancer has been well studied by Marie Ménoret[7] (1999). The association of the words 'long term' and 'prognosis' already contains the ambiguity of the situation confronting the patients. Their life expectancy depends on a destiny that has been sealed by the cancer and is symbolically interrupted. The patients lose the feeling of invulnerability which is the basis for our internal security, what psychoanalysts call our narcissism. Man is conscious that he will die, but the knowledge remains hypothetical and can be displaced in time, which we all have the illusion that we can control. Cancer abruptly shatters those certainties and, above all, our feeling of inner freedom. 'Why is my life expressed in terms of survival while yours is not?' The question full of anger and complaint clearly expresses what subjects experience when they are forced to know what each of us rejects: they are mortal, held in a limited timeframe. The time of cancer is not that of other mortals.

To studying patients over the long term is thus to enter a universe where the words 'time', 'term' and 'death' associated in the subject's mind do not have their usual resonance.

This feeling is exacerbated by what we may term hospital time: repeated constraints and post-treatment follow-up. The hospital time further exacerbates the feeling of not being master of one's own time or of one's own choices.

This experience of a different time is to be taken into account in the patients' assessment of their quality of life. The experience changes the perception of the effects of the disease and treatment. These changes in temporal experience take on different meanings: for certain patients, each year lived is a gift they appreciate all the more for their future being threatened; for others, the simple idea of not being in control of their destiny is a wound that cannot be healed. Such reactions are not always a function of the prognostic reality.

Of course, the structure of the personality and the personal and familial history before the disease intervene in how each individual reacts to the diagnosis of cancer. Two examples are illuminating:

- that of families at high genetic risk in which the disease is experienced, irrespective of the information given, as a function of a genetic status that freezes affective experience. The experience is very difficult or even impossible to modify using scientific arguments. Independently of the risk, women who have had the experience of breast cancer in their family will be largely dependent on that experience even if there is no true genetic risk;
- that of persons already strongly affected in their personal or family life: frustration or early bereavement, other diseases, immigrants or war victims.

Of course the 'evil' image of cancer is strengthened by the impairment of body image induced by the disease and frequently by the treatments. The example of breast cancer is, of course, an archetypal form of mutilation of an organ in which we invest heavily, symbol of beauty, femininity, sexuality and, of course, linked to fecund and nourishing maternity. Even before surgery, breast cancer is already a violent assault on the woman's self-image, on the role of her breasts in her erotic, social and professional life. There are variations linked to the social representation of the woman; the role of the feminine image in society: mastectomy is more readily accepted in the Netherlands than in France.

Obviously, surgery, even though it induces less and less mutilation, gives life to the anxiety related to the diagnosis. The complementary treatments: radiotherapy and chemotherapy will also constitute assaults on the woman's self-image. This, of course, calls into question the woman's self-image and the importance attached to her appearance. The same applies to affective and professional life: if that life is successful, external support exists; if affective

[7] MENORET M. Les temps du cancer. Editions du CNRS, 1999

problems preceded the cancer, the latter will exacerbate them. Due to the mean age of the women affected, the solitude of some unmarried, widowed or divorced women, who have frequently retired, may make management difficult. Some women who would never have had children will not be able to bear cancer 'preventing them from having children'. For others, a violent desire for a child is a way of wishing to 'repair' the assault of cancer on their body. From the exterior, some observers are surprised by the violence of the trauma constituted by baldness, even temporary baldness. For others, the stake, survival, or even recovery, justify those treatments since their effects are reversible. The traumatic effect of the accumulation of losses should never be forgotten.

Breast cancer: a crisis in any woman's life

Experience shows that many patients resume a 'normal' life. Medical progress has greatly contributed. But the woman will never be 'as she was before'. The discovery of human fragility is never devoid of effect, but many patients say that they are able to envisage their lives in another manner; they know what their life is worth. They have discovered their loved ones, professional relationships and the solidarity which they ignored, even between patients. Changes in orientation and choices that one did not authorize oneself may now be made.

The resilience studied by Cyrulnik is also present in cancer, as he has described it for children. Women will reestablish themselves better if they are supported by a 'helpful' encounter. The caregivers play a capital role: a physician who is supportive; a nurse who knows how to talk to her patient; the discovery of psychological interviews enabling elaboration of the trauma and restitution of a psychological continuity that is always severely shaken by cancer.

The associations enable us to meet with those women who feel themselves different or even enriched by their experience of the disease, if it has enabled them to make progress towards 'another' or even a better manner of envisaging their lives. Research in that context would appear of capital importance:

- in order to evaluate, over the long term, the adverse effects, handicaps and effects of treatment, particularly hormone therapy, on physical and psychological health;
- in order to evaluate the social and professional difficulties and financial handicaps;
- in order to evaluate the consequences on family life by truly taking into account personal history and the couple's history.

It is of capital importance to be able to determine the effects of the disease 'cancer' and its treatments. Instruments that enable connection with all those women must be found. The negative effects of breast cancer are better known than the satisfactory outcomes. It is, however, just as important to evaluate the latter.

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Quality of life and cancer - A survey by *Jeunes Solidarité Cancer*

The first General Proceedings for cancer patients organized by the French National League against Cancer (LNCC) in 1998 and 2000 showed the precarious conditions of people affected by cancer. Following the meetings, *Jeunes Solidarité Cancer* (JSC, Young People Solidarity Cancer), an association of young adults having confronted cancer was formed and took off with the vocation of breaking the isolation of young patients and creating links for mutual assistance.

Jeunes Solidarité Cancer against the precariousness related to cancer

The combat against the precariousness related to cancer and to the age of people affected is one of the actions of *Jeunes Solidarité Cancer*[8]. The association's objective was to quantify and qualify the difficulties related to the social, economic and familial precariousness and the difficulties encountered in beginning and resuming professional life. With that aim, a survey intended to map, as accurately as possible, the everyday experience of patients or former patients of all ages and both genders having experienced all types of cancer, was implemented by JSC. The Quality of Life and Cancer survey (EQVC) was implemented using the questionnaires of the *AIDES* (AIDS) and *Vaincre la Mucoviscidose* (cystic fibrosis) associations in order to compare the results, differences and similarities between the diseases in a joint effort. The League against Cancer and the Ministry of Health and Social Protection were partners in the study.

The EQVC survey addressed people who had or had had cancer aged between 15 and 60 years. The survey was circulated through the JSC (on the website) and made available on association stands during healthcare professional congresses (Eurocancer, congress of psycho-oncology, congress of the *Société Française d'Hématologie*, *Biennales Monégasques*, *Salon Infirmier*). Several associations and organizations were partners in circulating the survey: the National League against Cancer (intranet site and via its 103 committees), *Europa Donna, Vivre comme avant, Psychisme et Cancer* and the French National Federation of Cancer Centers.

The JSC association presents herein the principal results of the EQVC survey. The results are available from the association website[9] and will be published shortly.

A few key figures relating to the respondents

In all, 152 questionnaires were analyzed for the EQVC survey. A majority of women, 80.9%, responded to the survey vs. 19.1% men. The mean age[10] of the respondents was 41 years. This figure is to be distinguished from the mean age of cancer onset which is 65 years.

[8] http://www.jscforum.net/

[9] http://www.jscforum.net/docs/QualiteVieEtCancer.pdf

[10] Person's age at the time of cancer diagnosis and not at the time of responding to the questionnaire.

The most strongly represented cancers were breast cancer (50.7%), leukemia and lymphoma (12.8%) and Hodgkin's disease (7.4%). The high percentage of breast cancers was in part due to the number of respondents in the breast cancer patient associations. Leukemia, lymphoma and Hodgkin's disease are, unfortunately, frequent neoplastic diseases in young people. The latter responded massively to the survey.

Male respondents were mainly found to live alone because they were single (27.6%) or widowed or divorced (10.3%) while the female respondents were married or living as a couple (65.6%).

Economic and social situation

For many people suffering from cancer, material distress is suffered in addition to the physical and psychological distress induced by the neoplastic disease: that was the case for 35.2% of respondents who reported that they had encountered financial difficulties. The disease too frequently induces partial or total loss of resources while expenses remain. The situation forced 8% of the respondents to ask their close family or friends for help. Financial aid was necessary for 35.2% of respondents. The aid was difficult to obtain for 72.3% of them. Requests to associations are only formulated by 22.2% of respondents in financial difficulty.

In addition to the financial precariousness, there is social precariousness. The access to social rights (social services, replacement revenues, solidarity allocation, home help, etc.) constitutes a recurrent problem, in particular for those aged less than 35 years at the time of diagnosis. Home help service was refused for 20.8% of them despite their need for help in everyday activities (washing, shopping and cooking).

Living with cancer

From the diversity of the neoplastic diseases cited and the treatments they require, shared problems emerged: sequelae, drugs and reimbursement, changes in projects and relationships, etc.

Physical and/or psychological sequelae related to cancer were experienced by 78.5% of the respondents. Permanent fatigue, both physical and psychological, was the most frequently cited (59.2% of respondents). Pain was reported by 14.8% of the respondents. The fatigue and pain are as much adverse effects as sequelae of cancer. The risk of sequelae was indicated in medical information to 62.7% of respondents. However, in 40% of cases, the sequelae did not undergo medical management.

Non-reimbursed or partially-reimbursed medications are frequently prescribed after the treatments administered: vitamins, trace elements, tonics, laxatives, dietary supplements, moisturizing and protective creams, lubricants, ocular antiseptics, osmotic diuretics, dressings, wigs, bra for prosthesis. Many of the medications or services are only considered to procure 'comfort' although they treat the real deficiencies suffered by the patient depressed by treatment. In all, 33.8% of the respondents were prescribed non- or partially-reimbursed drugs. The mean cost of those prescriptions was €70 per month.

In addition, after the disease, personal projects were seriously compromised for 72.5% of respondents. Similarly, the family situation undergoes change: 25.7% of respondents reported experiencing changes (separation, deterioration followed by improvement in a relationship, strengthening of the couple, etc.) and 84.2% of them considered cancer responsible for the change.

The change in the couple's sexuality was very marked and was common to all subgroups. One figure in itself clearly indicates this finding: 60.2% of the respondents regretted a loss of desire resulting in a decrease or even absence of sexual relations.

Relationships with friends are also changed: 33.3% of respondents—of whom 55.8% aged less than 35 years—lost friends. The concept of friendship in that age group is already unstable and most frequently cannot withstand the disease. This phenomenon leads the young patient to ponder the nature of their friendly relationships and to forge new friendships born of the disease and no doubt more lasting.

Professional situation

Several factors seem to condition the return to work of cancer patients, namely: age, gender and state of health.

Age appears to influence the maintenance of, or return to, employment more strongly in the respondents aged less than 35 years (49.1%) than in the overall responding population (42%). The percentage of respondents looking for work was highest among those aged less than 35 years: 9.4%. Paradoxically, 34% of the 76.5% respondents did not encounter difficulty finding work despite their medical history. The percentage recruitment on unlimited-duration employment contracts was lower for those aged less than 35 years (48%) than for the overall respondent population (60%), while short-term employment was more frequent (20 vs. 11.7%). Age also influenced the overall duration of working life: 52.3% of those aged 25-34 years had worked less than 10 years. Thus, the under-35s were at a disadvantage in the calculation of various social services (daily indemnities, invalidity pension). That age group was less refractory with regard to telling their prospective employer about their disease at the time of hiring (26.3%) than those aged 35 years and over (12.5%). Similarly, the group aged less than 35 years more readily informed the occupational physician during the hiring consultation than those aged 35 years and older (42.1 vs. 8.3%).

Gender influences the problems of work discrimination. Men report discrimination more frequently than women (33 vs. 17%). Physical and psychological state of health was decisive at all levels. It determined the choice or ability to work or not. State of health was largely responsible for the professional difficulties encountered by 44.6% of respondents and directly influenced the working conditions negotiated for 41.8% of them. While work is obviously a factor in resuming a normal life, it was no longer a priority for 15% of respondents, who were not looking for work but placing the accent on their personal life or opting for voluntary work.

In conclusion, the EQVC survey is a contribution to taking stock of patients' needs and expectations in order to improve their quality of life during and after treatment. In short, this survey paints a rather mixed picture of life with cancer characterized by inequalities and the patients' strong expectations with respect to the medical profession, working world and public authorities. This survey needs to be repeated on a wider scale and refined.

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Cancer mortality in the European Union and the situation in France

The objective of this communication is to analyze the weight of cancer mortality in the European Union (EU) and characterize the particular situation in France (Jougla *et al*., 2003)[11]. The analysis is based on the 1999 mortality data for the EU (15 members)[12] available from Eurostat in the form of a list summarizing the initial causes of death (including 18 sub-categories for cancer). The indicators used are the number of deaths, the EU population age-standardized mortality rates (all ages and less than 65 years) and the between-gender mortality ratios. The short-term trends (1994-1999) are also analyzed.

The leading cause of premature death in the European Union: cancer

Cancer mortality accounts for a quarter of the total annual mortality in the 15 countries of the EU (960,000 cancer deaths per year). Among the premature deaths (before age 65 years), cancer death accounts for 37% (261,000 deaths). Cancer constitutes the leading cause of premature death. Cardiovascular mortality ranks second.

An overall improvement in the EU mortality rates (tables I and II) occurred for most disease sites from 1994 to 1999. The most marked progress was observed for stomach cancer (both genders), bladder and kidney cancer (men) and uterine cancer. In contrast, the European mortality rates increased for two forms of cancer: lung cancer in women and cutaneous melanoma in men. For the deaths of males before age 65 years, the reduction in rates was a little more pronounced than for all ages taken together irrespective of the anatomical site. For women, the rate reduction was of the same order for premature deaths and for all deaths. However, marked progression of female mortality before age 65 years due to lung cancer and upper aero-digestive tract cancer was observed.

[11] Thanks to the *Bulletin Épidémiologique Hebdomadaire* for authorization to reprint the article: JOUGLA E, SALEM G, RICAN S, PAVILLON G, LEFEVE H. *Disparités de mortalité par cancer dans l'Union européenne*. *BEH* 2003, 41-42: 198-201.

[12] For data on the 25-member European Union, cf. Boyle and Ferlay, 2005.

Table I: Cancer mortality rates for the European Union and France[1]: males

	All ages					< 65 years				
	EU 1999	Fr 1999	Fr/EU 1999	Change[2] 94/99 EU	Change[2] 94/99 Fr	EU 1999	Fr 1999	Fr/EU 1999	Change[2] 94/99 EU	Change[2] 94/99 Fr
Lung	70.9	74.4	1.05	-9%	-4%	29.4	38.6	1.31	-11%	-4%
Colon-rectum	26.8	26.9	1.00	-4%	-1%	8.4	7.7	0.92	-6%	-4%
Prostate	25.7	27.8	1.08	-7%	-7%	2.5	2.5	1.00	-7%	-14%
Hemolymphatic tissues	18.2	19.2	1.05	-1%	-1%	7.4	7.5	1.01	-5%	-1%
Upper aero-digestive tracts	16.3	26.2	1.61	-7%	-13%	9.8	17.3	1.77	-8%	-13%
Bladder-kidney	15.9	16.9	1.06	-11%	-3%	4.4	5.4	1.23	-15%	-5%
Stomach	14.8	10.2	0.69	-19%	-15%	5.0	3.5	0.70	-17%	-5%
Pancreas	11.0	11.7	1.06	-1%	+2%	4.5	4.9	1.09	0%	+2%
Liver	10.8	16.7	1.55	-1%	-2%	4.0	6.5	1.63	-5%	-3%
Skin melanoma	2.4	2.2	0.92	+4%	+5%	1.4	1.4	1.00	0%	+8%
Other	41.5	51.1	1.23	-3%	-9%	17.5	24.3	1.39	-5%	-10%
Total	254.3	283.3	1.11	-7%	-6%	94.3	119.6	1.27	-8%	-6%

[1] Standardized rates per 100,000 people, EU population; [2] (1999 rate - 1994 rate)/(1994 rate)

Table II: Cancer mortality rate in the European Union and France[1]: females

	All ages					< 65 years				
	EU 1999	Fr 1999	Fr/EU 1999	Change[2] 94/99 EU	Change[2] 94/99 Fr	EU 1999	Fr 1999	Fr/EU 1999	Change[2] 94/99 EU	Change[2] 94/99 Fr
Breast	27.9	28.5	1.02	-9%	0%	17.2	18.0	1.05	-10%	+1%
Colon-rectum	16.8	15.2	0.90	-8%	-4%	5.6	4.9	0.88	-7%	-4%
Lung	15.8	11.3	0.72	+5%	+26%	7.7	6.6	0.86	+10%	+38%
Hemolymphatic tissues	11.8	11.7	0.99	+1%	-1%	5.0	4.5	0.90	-4%	-8%
Ovary	8.3	7.9	0.95	-7%	-2%	4.5	4.1	0.91	-8%	-5%
Pancreas	7.5	6.9	0.92	+1%	+10%	2.5	2.5	1.00	0%	+19%
Stomach	6.9	4.0	0.58	-19%	-15%	2.4	1.3	0.54	-14%	+8%
Uterus	6.7	7.0	1.04	-13%	-9%	3.6	3.5	0.97	-12%	-15%
Bladder-kidney	4.9	4.7	0.96	-6%	+2%	1.5	1.4	0.93	-6%	0%
Liver	3.8	3.4	0.89	-3%	+3%	1.2	1.2	1.00	0%	0%
Upper aero-digestive tracts	3.6	3.5	0.97	0%	+3%	1.8	2.1	1.17	+13%	+5%
Cuteaneous melanoma	1.6	1.6	1.00	-6%	0%	1.0	1.0	1.00	-9%	0%
Other	27.3	25.7	0.94	-5%	-9%	10.6	10.5	0.99	-9%	-7%
Total	142.9	131.4	0.92	-5%	-1%	64.6	61.6	0.95	-6%	+1%

[1] Standardized rates per 100,000 people, EU population; [2] (1999 rate - 1994 rate)/(1994 rate)

Differences between male and female mortality rates

Male excess cancer mortality was observed in all countries (table III) but the between-gender differences were greatest in Spain and France (mortality rate 2.2-fold higher for men). With regard to disease site, tumors of the upper aero-digestive tracts and lungs gave rise to the greatest male excess mortality (4.5 for the entire EU). Between 1994 and 1999, the male excess mortality remained stable except for lung cancer and upper aero-digestive tracts tumors for which the gap between men and women became smaller.

Table III: Male/female cancer mortality rate ratios for the countries of the EU[1]; all ages; 1999

	Total[2]	Upper aero-digestive tracts	Lung	Liver	Kidney-bladder	Stomach	Colon-rectum	Hemolymphatic tissues
Spain	2.3	9.1	12.0	2.7	5.1	2.3	1.8	1.6
France	2.2	7.5	6.6	4.9	3.6	2.6	1.8	1.6
Italy	1.9	4.8	6.5	2.7	4.6	2.2	1.7	1.6
Belgium[3]	1.9	4.8	6.3	2.1	3.1	2.2	1.5	1.7
Greece	1.9	3.3	7.3	2.3	4.3	2.3	1.3	1.6
Portugal	1.9	7.1	6.4	2.9	3.4	2.1	1.8	1.3
Luxemburg	1.8	3.2	3.7	4.1	2.7	2.1	1.3	2.0
Finland	1.7	2.8	5.1	1.9	2.9	2.1	1.6	1.5
The Netherlands	1.7	3.0	3.7	2.2	2.8	2.4	1.5	1.5
Austria	1.6	4.9	3.7	3.0	2.6	1.8	1.7	1.5
Germany	1.6	4.7	4.3	2.5	2.9	1.9	1.5	1.5
Ireland	1.5	2.6	2.2	2.1	2.7	1.9	1.8	1.6
United Kingdom	1.4	2.5	2.1	2.0	2.7	2.5	1.6	1.5
Sweden	1.4	3.3	1.8	1.8	2.2	2.0	1.4	1.5
Denmark[3]	1.3	3.1	1.7	1.5	2.6	2.3	1.4	1.7
EU	1.8	4.5	4.5	2.8	3.2	2.1	1.6	1.5

1 Male/female standardized mortality rate ratio; 2 Including lymphoma; 3 Estimated ratios

Between-country data comparability

Even though the methods of generating cause of death data have become increasingly standardized over time, numerous analyses have demonstrated between-country disparities in practices with respect to the level of medical certification of the causes of death and to coding (selection of an initial cause for each death).

Among the various causes of death, cancer is one of the causes for which the level of international comparability is the most reliable (compared to diseases such as cardiovascular disease or violent deaths), particularly when fairly large disease-site subgroups are used (Jougla *et al.*, 2003). Some sites are, however, associated with more recording problems than others. Lung cancer is characterized by satisfactory concordance between mortality information and morbidity information. For breast cancer, the studies based on comparison of the 'official' initial cause of death and that determined from other clinical sources points to a slight underestimation in the official statistics. For other disease sites, different recording parameters inducing comparability biases are possible. The bias may be due to the difficulty

of confirming the malignant or primary nature of the tumor (liver) or distinguishing the primary site from neighboring organs (stomach-esophagus, pancreas-bile ducts, cervix-*corpus uteri*), particularly when the clinical signs and symptoms or even the histological types are similar. Lastly, the role in the process leading to death of certain neoplastic diseases with a fairly good prognosis may be overestimated relative to the associated serious diseases (prostate and colon). In addition to those potential biases related to diagnostic difficulties or imprecision in the death certificates, the data may be affected by random fluctuations, in particular when the mortality rates analyzed for a country are low (skin melanoma, 'premature' urinary tract cancer, etc.).

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Appendix

Mortality table, years 2000-2002 (source: Insee, demographic situation)

S(x) = survivors at age x; Q(x, x+1) = mortality quotient for 100,000 survivors of age x; E(x) = life expectancy at age x

	Males			Females		
Age x	S(x)	Q(x, x+1)	E(x)	S(x)	Q(x, x+1)	E(x)
0	100,000	489	75.51	100,000	384	82.90
1	99,511	38	74.87	99,616	33	82.22
2	99,473	27	73.90	99,583	21	81.24
3	99,446	22	72.92	99,562	16	80.26
4	99,424	17	71.94	99,546	15	79.27
5	99,406	16	70.95	99,531	12	78.29
6	99,391	15	69.96	99,519	11	77.30
7	99,376	14	68.97	99,508	9	76.30
8	99,363	13	67.98	99,499	10	75.31
9	99,350	13	66.99	99,489	10	74.32
10	99,337	13	66.00	99,478	11	73.33
11	99,325	14	65.01	99,467	11	72.33
12	99,311	16	64.02	99,456	13	71.34
13	99,295	20	63.03	99,443	12	70.35
14	99,275	27	62.04	99,431	15	69.36
15	99,248	37	61.06	99,417	21	68.37
16	99,211	46	60.08	99,396	23	67.38
17	99,166	62	59.11	99,373	27	66.40
18	99,104	88	58.14	99,346	37	65.42
19	99,017	101	57.19	99,309	36	64.44
20	98,917	101	56.25	99,273	34	63.47
21	98,817	105	55.31	99,240	34	62.49
22	98,713	105	54.36	99,206	33	61.51
23	98,610	103	53.42	99,173	33	60.53
24	98,508	103	52.47	99,140	37	59.55
25	98,407	105	51.53	99,104	35	58.57
26	98,303	108	50.58	99,069	36	57.59
27	98,198	109	49.64	99,034	37	56.61
28	98,090	112	48.69	98,997	37	55.63
29	97,980	115	47.74	98,960	38	54.65
30	97,868	117	46.80	98,923	43	53.67
31	97,754	120	45.85	98,881	47	52.69
32	97,636	124	44.91	98,834	51	51.72
33	97,516	131	43.96	98,783	58	50.75
34	97,387	142	43.02	98,726	62	49.77
35	97,249	155	42.08	98,664	72	48.81
36	97,098	167	41.14	98,593	75	47.84
37	96,935	178	40.21	98,519	83	46.88
38	96,763	197	39.28	98,437	92	45.91

	Males			Females		
Age x	S(x)	Q(x, x+1)	E(x)	S(x)	Q(x, x+1)	E(x)
39	96,572	210	38.36	98,346	103	44.96
40	96,368	235	37.44	98,245	116	44.00
41	96,142	266	36.53	98,131	128	43.05
42	95,886	296	35.62	98,006	134	42.11
43	95,602	325	34.73	97,875	151	41.16
44	95,291	357	33.84	97,727	165	40.22
45	94,951	394	32.96	97,566	181	39.29
46	94,577	436	32.09	97,389	194	38.36
47	94,164	479	31.22	97,199	206	37.43
48	93,713	508	30.37	96,999	223	36.51
49	93,237	536	29.53	96,782	247	35.59
50	92,737	587	28.68	96,543	246	34.68
51	92,193	626	27.85	96,305	256	33.76
52	91,616	665	27.02	96,059	289	32.85
53	91,007	711	26.20	95,781	301	31.94
54	90,359	765	25.38	95,493	320	31.04
55	89,668	827	24.57	95,187	346	30.13
56	88,927	882	23.77	94,858	372	29.24
57	88,142	931	22.98	94,504	393	28.35
58	87,322	982	22.19	94,133	415	27.46
59	86,464	1,069	21.41	93,742	436	26.57
60	85,540	1,155	20.63	93,333	469	25.68
61	84,552	1,233	19.87	92,896	500	24.80
62	83,510	1,330	19.11	92,432	548	23.92
63	82,399	1,451	18.36	91,925	588	23.05
64	81,203	1,569	17.62	91,385	638	22.18
65	79,929	1,720	16.90	90,801	695	21.32
66	78,554	1,885	16.18	90,170	769	20.47
67	77,074	2,043	15.49	89,476	837	19.62
68	75,499	2,237	14.80	88,727	919	18.79
69	73,810	2,426	14.13	87,912	1,017	17.96
70	72,019	2,651	13.46	87,018	1,136	17.14
71	70,110	2,895	12.82	86,029	1,260	16.33
72	68,080	3,202	12.19	84,946	1,410	15.53
73	65,900	3,451	11.57	83,748	1,558	14.74
74	63,626	3,733	10.97	82,443	1,754	13.97
75	61,250	4,123	10.37	80,998	1,961	13.21
76	58,725	4,512	9.80	79,409	2,220	12.46
77	56,075	4,964	9.24	77,646	2,547	11.73
78	53,292	5,469	8.69	75,668	2,881	11.03
79	50,377	5,928	8.17	73,489	3,264	10.34

	Males			Females		
Age x	S(x)	Q(x, x+1)	E(x)	S(x)	Q(x, x+1)	E(x)
80	47,391	6,642	7.65	71,090	3,772	9.67
81	44,243	7,399	7.16	68,408	4,278	9.03
82	40,969	8,307	6.69	65,482	4,945	8.41
83	37,566	9,362	6.25	62,244	5,730	7.83
84	34,049	10,266	5.85	58,678	6,591	7.27
85	30,554	11,268	5.46	54,810	7,489	6.75
86	27,111	12,554	5.09	50,705	8,514	6.25
87	23,708	13,747	4.75	46,388	9,642	5.79
88	20,449	15,184	4.42	41,915	10,891	5.35
89	17,344	16,678	4.13	37,351	12,356	4.95
90	14,451	18,417	3.85	32,735	13,835	4.57
91	11,790	20,419	3.61	28,206	15,703	4.23
92	9,382	22,268	3.41	23,777	17,642	3.92
93	7,293	23,874	3.24	19,582	19,482	3.66
94	5,552	25,520	3.10	15,767	21,097	3.42
95	4,135	26,630	2.99	12,441	23,215	3.20
96	3,034	28,216	2.89	9,553	24,731	3.02
97	2,178	29,215	2.83	7,190	26,190	2.84
98	1,542	27,860	2.79	5,307	27,668	2.67
99	1,112	27,740	2.67	3,839	28,570	2.50
100	804	28,529	2.51	2,742	30,841	2.31
101	574	32,569	2.31	1,896	34,364	2.11
102	387	43,348	2.18	1,245	38,582	1.95
103	219	41,193	2.47	764	41,345	1.87