Collective Expert Report

Cancers

Long-term prognoses

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Inserm

Institut national de la santé et de la recherche médicale
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This document summarizes 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.

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.

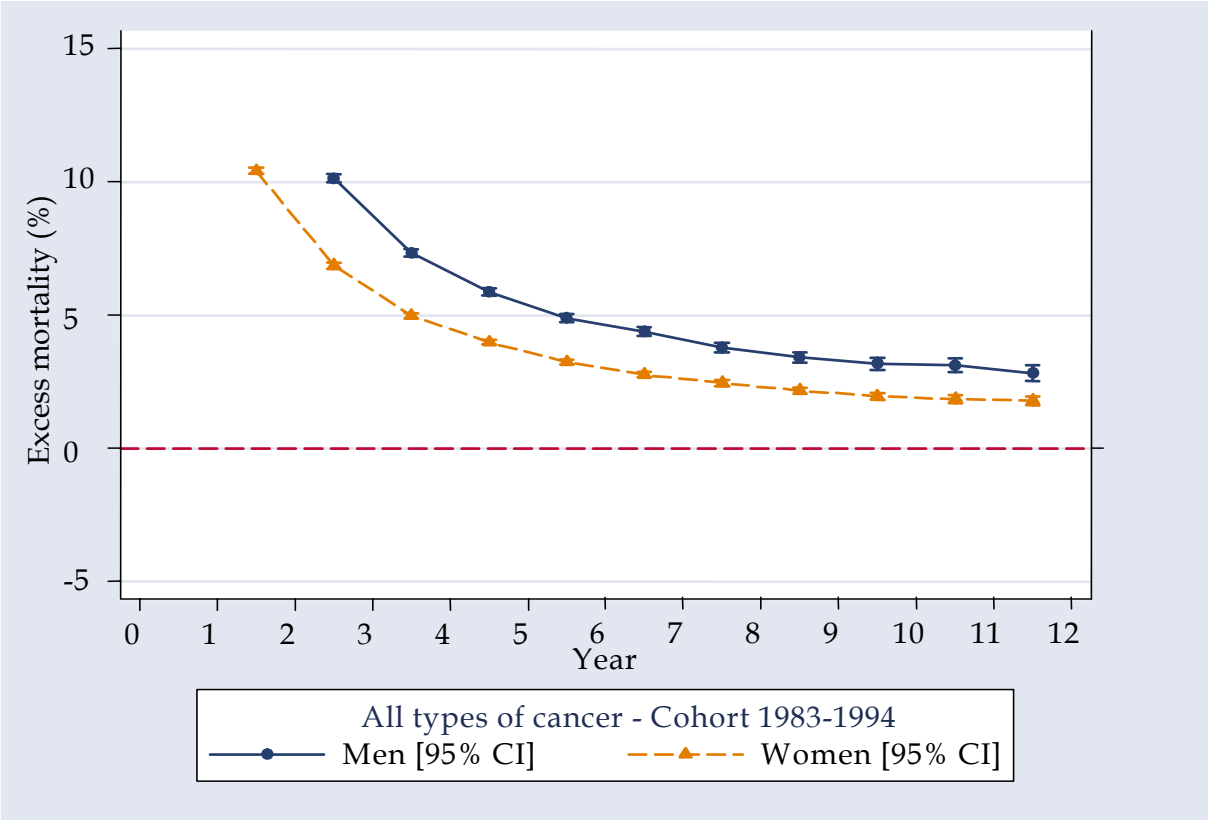
Annual excess mortality for all forms of cancer

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.