Survival in patients with cancer in European Latin countries

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1- ABSTRACT

Data on survival of cancers are of growing interest. It is a major indicator in oncology that makes it possible to determine the efficacy of a healthcare system. Cancer registries, which collect all of the cases diagnosed in a well-defined population, are an excellent tool to assess survival in cancer, without the recruitment bias of specialised centres or therapeutic trials.

The present project concerns cancer registries in European latin countries (Belgium, Spain, France, Italy, Portugal and Switzerland). The project will be conducted by the Groupe pour l'épidémiologie et l'Enregistrement des Cancers dans les pays de Langue Latine (GRELL) using the EUROCARE database (database that has gathered incidence and survival data from most European registries for more than 20 years), the team of the Biostatistics unit of the 'Hospices Civils de Lyon' will be responsible for the statistical analyses, and the national network of Cancer Registries will also be involved. For every cancer location and every country, overall survival, net non-standardised survival and survival standardised for age at 1, 3, and 5 years in patients diagnosed between 2000 and 2004 will be estimated. In addition, a detailed description of the evolution of net survival according to the period of diagnosis will be provided depending on the data available in every country. The method to estimate net survival will be based on the two methods recognised at present as being able to estimate net survival in a non-biased manner, namely: the non-parametric Pohar Perme method and the multivariate regression model for excess mortality.

2- Detailed research project

Context of the present project

General situation concerning the issue and justification for the project

Cancer is still a major problem of public health: in 2011, there were an estimated 3,500,000 new cases in Europe and the number of deaths was 1,750,000 [Ferlay 2013]. To conduct the fight against cancer more effectively, it is important for clinicians, researchers, and public health managers to have indicators to follow the evolution of cancers with regard to the frequency and the nature and quality of care provided to patients. Among the principal health indicators that should be available, at least for principal cancer sites, are mortality ENREF_1 [WHO 2008], indicators of morbidity, namely incidence ENREF_2 [Curado 2009] and prevalence ENREF_3 [Gatta 2013], and finally survival. Each of these indicators is useful in itself and in its particular field of application. However, they have proved to be extremely complementary in their construction and use in terms of healthcare surveillance. Monitoring the number of deaths due to cancer has long been the only way to know the impact of measures to fight against the disease. Nonetheless, indicators of mortality are far from perfect, and they are difficult to interpret because they result from complex phenomena that associate the evolution of incidence and survival in the previous decade. The limits of mortality indicators led to the creation of population-based registries to determine the incidence of cancers. The data on cancers provided by registries are crucial given the problem of public health caused by these diseases. The improved efficacy of healthcare systems in the field of cancers in terms not only of therapeutic management, but also screening and primary prevention relies on the development of information systems that are reliable, accurate and perennial. In this context, cancer registries are an unparalleled source of data for the wealth of high-quality scientific information they provide. They have the dual purpose of describing and monitoring cancer risk as well as conducting research from the analysis of data collected routinely or from one-off surveys.

Survival

Information on survival in cancer patients can be used to calculate prevalence, but it is also essential to know the efficacy of the management of patients with cancer. This information comes from three major types of source: therapeutic trials, hospital series and population-based studies. Even though the analysis methods used may seem quite similar, these three types of study do not have the same objectives and must be interpreted in completely different ways. Therapeutic trials provide information on the best possible survival; in contrast, population-based studies measure the mean survival obtained in the conditions at the time.

The aim of therapeutic trials (here, we are essentially speaking about phase 3 trials) is to test new treatments or novel therapeutic strategies hoping to show that they are more effective or more efficient than reference approaches. The effects of selection (small proportion of patients included, predominance of specialised centres, age limits) and the specific nature of the care in therapeutic trials explain why survival observed in trials, even that in the control group cannot be extrapolated to other patients. Hospital series and

hospital registries present a lesser degree of selection bias than therapeutic trials, but the recruitment bias and the specific nature of the care prevent the results from being generalized to the population at large. Studies conducted using population-based data, that is to say survival studies done using data collected by registries, can be used to assess the overall effectiveness of a healthcare system, that is to say both the quality of care and habits concerning the use of the healthcare system, which affects in particular the earliness of the diagnosis. Such studies can thus be used to compare different healthcare strategies by comparing, for example, survival in different countries, or the performance in a supposedly identical system by comparing survival for different populations within the same country (regions or sub-populations). These studies, when they make it possible to compare several successive periods, can also provide information on improvements in the performance of a healthcare system.

Overall survival at 5 or 10 years corresponds to the proportion of patients still alive 5 or 10 years after the diagnosis, whatever the cause of death (cancer or other cause). Though overall survival is simple to interpret, it does not reflect mortality associated with the disease in question since all deaths are taken into account, whether or not they are related to the disease. Net survival is defined as the survival that would be seen if the cancer in question was the only possible cause of death. This survival, on the assumption that we know how to assess it, is not affected by deaths unrelated to the cancer and it thus reflects mortality associated with the cancer. Net survival is an indicator defined in a hypothetical world, but in eliminating possible differences in mortality due to causes other than the cancer in question, it is the only survival indicator that can be used for comparisons between time periods or countries, as is the case in our project. Recent developments have occurred in the methodology to calculate net survival in population-based studies, and the present project will benefit directly from these.

Above, we raised the notion of mortality associated with cancer; this notion suggests that information on the cause of deaths is available. This is not the case for population-based survival studies. This information is generally recorded in clinical studies (net survival is thus estimated by so-called « specific » survival), but limitations related to the quality, reliability and the relevance of this information are quickly reached in elderly patients and in the long term. The method to estimate net survival in population-based studies does not require the cause of death to be known. Indeed, net survival is estimated from «excess mortality», which is calculated by subtracting: (i) the mortality observed in the population of persons with the cancer in question, whatever the cause of death; from (ii) the mortality due to other causes of death. The latter is assumed to accurately reflect «all-cause» mortality in the population at large. The originality of the present project lies in the fact that it will use the new method proposed by Pohar-Perme in 2012 to estimate net survival [Perme 2012]. This method provides better estimations of net survival than those obtained using classical relative survival methods («better» in that they are «non-biased»). This result was formally established by Pohar-Perme et al [Perme 2012] and confirmed by different studies conducted by the Biostatistics Department of the Hospices Civils de Lyon [Danieli 2012, Roche 2013] in the context of a joint international study supported by the Agence Nationale de la Recherche (Méthodes d'Estimation de la Survie Relative – groupe MESURE). These studies showed that classically-used relative survival methods generally overestimated net survival. This overestimation is all the greater when the proportion of the mortality related to other causes is large compared with mortality due to the cancer, therefore in elderly people and for long-term follow-up (10 years after the diagnosis) and in cancers with a good prognosis [Roche 2013]. The underlying mechanism is the impact of informative censoring induced by

other-cause mortality (such as that reflected by mortality in the population at large) on cancer-related mortality. Indeed, demographic variables that define mortality tables (age, year of diagnosis..) can also have an impact on cancer-related mortality. Other-cause mortality thus censors individuals in a non-independent manner with regard to the phenomenon studied. Two approaches now appear able to estimate net survival in a non-biased manner, since they correct the effect of informative censoring: the Pohar-Perme method (by applying weighting to every individual to counteract expected survival) and a regression model for the excess mortality rate, which includes censored demographic variables. Both of the above approaches will be used in this project as each has certain advantages and limits depending on the purpose of the analysis. The first method estimates net survival but is non-parametric and cannot estimate the impact of prognostic variables directly. Only the multivariate model can estimate this impact by providing values for excess mortality rates depending on the different modalities of a prognostic variable.

International comparisons of survival

As is the case for survival in all chronic diseases, survival in patients with cancer is one of the most reliable indicators to measure the effectiveness of care ENREF_4 [Bossard 2007]. In Europe, the first population-based studies were conducted by registries in Nordic countries and Scotland, but the most complete information on this subject in Europe is provided by the "EUROCARE project" [Berrino 2007]. This is a joint European project, started in 1988 and based on a European network of around fifty regional or national registries. It has revealed large inter or intra-national variations in cancer survival in Europe. These variations are particularly marked for cancers in which survival is highly dependent on the stage at the diagnosis ENREF_5 [Berrino 2007]. Since the publication of these results, a large-scale debate has been under way on the origin of these differences in survival, which reflect the healthcare systems in the countries concerned [Autier 2011, Beral 2010, Woods 2011]. Indeed, these differences may stem from true heterogeneity in the management of diagnostic and/or therapeutic strategies. New population-based studies coordinated at the national and international level are necessary to explain in a reliable manner the observed differences in survival.

This project will make it possible to estimate and compare net survival in European Latin countries for every cancer location. Compared with the EUROCARE project, its originality lies in the use of the most recent advances in methodology for the estimation of net survival as well the production of supplementary indicators. Indeed, as well as enabling comparisons of survival at fixed times after the diagnosis, this project will make it possible to study and to compare the dynamics of cancer-related mortality (i.e., the evolution of excess mortality according to the time since diagnosis) for each of the five years following diagnosis. Finally, this project will study how the dynamics of the mortality rates varies according to the age at diagnosis and the period of diagnosis.

Objectives

For every cancer site and for every country, the objectives of this project are:

1) to estimate net survival for the most recent period of diagnosis available (period 2000-2004). The indicators produced will be:

- overall survival and net survival at 1, 3 and 5 years according to sex and age, together with their 95% confidence intervals

- net survival standardised for age at 1, 3 and 5 years according to sex, together with its 95% confidence intervals

- The evolution of excess mortality with regard to time since diagnosis up to 5 years, according to sex and age.

2) to provide trends in net survival according to the year of diagnosis. The indicators produced will be net survival at 5 years standardized for age, for every period of diagnosis and for both sexes.

3) to show, for every age, how the dynamics of excess mortality changes according to the number of years since the diagnosis. The dynamics of excess mortality shows the intensity of mortality at every moment after the diagnosis. In cases, for example, of an improvement in net survival with time after the diagnosis, studying the evolution of the dynamics will make it possible to determine at what time after the diagnosis the improvement occurred: is it post-operative mortality that is falling or rather (for example) mortality between 3 and 5 years [Corm 2012].

In summary, we will have at our disposal a detailed description of the evolution of cancer-related mortality for every location, every country and every class of age.

Materials

Registries included

The EUROCARE database includes more than 22 million cases of cancer recorded by 116 registries in 30 European countries. The present study will bear on cancers registries in latin European countries: Belgium, Spain, France, Italy, Portugal and Switzerland. Table 1 describes the period during which cases were recorded and the date case follow-up ended (end date) for every registry taking part. Therefore, depending on the objective, the list of registries taking part will vary.

For objective 1, all of the registries of the Romance language countries that recorded incident cases from 2000 to 2004 with a follow-up until 31/12/2007 at least will take part. This will represent a total of more than 3 million cases of cancer.

For the study of trends (objectives 2 and 3), only registries with more than 10 consecutive years of recording cases of cancer will be retained for France, Italy, Spain and Switzerland. Thus 14 registries for France, 22 for Italy, 7 for Spain and 5 for Switzerland will be included. No registries in Belgium and Portugal

have recorded cancer cases for 10 consecutive years. For these two countries, only registries with the longest recording periods will be used, namely, for Belgium, the Flanders registry (covering 9 consecutive years) and for Portugal, the South Region Cancer Registry and the Azores Cancer Registry (each covering 8 consecutive years) and the North Region Cancer Registry (covering 7 consecutive years).

Collection of vital status data

The procedure to collect vital status varies from one country to another depending on the way healthcare is organised. Whatever the methodology, however, the vital status (alive or dead) is available in almost all cases.

Control of data coherence

The data necessary to reach the objectives of the study will be extracted from the EUROCARE database, which covers the period 1978-2008. It is housed at the Istituto Superiore di Sanita in Rome. This institute received data from the registries taking part using a precise protocol and a standardised procedure. Coherence was controlled by using specific requests and « IARCTools » software published by the International Agency for Research on Cancer. In cases of error or incoherence the Registries will be contacted to correct their data. The cleaned database will be transferred to the «Biostatistics Department of Hospices Civils de Lyon» which is responsible for the analyses.

Inclusion criteria

All primary tumours in patients older than 15 years will be included, including multiple tumours in the same person, as recommended by Rosso et al [Rosso 2009]. Cancers will be classified according to the «International Classification of Diseases for Oncology, 3rd edition » and only confirmed invasive or malignant cancers will be taken into account.

The data will have been rendered anonymous and contain the following items for every case of cancer: case identification number, identification of the registry, sex, date of birth, date of diagnosis, topography, morphology, date of the last news, vital status.

Thus, for objective 1, the database contains 195,838 cases in France, 631,757 cases in Italy, 139,639 cases in Spain, 52,734 cases in Switzerland, 141,556 cases in Portugal and 162,414 cases in Belgium.
For objective 2, the database contains 389,074 cases in France, 1,435,258 cases in Italy, 368,356 cases in Spain, 188,318 cases in Switzerland, 218,917 cases in Portugal and 307,290 cases in Belgium.

Mortality data in the population at large

Mortality data for the population at large will also be provided by the members of the EUROCARE project. For every registry, these data are detailed by year, sex, age (detailed in classes from 1 to 99 years old).

Methods of analysis

For objective 1, the Kaplan Meier method will be used for the estimation of overall survival, and the Pohar-Perme method [Perme 2012] will be used for net survival. Net survival will be standardised for age using weighting from the International Cancer Survival Standard (ICSS) [Corazziari 2004]. The profile for the rate of excess mortality according to the time since diagnosis will be obtained by smoothing and by deriving the cumulative rate from the Pohar-Perme method.

For objective 2, for both sexes, the period of diagnosis will be divided into periods of 3 years. For each of these periods, standardised net survival at 5 years will be estimated using the Pohar-Perme method.

For objective 3, after stratification on age, the effect of the year of diagnosis on the rate of excess mortality will be modeled using a regression model that authorises non-linear and non-proportional effects [Remontet 2007]. This will make it possible to determine whether any improvement in net survival over the years following diagnosis:

- is not «linear» (for example, if there is an improvement in net survival until a given year following diagnosis and then stagnation)

- is not «proportional» (for example, if the improvement only concerns post-operative mortality but not mortality between 3 and 5 years)

Organisation of the study

These registries are gathered together in the GRELL (Groupe pour l'épidémiologie et l'enregistrement des cancers dans les pays de langue latine), which was created in 1976. It organises an annual scientific meeting, methodology seminars, and joint research projects. The GRELL will coordinate this study on survival, under the leadership of Jean Faivre, who proposed the study.

Data for the study will be provided to the Biostatistics Department of the HCL by the Istituto Superiore di Sanita with the agreement of all of the registries taking part.
The results of the analysis will be provided by the Biostatistics Department to the coordinator who will be responsible for organizing drafting of the texts for the interpretation of the results for every location. The Directors of the national networks of registries of the countries taking part will be given the task of writing the texts.

Publication policy

It is proposed to follow the EUROCARE rules which have already been accepted by all participating registries.

The project is to publish a monography in a medical journal including at least 15 articles on the main cancer site. We expect that any cancer registry researcher willing to actively participate to a paper will have an opportunity to do so. The list of first authors in charge of writing the first version of a chapter will be established by the Scientific Committee among the list of volunteers. He will have to accept to strictly follow the time table of the project. The first author will have to provide a justification to the Scientific Committee for the name of all authors appearing separately in the authorship list. The list should be kept short (around 6 authors). All publications will mention the GRELL/EUROCARE working group with one or two members per registry listed in an appendix to the article.

Timetable

Transfer of data: January 2014

Analysis of results: January 2014- November 2014

Interpretation and drafting of comments: December 2014- April 2015

Publication: June 2015

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Tableau 1 : liste des registres participants par pays, accompagnés de la période de couverture des cas de cancer, de la date de point correspondante et du nombre de cas.

Pays	Registre	Période de couverture	Date de point	Nombre de cas
Belgique				
	Flanders	1999-2007	01/2010	307 290
France				
	Bas Rhin	1989-2004	01/2010	72 537
	Basse Normandie, HM	2004-2005	01/2008	1 461
	Calvados, noHM2004	1989-2005	01/2008	34 502
	Calvados, dig.	1989-2005	01/2008	11 398
	Burgundy, dig.	1982-2007	01/2008	31 418
	Cote dOr, gyn.	1989-2004	01/2010	5 537
	Cote dOr, HM	1980-2007	01/2009	6 100
	Doubs	1989-2004	01/2009	31 918
	Finistere, dig.	2000-2004	01/2008	5 337
	Gironde, HM	2002-2004	01/2009	2 081
	Gironde, SNC	2000-2004	01/2008	521
	Herault	1995-2004	01/2008	43 523
	Isere	1989-2004	01/2008	68 947

	Loire Atlantique, CB1997_gen	1991-2006	01/2010	59 722
	Manche, noHM2004	1994-2004	01/2008	24 370
	Marne-Ardennes, thyroid	1989-2006	01/2008	1 309
	Somme	1989-2004	01/2008	37 594
	Tarn	1989-2004	01/2008	28 092
Italie				
	Alto Adige	1995-2005	09/2010	26 941
	Biella	1995-2006	01/2009	17 493
	Catanzaro	2003-2005	12/2008	3 591
	Ferrara	1991-2007	12/2009	51 920
	Firenze-Prato	1985-2005	12/2008	161 485
	Friuli Venezia Giulia	1995-2007	12/2009	131 702
	Genova	1986-2004	12/2008	121 383
	Latina	1996-2006	12/2008	25 183
	Liguria, mesotheliomas	1996-2008	12/2008	1 951
	Mantova	1999-2005	12/2005	14 311
	Milano	1999-2006	06/2010	81 090
	Modena	1988-2008	07/2009	92 548
	Napoli	1996-2007	12/2010	23 666
	Nuoro	2003-2005	12/2007	4198
	Palermo, breast	1999-2007	01/2010	5 881
	Palermo	2003-2006	01/2010	20 962
	Parma	1978-2008	12/2008	81 330
	Ragusa	1981-2006	03/2009	30 445
	Reggio Emilia	1996-2007	12/2008	40 122
	Romagna	1986-2007	12/2008	148 054
	Salerno	1996-2005	12/2009	47 928
	Sassari	1992-2006	12/2008	34 935
	Siracusa	1999-2006	12/2009	15 168
	Sondrio	1998-2007	03/2010	12 819
	Torino	1985-2007	01/2009	121 150
	Trapani	2002-2004	01/2010	6 187
	Trentino	1995-2006	12/2009	35 513
	Umbria	1994-2008	12/2009	88 819
	Varese	1978-2004	12/2008	118 448
	Veneto	1987-2005	08/2009	251 088
Portugal				
	Açores	2000-2007	01/2007	4 820
	Northern Portugal	2000-2006	12/2008	75 864
	Southern Portugal	1998-2005	01/2010	138 233
Espagne				
	Albacete, CLBP	1991-2004	01/2010	7 800
	Basque Country	1986-2004	01/2009	164 242
	Castellón-Valencia, breast	2000-2005	12/2007	1 344
	Cuenca	2000-2004	01/2009	4 729

	Girona	1994-2007	12/2008	38 002
	Granada	1995-2005	12/2008	31 152
	Murcia	1990-2003	12/2007	51 198
	Navarra	1978-2005	12/2008	57 176
	Tarragona	1985-2005	12/2008	49 938
Suisse				
	Basel	1981-2007	12/2008	53 022
	Geneva	1978-2007	12/2009	54 114
	Grisons	1989-2007	12/2008	18 167
	St. Gallen	1988-2007	12/2008	40 499
	Ticino	2000-2007	12/2009	14 193
	Valais	1989-2007	01/2009	22 516