The BETWEEN project

Cancer net survival for between countries comparisons

SYNOPSIS

Rational

Net survival is defined as the survival which might occur if all risks of dying from other causes than the disease of interest, here cancer, were removed. Net survival is a major epidemiological indicator since it enables between countries comparisons, and is routinely estimated in many countries from data collected by cancer registries. Two approaches may be adopted to estimate net survival. The first one is the cause-specific approach, which requires knowing the causes of death. The second approach uses the all-cause mortality of the study group and the "expected" mortality of a disease-free group having the same demographic characteristics as the study group. Here, the expected mortality is assumed to reflect correctly the mortality due to other causes than cancer and is usually obtained from the general population life-tables. The mortality due to cancer is then deduced from the all-cause and other-cause mortalities. The second approach is preferred in epidemiological studies because the causes of death are often unavailable or unreliable. Within that approach, many methods have been adopted in national or international cancer-survival studies: excess-rate regression models (England and Wales, France, Spain, ICBP group) and relative survival ratio methods i.e Ederer I (EI), Ederer II (EII), and Hakulinen (H) methods (US SEER program, EUROCARE, CONCORD, Norway, Finland, NORDCAN).

Until recently, there was no clear consensus on which method to choose for point estimations of net survival from cancer registry data. Pohar-Perme *et al*[1] have recently investigated this issue and have *theoretically* shown that, generally, the previously cited methods do not correctly estimate net survival because of the so called "informative censoring mechanism" (ICM) due to other causes mortality. They identified EII estimator as the "observable net survival" which is dependant from the background mortality and thus influenced by ICM. They proposed then a new non-parametric estimator (hereafter "Pohar-Perme estimator", PPE) obtained by weighting the individual observation with their "expected" survival and showed that this new estimator was an unbiased estimator of net survival, even in the presence of the ICM induced by the life-table variables. The excess-rate regression models can also provide unbiased estimates but only if the excess mortality rate is modelled as a function that depends on all life-table variables and if these functional dependencies are

correctly specified. The model building strategy is known to be difficult and, to our knowledge, there was no satisfactory solution for routine estimation of net survival from cancer registry data for a large variety of tumour sites. Thus, up-to-now, PPE appears to be the only unbiased estimator of net survival available in this context. Furthermore, a recent simulation study pointed out the substantial biases associated with Ederer I and Hakulinen methods, with an excess-rate regression model with only the effect of time since diagnosis modelled, and, to a lesser extent, with Ederer II method[2]. In the same time, Hakulinen et al [3] published an article arguing that the Ederer II method should be adopted but the PPE estimator was not considered in that paper. Roche et al[4] have illustrated, on real data from the FRANCIM network, the magnitude of the errors made with the classical estimators used in cancer registry studies (i.e., Ederer I, Ederer II, Hakulinen, and a method derived from the strategy of Remontet *et al*[5]) when compared to PPE. Net survivals were estimated at 5, 10, and 15 years post-diagnosis. At 5 years, the errors were generally small. At 10 years, in good-prognosis cancers, the errors made in non-standardised estimates of all classical methods were generally great (+2.7% to +9% for prostate cancer) and increased in age-class estimations (vs. 5-year ones). At 15 years, in bad- or average-prognosis cancers, the errors were often great whatever the nature of the estimation. In good-prognosis cancers, the errors in non-standardised estimates of all classical methods were great, even very important. With all classical methods, large errors occurred in age-class estimates resulting in important errors in age-standardised estimates (+1.6% to +4.1% in breast cancer). Among the classical methods, the Ederer II method was the less biased. It was concluded that when estimating net survival, cancer registries should abandon all classical methods and adopt the new PPE estimator. This article was strongly criticized by Dickman et al [6] who recognized that PPE was unbiased and hoped it will be widely used, but mentioned an issue regarding a higher variance of the PPE. The fact is that the variance of PPE may be large for long-term NS estimations in elderly groups; however, this is a feature of the data and not an undesirable property of PPE[6]. Finally, despite some considerations favoring the Ederer II methods, it was unclear which method they would finally recommend to cancer registries.

In the next Eurocare V publication, the Ederer II method was used. The reasons were 1) the superiority of Ederer II method in comparison with all other classical methods and 2) some technical obstacles due to a lack of software implementation for the PP with “big dataset”. The Eurocare V study will provide net survival estimates à 5 and 10 years, and will compare these estimates between several European countries and between different periods. As mentioned before, the ICM induced by the life-table variables induces a bias in estimates.

Since this mechanism is not counteracted in the Ederer II method, consequences when comparing different countries with different background mortality may occur. However, this consequence has never been explored neither theoretically nor empirically. The Eurocare group invited the Biostatistic department of the Hospices Civils de Lyon to collaborate for a study aiming to illustrate and understand the impact of using the Ederer II method instead of the PPE method when comparing countries. The protocol outline is presented here.

Aims

1 - To explore if there is any systematic enhancement or shrinkage of geographical differences using EII instead of PPE.
2 - To explore how significant survival differences between two countries become non significant (and vice-versa), when using EII instead of PPE.

These aims will be achieved using mathematical/simulation tools. Additionally, these two aims will be empirically illustrated using EUROCARE data.

Obviously, the magnitude of this impact should not give any argument to support the use of EII instead of PP.

Methods

As demonstrated by Pohar Perme et al, EII is an estimator of the observable net survival (ONS) whereas PP is an estimator of the true net survival (NS), which is the desirable quantity to estimate.

1- For the objective 1, we will calculate the theoretical difference between NS (PP) et ONS (E2) according to:

- the design (ie distribution of age)
- the excess mortality rates
- the expected mortality rates

Then, the impact of this theoretical difference in terms of geographical comparisons will be studied. This last point will be illustrated in the « real life » using EUROCARE survival data.

2- For the objective 2, we will compare NS1 and NS2 (corresponding to NS of two different countries) - under the null hypothesis H0 : NS1=NS2 and under the alternative hypothesis H1 : NS1≠NS2 and we will explore the error committed when the analysis in based on E2 instead of PP. Specifically:

Firstly, simulating data under H0, we will calculate how many times H0 is rejected when using a test based on E2 estimator (beyond the alpha risk allowed). This will answer the question « how many non-significant survival differences between countries become significant when using E2 instead of PP ».

Secondly, simulating data under H1, we will compare the power of statistical tests based on E2 and PP estimators (for similar alpha risks). This will answer the question « how many significant survival differences between countries become non significant when using E2 instead of PP ».

This objective 2 cannot be achieved with studies of real data. Thus, we will perform a simulation study in which several scenarios will be considered regarding the parameters that may influe the result (ie the distribution of age, the differences between the 2 country of the excess rates and of the expected rates).

Simulation study allows to assess the performance of a statistical test in a more objective way than in an extensive application to empirical data, because in simulation study the truth is known, which is never the case in empirical data.

Then, the impact in the « real life » using EUROCARE survival data will then be illustrated.

Material

Empirical comparisons will be performed using the Eurocare V database. Participating registries will have to give their authorization for the use of the following data for patients diagnosed until 2004:

- id
- registry
- id of area covered (useful to merge the corresponding expected mortality rates)
- Sex,
- date of birth,
- date of diagnosis,
- age at diagnosis,
- topography,
- morphology,
- Last known vital status
- date of last known vital status.

The participation in the study of

- Representative registries of Northern Europe (Finland, Island, Norway)
- Scotland/UK registries or Ireland
- Representative registries of Central Europe (France, Netherlands, Switzerland)
- Representative registries of Eastern Europe (Czech republic, Bulgaria, Baltic countries : Estonia)
- Representative registries of Southern Europe (Italy, Malta, Portugal, Slovenia, Spain)

will be required.

The selection criteria should take into account methodological considerations (i.e exploring different sizes of countries, different background mortality rates…).

Expected mortality rate for each country should be provided and detailed by sex, age (in 1 year age classes), year and area covered by the registry.

Cancer sites will be selected according to their prognosis and/or incidence and/or age at diagnosis. Thus, breast, prostate, colorectal, thyroid, lung cancer, Hodgkin disease, ovarian and cervical cancer are planned to be analysed.

References

1- Perme MP, Stare J, Estève J. On estimation in relative survival. Biometrics 2012; 68(1):113-120.

2- Danieli C, Remontet L, Bossard N, Roche L, Belot A. Estimating net survival: the importance of allowing for informative censoring. Statist Med. 2012;31(8):775-786.

3- Hakulinen T, Seppa K, Lambert PC. Choosing the relative survival method for cancer survival estimation. *Eur J Cancer* 2011;**47**:2202-10.

4- Roche L, Danieli C, Belot A, Grosclaude P, Bouvier AM, Velten M et al. Cancer net survival on registry data: Use of the new unbiased Pohar-Perme estimator and magnitude of the bias with the classical methods. Int J Cancer 2013;132:2359-2369.

5- Remontet L, Bossard N, Belot A, Esteve J. An overall strategy based on regression models to estimate relative survival and model the effects of prognostic factors in cancer survival studies. *Stat Med* 2007;**26**:2214-28.

6- Dickman P, Lambert P, Dickman PW, Lambert PC, Coviello E, Rutherford MJ. Estimating net survival in population-based cancer studies. Int J Cancer. 2013 Jan 22. doi: 10.1002/ijc.28041