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Original Research

Estimation of net survival for cancer patients: Relative survival setting more robust to some assumption violations than cause-specific setting, a sensitivity analysis on empirical data

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Abstract Net survival is the survival that would be observed if the only possible underlying cause of death was the disease under study. It can be estimated with either cause-specific or relative survival data settings, if the informative censoring is properly considered. However, net survival estimators are prone to specific biases related to the data setting itself. We examined which data setting was the most robust against violation of key assumptions (erroneous cause of death and inappropriate life tables).

We identified 4285 women in the Geneva Cancer Registry, diagnosed with breast, colorectal, lung cancer and melanoma between 1981 and 1991 and estimated net survival up to 20 years using cause-specific and relative survival settings. We used weights to tackle informative censoring in both settings and performed sensitivity analyses to evaluate the impact of misclassification of cause of death in the cause-specific setting or of using inappropriate life tables on net survival estimates in the relative survival setting.

For all the four cancers, net survival was highest when using the cause-specific setting and the absolute difference between the two estimators increased with time since diagnosis. The sensitivity analysis showed that (i) the use of different life tables did not compromise net

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survival estimation in the relative survival setting, whereas (ii) a small level of misclassification for the cause of death led to a large change in the net survival estimate in the cause-specific setting.

The relative survival setting was more robust to the above assumptions violations and is therefore recommended for estimation of net survival.

1. Introduction

Net survival measures the survival that would be observed if the only possible cause of death was the disease of interest [1]. It is the most defensible method of estimating survival from cancer. Two main settings have been described for its estimation: the relative survival setting and the cause-specific setting. The latter requires information on underlying cause of death so that deaths due to causes other than the cancer of interest can be censored. Such information is not needed in the relative survival setting. Here, the overall survival of the cancer patients is compared with the survival they would have experienced if they had had the mortality of the general population from which they were drawn [2].

In both settings, net survival estimation is susceptible to bias due to informative censoring. Informative censoring occurs when patients are removed from the risk set (censored) under a non-random way: these patients would experience a different mortality hazard compared with those that remain in the risk set [3]. In the cause-specific setting, when the interest is in estimating the cancer-specific mortality hazard, patients who died due to other cause are censored (and so removed from the risk set). It means that patients with higher risk of dying from causes other than cancer (for example, elderly compare to young patients) are more likely to be removed from the risk set. However, because age is also an important prognostic factor for cancer, censoring these patients is informative for the cancer-survival estimation. In the relative survival setting, this mechanism of informative censoring is less easy to conceptualise (because the cause of death is unknown and/or not used); any variable with an effect on both cancer-specific and other cause mortality hazards induces informative censoring. Demographic variables which define the life tables may lead to informative censoring and need to be accounted for. A new estimator has been described by Pohar-Perme which is able to take account of this bias within the relative survival setting [4] and its performances have been assessed in an extensive simulation study [5]. We have recently proposed a similar strategy for the estimation of net survival in the cause-specific setting [6].

If informative censoring is accounted for, estimates of net survival derived in each of these settings are theoretically unbiased. However, biases relating to the data setting itself may still occur. In the relative survival setting, bias can originate from the non-comparability between the cohort and the general population from which rates of expected mortality are drawn, due to unmeasured variable(s) affecting both expected and excess hazard rates (this latter being the rate from which the net survival is derived). In the cause-specific setting, bias can arise from the misclassification of the underlying cause of death. Our previous analyses of patients diagnosed with breast cancer in Geneva showed that the estimation of net survival using the cause-specific setting was very sensitive to the codification of underlying cause of death, but, in contrast, the relative survival setting was robust to non-comparability in the estimation of background mortality [6].

Breast cancer may, however, represent a special case. Survival among breast cancer patients is high, but deaths directly caused by the original cancer still occur into the second and third decades following diagnosis: a pattern of excess mortality which is seen for very few other anatomic sites. As such, our previous conclusion may not hold for every cancer type. Here, we extend our analysis of breast cancer patients to patients diagnosed with cancers of three other anatomic sites (according to the international classification of disease, 10th version, ICD-10)to establish whether the same conclusions hold for other malignancies.

2. Material and methods

The Geneva Cancer Registry records underlying cause of death for all cancer patients. More unusual, the registry also validates the accuracy of this variable by reviewing all clinical information available for each patient. The overall agreement between the variables (revised cause of death versus cause of death based on death certificates) was high. However, several subgroups presented a lower concordance, suggesting differences in calendar time and less attention given to older patients and more advanced diseases [7]. This context thus represents a unique opportunity to compare relative survival and cause-specific settings when estimating net survival, because the registry holds more accurate information on the underlying cause of death.