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Development of a model to predict the 10-year cumulative risk of second primary cancer among cancer survivors

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ABSTRACT

Background: To develop a prediction model to quantify the cumulative risk of Second Primary Cancer (SPC) among cancer patients given that they survive their disease.
Methods: A cohort of 293,435 patients based on data from twelve French cancer registries was analyzed. For five first cancer sites, SPC incidence rates were estimated using Poisson regression models. The cumulative risks of SPC were computed for different follow-up times. For comparison purpose, the same method was used to estimate the probability of cancer in the general population.
Results: In this population-based cohort, 27,320 patients presented with a SPC. The cumulative risk of SPC varied depending on first cancer site, with a 10-year cumulative probability of SPC ranging from 6.2% for women with breast cancer to 44.0% for men with head and neck cancer. Compared with the general population, the 10-year cumulative risk of SPC was dramatically elevated for tobacco-related first cancers, with an increase of +7.3% for men aged 55 to 64 with a first lung cancer and +35.6% for men aged 45 to 54 with a first head and neck cancer. Lower differences were observed among patients diagnosed

Abbreviations: SPC, second primary cancer; CI, cumulative incidence; IARC, International Agency for Research on Cancer.

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with a first prostate cancer (+5.5% among men aged 55 to 64), colorectal (+4.1% for women aged 55 to 64 and +6.3% for men aged 55 to 64), and breast (+2.0% among females aged 75 and older) cancers.
Conclusion: This study provides physicians with a practical estimate to assess the risk of SPC of their patients more accurately.

1. Introduction

Over the past decades, the improvements in early diagnosis and cancer treatments have led to an increase of the population of cancer survivors, with over 32.4 million patients living with a cancer in 2012 worldwide and more than one million in France [1].

However, the improvement of cancer patients' survival goes along with an increase of the risk of second primary cancers (SPC) [2,3]. Indeed, population-based studies have pointed out that cancer survivors are at greater risk of developing a SPC as compared with the general population [2,4–7]. In France, a recent study showed that people with a first primary cancer face a 36% increased risk of SPC relative to the overall population without cancer [4]. Several hypotheses have been put forward in the literature to explain this increased risk: persistent exposure to lifestyle risk factors (such as tobacco, alcohol consumption or obesity), viral infections, hormonal factors, genetic susceptibility or late adverse effects of first cancer treatments [3,8]. Some of these risk factor exposures can be modified, and to achieve this goal, time of diagnosis provides a "teachable moment" for physicians to intervene given that patients show a true interest in counsel and effective means to adopt healthier lifestyles [3]. In this perspective, a better understanding of the patients' probability of SPC could be a valuable step.

In population-based studies, estimates of the probability of SPC are commonly provided by the measure of the cumulative incidence (CI) defined as the percentage of patients diagnosed with a first cancer that will ultimately develop a SPC by a specified time (e.g. 5 or 10 years) [2]. As it takes into account the risk of death as a competitive event [9], the CI of new malignancy among patients diagnosed with a cancer carrying a bad prognosis (e.g. lung cancer) is rather low due to a very high competitive risk of death [2]. In the perspective of a clinical follow-up, it seems more relevant to quantify the risk of a new primary assuming that patients survive their disease. Although this information may be of great interest to encourage patients to adopt a healthier lifestyle during their cancer survivorship, such an estimate is not available to date.

The aim of this study was consequently to develop a prediction model to quantify the cumulative risk of SPC among cancer patients given that they survive their disease.

2. Materials and methods

Data were provided by twelve population-based cancer registries from eleven administrative regions of France (Bas-Rhin, Calvados, Doubs, Hérault, Isère, Lille area, Loire-Atlantique, Manche, Somme, Tarn, Vendée), covering 14.5% of the metropolitan French population in 2012. These registries have a high degree of case ascertainment completeness and incidence data are regularly included in the 'Cancer Incidence in Five Continents' monograph series [10]. Patients included presented with a first invasive cancer diagnosis between January, 1 st of 1989 and December, 31 st of 2010 and were followed-up until December, 31 st of 2012. From the original cohort of 646,284 cancer patients, our study focused on the most common first cancer sites or on first cancer sites with an elevated risk of SPC: breast cancer in women, lung, head and neck or prostate cancer in men and colorectal cancer in both sexes.

The third edition of the International Classification of Diseases for Oncology (ICD-O-3) was used to code invasive tumors [11]. Cancer sites and subsites were defined in accordance with the topography and morphology codes used in the EUROCARE-5 project [12]. Non-melanoma skin cancers were not included.

The outcome was the occurrence of a SPC, defined as the first subsequent invasive primary cancer occurring at least two months ($\geq$61 days) after the first invasive cancer diagnosis. Patients presenting with a synchronous second cancer ($<$61 days) were excluded from the analysis. Consequently, the computation of person-years at risk began 2 months after initial diagnosis and ended with the diagnosis of a SPC, death, last known vital status or December 31st, 2012, whichever came first. We focused the analyses on SPCs occurring in a subsite different from that of the primary cancer [4]. According to the International Agency for Research on Cancer (IARC) registration rules for multiple primary cancers, extensions, recurrences, metastases and tumours occurring in the same topographic and morphological groups were not considered as SPCs [13]. From the 293,435 patients included in our dataset, only 7779 (2.7%) were lost to follow-up (i.e. alive at some date before December 31st, 2012 and with no SPC). Data concerning first cancer treatments and risk factors, particularly alcohol and tobacco consumption, were not available.

3. Calculation

The cumulative risk of developing a SPC is defined as the probability that an individual with a first cancer will develop any type of SPC assuming that he is still alive at the end of different follow-up times running from the first cancer diagnosis. Considering the occurrence of a SPC as the event, the competing risk of death is thus taken into account as censoring.

We first computed incidence rates of SPC among cancer survivors by gender and first cancer site using an adaptation of age-period models [14]. To this end, we used Poisson regression models taking into account attained age, attained year of follow-up and time elapsed since the first cancer diagnosis. We provided projections until 2020 assuming the continuation of the observed trends over periods of first cancer diagnosis.

We then calculated the cumulative risk of SPC using the standard formula by Breslow and Day [15] for five and ten years of follow-up for the different combinations of gender, first cancer site, age and period of first cancer diagnosis. For comparison purposes, a similar methodology was used to estimate the cumulative risk of first cancer in the general population. Finally, we described the second cancer distribution by first cancer sites.

All the analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). Reporting of our model was made using the TRIPOD statement [16].