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Original article

Use of a case-mix approach to study the trends in the incidence of second primary cancers

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ABSTRACT

Purpose: To analyze trends in second primary cancer (SPC) incidence by using a case-mix approach to standardize on first cancer site distribution.
Methods: Cases registered by 13 French cancer registries between 1989 and 2010 and followed-up until June 2013 were included. The person-year approach was used to compute standardized incidence ratios (SIRs) of metachronous SPC. Usual SIRs and cancer site–specific weighted SIRs called "case-mix SIRs" (cmSIRs) were estimated by sex and calendar period of first cancer diagnosis. Calendar trends in SIRs and cmSIRs were compared.
Results: More than 2.9 million person-years at risk were included. Among males, SIRs dropped from 1.49 to 1.23 between 1989–1994 and 2005–2010, while cmSIRs decreased from 1.40 to 1.27. This difference seems mainly related to a stronger representation of prostate cancers (at lower risk of SPC) and a weaker contribution of bladder and head and neck cancers (at higher risk of SPC) in recent periods of diagnosis. Among females, both SIRs and cmSIRs have remained stable at around 1.22 and 1.21, respectively.
Conclusions: The cmSIR is an indicator that is not influenced by changes in first cancer site distribution. Its use should be encouraged to assess second cancer incidence control.
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Introduction

Earlier detection of cancer and recent therapeutic progresses have led to an increase in survival among cancer patients [1]. Accordingly, new concerns have emerged such as quality of life, risk

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of relapse, or risk of developing a second primary cancer (SPC) [2]. Data from cancer registries have been frequently used to assess overall incidence of SPCs at a population-based level [3–5]. The person-year approach usually used in these studies allows the calculation of standardized incidence ratios (SIRs) to quantify the risk of new malignancies. SIRs can be interpreted as "relative risks" of SPC among cancer survivors compared with the general population without cancer. In the United States, Curtis et al. used the data from the Surveillance, Epidemiology and End Results program to estimate an overall SIR for all sites of first and second cancer combined of 1.14 [6], meaning that cancer survivors faced a 14% increase in the risk of new malignancies compared with the overall U.S. population.

The increase in the risk of new malignancies among cancer patients has been related with high tobacco and/or alcohol consumption, hormonal and nutritional factors, exposure to virus and immunosuppression, genetic predisposition, increased site-specific medical surveillance, late adverse effects of first cancer treatments, and interactions among these factors [7–9]. The reduction of SPC incidence has become a relevant part of cancer control and has been included in several cancer plans led by National Cancer Institutes [10,11]. Strategies to adopt healthier habits (smoking cessation and increased physical activity) have been promoted [12–14], and the monitoring of trends in SPC incidence has become an emerging topic.

However, one major drawback of the SIRs produced for all sites of first and second cancers combined is that SIRs are strongly impacted by the distribution of first cancers in the studied cohort. Indeed, first cancer site is very strongly associated with the risk of SPC (e.g., SIR of 3.89 after a first head and neck cancer among males in France compared with 1.11 after a first prostate cancer [7]). Trends in SIRs may be confounded on this factor, given that the distribution of the first cancer sites might vary with calendar periods.

The "case-mix" approach has already been used to compute overall indicators to monitor trends and make international comparisons of cancer survival in England and in EUROCARE countries [15,16]. Briefly, this method uses standard weights by cancer sites to produce an overall survival estimate that is not impacted by first cancer site distribution. We therefore propose in the current article to use a case-mix approach in the field of SPC incidence to provide a standardized indicator to monitor calendar trends in SPC incidence.

Methods

Data from 13 population-based registries from the French Network of cancer registries FRANCIM were used to establish a population-based cohort of all patients presenting with a first cancer diagnosed between 1989 and 2010, excluding non-melanoma skin cancers. This database is an update of a previous cohort that was designed to study SPC incidence in France (10 cancer registries and cases diagnosed between 1989 and 2004), from which results have been published elsewhere [7]. Included registries in the present study cover 12 administrative regions of France (Bas-Rhin, Calvados, Doubs, Haut-Rhin, Hérault, Isère, Lille area, Loire-Atlantique, Manche, Somme, Tarn, and Vendée). These registries have achieved a high degree of completeness of ascertainment and incidence data are regularly included in the "Cancer Incidence in Five Continents" monograph series [17–19]. Vital status of all patients was updated to June 30, 2013. The proportion of patients lost to follow-up (i.e., alive at some date before June 30, 2013 and with no SPC) was 2.3%.

SPC was defined as the first subsequent primary cancer occurring at least two months (≥61 days) after first cancer diagnosis. Extensions, recurrences, or metastases were not considered as an SPC according to the International Agency for Research on Cancer rules for multiple primary cancers [20]. Computation of the person-years at risk (PYR) for each individual began after two months of follow-up and ended at the date of SPC diagnosis, last known vital status, death, or June 30, 2013, whichever came first. Patients who developed a synchronous second cancer (<61 days of follow-up) were excluded from this analysis. Third and subsequent primary cancers were not considered as SPCs. Follow-up was limited to the first 10 years after diagnosis.

The third edition of the International Classification of Diseases for Oncology was used to code invasive tumors [21]. Cancer sites (e.g., head and neck) and subsites (e.g., oral cavity) were defined in accordance with topography and morphology codes used in the EUROCARE study [22]. We focused the analyses on the risk of SPC occurring in a different subsite than the first primary cancer.

The person-year approach to study SPC incidence was first used here [6,23]. The number of observed SPC was compared to the number expected if patients with a first cancer had experienced the same cancer rates as the general population without cancer. The number expected was computed by multiplying patient PYRs (allocated by sex, attained age, year of follow-up, and administrative region of diagnosis) with corresponding first cancer incidence rates estimated from the general population. Age-period-cohort models, where age and cohort effects were modeled using smoothing splines, were used to provide robust first cancer incidence rate estimates [24]. This enabled the calculation of the observed to expected ratio, also called SIR. As mentioned in the Introduction, SIR can be interpreted as a "relative risk" of SPC among patients with a first cancer compared with the general population. SIRs for all sites of second cancer combined were computed by sex, first cancer site, and calendar period of first cancer diagnosis (1989–1994, 1995–1999, 2000–2004, and 2005–2010). Although the SIR is an instantaneous indicator that is less impacted than cumulative incidence by follow-up time, the analyses were restricted to the first 10 years after diagnosis to increase the comparability of the follow-up between calendar periods.

The distribution of first cancer sites by sex published in EUROCARE was used to define weights for the construction of case-mix SIRs (cmSIRs) [16]. These weights are reported in Table 1. It can be noted that only tumor sites that represented more than 1.4% of

Table 1
Weights used for case-mix standardization (site distribution from EUROCARE)

Cancer site	Male (%)	Female (%)
Head and neck	2.8	*
Esophagus	2.2	*
Stomach	4.2	3.0
Colon	8.3	8.5
Rectum	5.8	4.5
Liver	1.7	*
Pancreas	2.5	2.7
Larynx	1.8	*
Lung	15.6	7.9
Melanoma	2.8	3.5
Breast	*	30.2
Cervix uteri	—	2.9
Corpus uteri	—	5.4
Ovary	—	4.3
Prostate	23.6	—
Testis	1.4	—
Bladder	5.8	2.1
Kidney	3.6	2.4
Thyroid	*	1.8
Non-Hodgkin lymphoma	4.4	4.1
Other cancers*	13.5	16.7

* Malignancies representing less than 1.4% of total cancer cases are included in the "other cancers" category.

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