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Original Articles

Distribution and risk of the second discordant primary cancers combined after a specific first primary cancer in German and Swedish cancer registries

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ABSTRACT

We aimed at investigating the distribution and risk of all second discordant primary cancers (SDPCs) after a specific first primary cancer in Germany and Sweden to provide etiological understanding of SDPCs and insight into their incidence rates and recording practices. Among 1,537,004 survivors of first primary cancers in Germany and 588,103 in Sweden, overall 80,162 and 32,544 SDPCs were recorded, respectively. Standardized incidence ratios (SIRs) of all SDPCs were elevated at levels between 1.1 and 2.1 after 23 (out of overall 29) cancers in Germany and at levels between 1.1 and 1.6 after 24 cancers in Sweden, and among them, elevated SIRs were found after 19 cancers in both populations. Decreased SIRs at levels ranging from 0.5 to 0.9 were found for some cancers with poor prognosis in Germany only. We found elevated risk after 19 out of 29 cancers in both countries, suggesting common etiology of SDPCs after most of first cancers and registration similarity. Decreased risks after some fatal cancers were found only in Germany, which may be attributed to reporting practices or missed death data in Germany.

Introduction

Second primary cancers (SPCs) have become a long-term outcome with increasing importance because of their steadily growing numbers as a result of continued improvement in early detection, treatment, and supportive care [1]. For instance, the total number of SPCs accounted approximately for one sixth of all cancers reported to the US Surveillance, Epidemiology, and End Results (SEER) program in 2012 [1], while this number reached one fifth of all registered cancers in Sweden in 2012 [2]. SPC can be classified as second concordant primary cancer (the same type of cancer as first cancer, e.g., newly diagnosed left breast cancer after right breast cancer) and second discordant primary cancer (SDPC, e.g., newly diagnosed breast cancer after melanoma).

Carcinogenesis of SPCs is a complex process as many risk factors could contribute to the etiology, including intensive medical surveillance after the diagnosis of the first primary cancer, therapy effect of first cancer, shared genetic or lifestyle factors between first cancer and SPC, or interactions among aforementioned factors [3,4]. Numerous studies on SPCs have been published, originating from the Nordic cancer registries (e.g., Sweden), the US SEER Program, and the International Agency for Research on Cancer (IARC) coordinated collaborations [5–7]. Although recent European studies showed steady increases in survival and incidence rates for cancer patients,

Abbreviations: SDPCs, second discordant primary cancers; SIRs, standardized incidence ratios; ICD, International Classification of Diseases; FCD, Family-Cancer Database.

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persistent difference between countries has been reported despite general improvement in overall cancer treatment (though detailed treatment information is commonly absent in population-based cancer registries) [8–12], which may influence SPC rates in different populations. Nevertheless, to our knowledge, investigations on the risk of SPCs after first primary cancers in different populations have not been reported. Additionally, the distribution of all SPCs combined after a specific first primary cancers has also not been reported, though our group has reported the distribution of five most common SPCs after ten common first cancers in the present populations [13].

We aimed at investigating the distribution and risk of all SDPCs combined (except for non-melanoma skin cancer) after a specific first primary cancer in the two populations, using the pooled database from 12 German cancer registries [14] and the nationwide Swedish Family-Cancer Database (FCD) [15]. While investigations on the distribution of all SPCs combined in different populations may provide an overall picture on SPCs, investigations on the risk of all SDPCs combined after a specific first primary cancer in two populations may provide insight into the epidemiology, etiology and registration practices of SDPCs in different populations. The findings may validate the use of data on SPCs in etiological studies, particularly regarding side effects of treatment when therapies are changing.

Materials and methods

German data

Details on the pooled German database were described elsewhere [14]. Briefly, data were originally collected from cancer registries covering 13 of 16 German federal states. According to the criteria related to data quality, e.g., cancer patients who had a Death Certificate or autopsy only (DCO) cancer were all excluded [14]. Finally, data from 12 cancer registries, covering a population of 26.7 million people (33% of the total German population), were retained in the pooled German database for further analyses [14]. According to the rules set up by the IARC [16], Germany cancer registries did not systematically register tumors occurring at the same organ or at the contralateral organ for SPCs; non-melanoma skin cancers were not collected. Therefore, second cancers in this study were only limited to second discordant primary cancers of any type except non-melanoma skin cancer (simply called SDPCs). Cancers were recorded according to the International Classification of Diseases, 10th version (ICD-10) [16], and the percentage of microscopically verified cancer diagnosis was larger than 95% in all registries [14]. Patients with a primary malignant tumor diagnosed in 1997–2010 at age ≥15 years and with follow-up information until the end of December 2010 were included in the current analyses.

Swedish data

Swedish FCD2010 (updated in 2013) was used for the current study and its details were described elsewhere [15]. For comparability and consistency, same criteria for German data were adopted for Swedish data, e.g., the definition of primary cancers was recorded and restricted to the study period 1997–2010; cancer DCO cases were excluded and only SDPC (second concordant cancers and non-melanoma skin cancers were excluded) cases diagnosed in 1997–2010 at age ≥15 years were selected. Briefly, we used all first primary cancer (except non-melanoma skin cancers) patients diagnosed 1997–2010, covering approximately 9 million Swedish population. Information on cancer cases was retrieved from the Swedish Cancer Registry for the years 1997–2010, relying on separate compulsory notifications from clinicians, pathologists and cytologists [17]; cancers during the study period were recorded according to both International Classification of Diseases, 7th version (ICD-7) and ICD-10 codes. The Swedish Cancer Registry only records primary cancers. Metastasized cancers to other sites were only registered at primary sites; for multiple primary cancers occurring in the same organ or same organ system, only clearly separated malignancies were accepted as multiple primaries and were registered [18]. Close to 100% of the registered neoplasms were histologically verified and approximately 98% of second neoplasms were correctly verified according to a re-evaluation study of 209 multiple primary tumors [17].

Statistical analyses

For both German and Swedish datasets, standardized incidence ratio (SIR), calculated as the ratio of observed to expected numbers of cases, was used to assess the risk of all SDPCs combined after a specific first primary cancer. The expected numbers of all SDPCs combined after a specific first primary cancer were calculated from the strata-specific incidence rate of the combination of first primary cancers (except non-melanoma skin cancer) in the Swedish and German general populations, respectively, multiplied by the corresponding person-years in survivors of first primary cancer. Person-years at risk were accumulated for each patient, starting from the date of diagnosis of the first primary cancer (diagnosed from 1997 to 2010), and terminating on the date of SDPCs of any type, date of death, date of emigration, or December 31, 2010 (end of the study), whichever came earliest.

All SIRs for Germany and Sweden were adjusted for three identical variables [sex, age (5-year bands), and calendar period (1995–2000, 2001–2005, and 2006–2010)] and a regional category (12 states in Germany and 4 categories in Sweden). The 95% confidence intervals (CIs) for SIRs were calculated assuming that the cases followed a Poisson distribution. Statistical significance for SIRs higher or lower than 1.00 was assessed by whether or not the 95% CIs for those SIRs included 1.00. Further analyses were stratified by characteristics of cancer patients [sex, age at diagnosis of first cancer (<65 years, 65–74, and ≥75 years), and follow-up time after first cancer (<1 year, 1–4, and ≥5 years)]. In order to avoid chance findings, we set up rules for showing results. Only cancer sites with a total number of all SDPCs ≥100 in both countries are presented in tables. Additionally, sensitivity analyses restricted to eight (out of 12 in total) German cancer registries with full follow-up period 1997–2010 were conducted because four German registries started cancer registration later than 1997, i.e., Lower Saxony in 2003, Schleswig–Holstein in 1999, and Bremen and Rhineland-Palatinate in 1998. SAS software (version 9.3, SAS Institute Inc., Cary, NC) was used for the data analyses. Data collection within the German Population-Based Cancer Registries was carried out according to state cancer registry laws and only completely anonymous data transferred from the cancer registries were analyzed, while although the data in the Swedish Family-Cancer Database were completely anonymous and their use did not entail ethical problems either, ethical approval by the Institutional Review Board, Karolinska Institute was obtained.

Results

Distribution of all SDPCs after a specific first primary cancer in the two populations

The distribution of all SDPCs after a specific first primary cancer is presented in Table 1. We found 80,162 SDPCs in Germany and 32,544 in Sweden. Overall, the frequency ranking order of all SDPCs after a specific first primary cancer was similar in Germany and Sweden, i.e., the ranking order of the four most frequent SDPCs was identical in Germany and Sweden in the sequence of prostate, colorectal, breast and urinary bladder cancers, while the ranking order after other cancers was generally similar, except for nervous system cancer (27th versus 12th) and unknown primary cancer (21st versus 15th). The total number of any first primary cancers (except non-melanoma skin cancer) diagnosed at age ≥15 years during the 1997–2010 period was 1,537,004 in Germany and 588,103 in Sweden (Table A1). Among them, the percentages for unknown primary, nervous system and non-thyroid endocrine cancers were low in Germany with 1.9% (28,418), 1.4% (20,872) and 0.1% (850), respectively, while in Sweden these were 3.5% (20,287), 2.8% (16,371) and 1.4% (8402), respectively. The percentages of other cancers were rather similar between Germany and Sweden (Table A1). The relationship of frequency (percentage and rank) between first primary cancer and all SDPCs combined after a specific first cancer in Germany and Sweden is presented in Table A2. The percentage for first primary cancer was generally similar to the percentage for all SDPCs combined after the same first cancer in both countries, with exceptions for fatal cancers (liver and gallbladder, pancreatic, lung, nervous system and unknown primary cancers), for which the percentages were halved.

SIRs of all SDPCs after a specific first primary cancer in the two populations

The overall SIRs of all SDPCs after a specific first primary cancer and the stratification by sex are presented in Table 2. We found that SIRs of all SDPCs were elevated at levels between 1.1 and 2.1 after 23 (out of overall 29) cancers in Germany and at levels between 1.1 and 1.6 after 24 cancers in Sweden, and among them, SIRs after 19 cancers were elevated in both Germany and Sweden. It shall be noted that elevated overall SIR reached ≥2.0-fold in Germany after urinary

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