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ORIGINAL PAPER

Incidence of second sarcomas: a cancer registry-based study

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Abstract
Background In high-quality cancer registration systems, about one in eight incident cancers are second primary cancers. This is due to a combination of careful diagnostic ascertainment, shared genetic determinants, shared exposure to environmental factors and consequences of treatment for first cancer.
Methods We used data derived from the Swiss population-based cancer Registries of Vaud and Neuchâtel, including 885,000 inhabitants.
Results Among 107,238 (52% males) first cancers occurring between 1976 and 2010, a total of 126 second sarcomas were observed through active and passive follow-up versus 68.2 expected, corresponding to a standardized incidence ratio (SIR) of 1.85 (95 % CI 1.5–2.2). Significant excess sarcoma risks were observed after skin melanoma (SIR = 3.0), breast cancer (2.2), corpus uteri (2.7), testicular (7.5), thyroid cancer (4.2), Hodgkin lymphoma (5.7) and leukemias (4.0). For breast cancer, the SIR was 3.4 ≥5 years after sarcoma diagnosis.
Conclusions The common denominator of these neoplasms is the utilization of radiotherapy in their management. Some sarcomas following breast cancer may be due to shared genetic components (i.e., in the Li–Fraumeni syndrome), as well as possibly to shared environmental factors, with sarcomas, including overweight, selected dietary and reproductive factors which are, however, too little defined for any quantitative risk assessment.

Keywords Second malignancy · Sarcoma · Cancer registry · Risk · Incidence

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Introduction

Over recent years, in high-quality cancer registration systems, about one in eight to one in ten incident cancers are second primary cancers. These are due to careful diagnostic ascertainment following the diagnosis of a first primary (synchronous cancers), but also to shared genetic determinants as well as to exposure to environmental factors. In addition, the occurrence of several neoplasms is influenced by the therapies of the first cancer, including chemotherapy and radiotherapy [1–4]. Colorectum, breast, prostate and lymphomas are among the commonest sites with multiple primary cancers [5].

Second sarcomas have been recognized as a growing issue over the last few years [6]. Besides genetic components, little is known, however, on the causes of sarcomas, and exposure to ionizing radiation is one of the few established risk factors [7–9]. Soft tissue sarcomas have also been associated with breast and other cancers in the Li–Fraumeni syndrome [10].

In order to quantify the risk of second sarcomas following another neoplasm (i.e., second sarcomas), we considered data from the cancer Registries of the Swiss Cantons of Vaud and Neuchâtel [11–13].

Materials and methods

Data for the present report were abstracted from the Vaud and Neuchâtel Swiss Registries' files, which include all incident cases of malignant neoplasms diagnosed in the resident populations of these cantons (respectively, 713,000 and 172,000 inhabitants, according to the December 2010 National Census) [12, 13]. The registries are tumor-based, and multiple primary malignancies found in the same person are entered separately. Most cases are notified repeatedly and from different institutions, thus improving the completeness and accuracy of the registration. Both registries adhere to the rules of registration for first and second primary cancers of the International Agency for Research on Cancer (IARC) [14] and have been included in the IARC Cancer Incidence in Five Continents volumes since 1982 [15].

Population-based incidence data have been available since 1974 and include information on demographic characteristics (age, sex), primary site and morphology of the tumor according to the standard International Classification of Diseases for Oncology (ICD-O-1 and both ICD-O-1 and ICD-O-3 since 2005) [16, 17] and the date of diagnostic confirmation (histological or clinical diagnosis). No adequate information was available on history of radiotherapy.

Both passive and active follow-ups are recorded, and subsequent items of information are used to complete the record of already registered cases. Information from the death certificate is added to the registration file.

For the present analysis, after the exclusion of basal and squamous cell carcinomas of the skin, 107,238 (52 % males) first cancers occurring in patients diagnosed between 1976 and 2010 were considered. These subjects were followed up for the occurrence of a sarcoma, emigration or death, for a total of 453,792 person-years at risk. Calculation of expected numbers of second sarcomas was based on sex-, age- and calendar year-specific sarcoma incidence rates, multiplied by the corresponding number of person-years at risk. The significance of the observed/expected/ratios (standardized incidence ratios, SIRs) and their corresponding 95 % confidence intervals (CI) was based on the Poisson distribution, or on exact test when required.

Results

Table 1 gives the number of registered first cancer cases overall according to major cancer sites, the person-years at risk and the number of second sarcomas.

Table 1 Number of registered first cancer cases according to major cancer sites, person-years at risk and number of second sarcomas Vaud and Neuchâtel, Switzerland, incidence period 1976–2010

Site of first primary (ICD-10)	Number of first primaries	Person-years at risk	Number of second sarcomas
Colorectum (C18–21)	13,186	61,510	14
Lung (C34)	12,665	19,502	6
Skin melanoma (C43)	4,884	26,808	11
Breast (C50)	17,329	113,037	34
Corpus uteri (C54)	2,882	21,426	9
Prostate (C61)	13,142	57,134	13
Testis (C62)	1,199	8,902	6
Thyroid (C73)	1,158	8,690	4
Hodgkin lymphoma (C81)	735	6,277	3
Non-Hodgkin lymphoma (C82–85)	3,467	16,171	3
Leukemias (C91–95)	2,598	9,432	5
Other and unknown sites[a]	33,990	104,902	18
Total, all sites[a]	107,235	453,792	126[b]

Vaud and Neuchâtel, Switzerland, incidence period 1976–2010

[a] Non-melanomatous skin cancers excluded

[b] ICD morphological codes for sarcomas: 8800–4, 8810–32, 8850–70, 8890–1, 8900–20, 8930, 8951, 8990, 9020, 9120, 9130,9140, 9180–4, 9220, 9240, 9260, 9370, 9522, 9560, 9580

Table 2 gives observed and expected numbers of sarcomas following all cancers (excluding non-melanomatous skin cancers) and following selected cancer sites, stratified by sex and in both sexes combined. A total of 126 sarcomas were observed following any previous cancer versus 68.2 expected, corresponding to a SIR of 1.85 (95 % CI 1.5–2.2). The SIR was 1.65 (1.2–2.1) in men and 2.03 (1.6–2.6) in women. There were 34 sarcomas following a diagnosis of breast cancer versus 15.3 expected (SIR 2.22, 95 % CI 1.5–3.1). Significant excess sarcoma risks were also observed following skin melanoma (11 cases, SIR 2.99, 95 % CI 1.5–5.3), corpus uteri (9 cases, SIR 2.72, 95 % 1.2–5.2), testicular cancer (6 cases, SIR 7.54, 95 % CI 2.7–16.4), thyroid cancer (4 cases, SIR 4.24, 95 % CI 1.1–1.8), Hodgkin lymphoma (3 cases, SIR 5.68, 95 % CI 1.1–16.6) and leukemias (5 cases, SIR 3.98, 95 % CI 1.3–9.3). There were 14 sarcomas following colorectal cancer versus 10.2 expected (SIR = 1.38), six following lung cancer (SIR = 2.05), 13 following prostate cancer (SIR = 1.13), and three following non-Hodgkin lymphomas (SIR = 1.3). None of these estimates was significant. Following all other cancers combined, there were 18 observed sarcomas versus 15.5 expected, corresponding to a SIR of 1.2 (95 % CI 0.7–1.8).

Table 3 gives observed and expected numbers of sarcomas following colorectal, skin (melanoma), breast and all cancers in strata of time since original cancer diagnosis

Table 2 Observed (O) and expected (E) sarcomas, and SIR, with corresponding 95 % CI, by sex, among 107,238 patients diagnosed with a first cancer. Vaud and Neuchâtel, Switzerland, incidence period 1976-2010

Site of first primary (ICD-10)	Sex	O	E	SIR (95 % CI)
Colorectum (C18–21)	M&F	14	10.15	1.38 (0.7–2.3)
Lung (C34)	M&F	6	2.93	2.05 (0.7–4.4)
Skin melanoma (C43)	M&F	11	3.68	2.99(1.5–5.3)
Breast (C50)	F	34	15.30	2.22(1.5–3.1)
Corpus uteri (C54)	F	9	3.30	2.72 (1.2–5.2)
Prostate (C61)	M	13	11.55	1.13 (0.6–1.9)
Testis (C62)	M	6	0.80	7.54 (2.7–16.4)
Thyroid (C73)	M&F	4	0.94	4.24 (1.1–1.8)
Hodgkin lymphoma (C81)	M&F	3	0.53	5.68 (1.1–16.6)
Non-Hodgkin lymphoma (C82–85)	M&F	3	2.30	1.31 (0.3–3.8)
Leukemias (C91–95)	M&F	5	1.26	3.98 (1.3–9.3)
Other and unknown sites[a]	M&F	18	15.46	1.16 (0.7–1.8)
Total, all sites[a]	M	55	33.30	1.65 (1.2–2.1)
	F	71	34.90	2.03 (1.6–2.6)
	M&F	126[b]	68.21	1.85 (1.5–2.2)

[a] Non-melanomatous skin cancers excluded

[b] ICD morphological codes for sarcomas: 8800–4, 8810–32, 8850–70, 8890–1, 8900–20, 8930, 8951, 8990, 9020, 9120, 9130,9140, 9180–4, 9220, 9240, 9260, 9370, 9522, 9560, 9580

Table 3 Observed (O) and expected (E) sarcomas, and SIRs, with corresponding 95 % CI, by time since diagnosis of selected first major neoplasm and by age at diagnosis of second sarcoma. Vaud and Neuchâtel, Switzerland, incidence period 1976–2010

Site of first primary (ICD-10)	Time since first neoplasm		Age at diagnosis of second sarcoma	
	<5 years O/E SIR (95 % CI)	≥5 years O/E SIR (95 % CI)	<70 years O/E SIR (95 % CI)	≥70 years O/E SIR (95 % CI)
Colorectum (C18–21)	7/5.3 1.32 (0.5–2.7)	7/4.8 1.45 (0.6–3.0)	6/5.3 1.14 (0.4–2.5)	8/4.9 1.64 (0.7–3.2)
Skin melanoma (C43)	6/1.7 3.50 (1.3–7.6)	5/2.0 2.54 (0.8–5.9)	6/2.5 2.38 (0.9–5.2)	5/1.2 4.33 (1.4–10.1)
Breast (C50)	7/7.3 0.97 (0.4–2.0)	27/8.1 3.35 (2.2–4.9)	18/10.5 1.71 (1.0–2.7)	16/4.8 3.36 (1.9–5.5)
Total, all sites[a]	58/36.0 1.61 (1.2–2.1)	68/32.2 2.11 (1.6–2.7)	66/41.6 1.59 (1.2–2.1)	60/26.6 2.25 (1.7–2.9)

[a] Non-melanomatous skin cancers excluded

(<5 vs. ≥5 years) and age at diagnosis of second sarcoma (<70 vs. ≥70 years). The excess risk became significant five or more years after breast cancer diagnosis (SIR 3.4, 95 % CI 2.2–4.9). No such pattern of risk with passing time was observed for any other major cancer considered. With reference to all cancers, the SIRs were 1.61 (95 % CI 1.2–2.1) under five years and 2.11 (95 % CI 1.6–2.7) five years or more following the diagnosis of the first primary. With reference to age at diagnosis of second sarcomas, all the SIRs were somewhat higher at age ≥70, in the absence, however, of heterogeneity. For all neoplasms, the SIRs were 1.59 at age <70 versus 2.25 at age ≥70.

Discussion

The present, population-based study provides quantitative evidence that the incidence of sarcomas is increased following a diagnosis of a number of cancer sites, including breast cancer, skin melanoma, testicular, uterine and thyroid cancers, Hodgkin lymphoma and leukemias. The common denominator of these neoplasms is the widespread utilization of radiotherapy in their management. These data, therefore, provide additional and definite evidence that the risk of sarcomas is strongly associated with ionizing radiation [7, 8].

Some of the excess sarcomas, moreover, may be due to shared genetic factors [5, 18]. Sarcomas, in fact, are one of the components of the Li–Fraumeni syndrome, linked to germline mutations of the TP53 tumor suppressor gene [19], characterized in its classical form by sarcomas and cancers of the breast, brain and adrenal glands. Shared environmental factors, including immune suppression, hormonal factors, height, body mass index (BMI) and related aspects of diet [7, 20–23], may also have some role on the excess sarcoma risk following another neoplasm.

Thus, immune suppression has been related to Kaposi's and also other types of cancers. In a cohort study linking data on solid organ transplant recipients from the US Scientific Registry of Transplant Recipients over the period 1987–2008 with 13 states and regional cancer registries, and including 175,732 solid organ transplants, the SIRs were 2.25 (95 % CI 1.74–2.87) for soft tissue sarcomas including heart (65 cases) and 1.98 (95 % CI, 1.09–3.33) for bone and joints (14 cases) [24]. Late age at first pregnancy and birth, a recognized risk factor for breast cancer, has been associated with excess risk of sarcomas [20]. In an Italian case–control study, the relative risk (RR) was over three for BMI ≥30 versus <20 [22], and overweight and obesity were related to colorectal, breast, endometrial

cancer, lymphoma and several other neoplasms [25–28]. In a companion study [21], whole grain was inversely related to the risk of soft tissue sarcomas, whereas selected foods rich in animal fats tended to be positively associated. This is compatible with our knowledge on favorable and unfavorable dietary patterns on the risk of several neoplasms [29, 30]. These factors, however, are too poorly defined and quantified in relation to sarcoma risk to provide any clue for the interpretation of the present results.

A major advantage of these Swiss datasets is that, in the populations considered, there is a long tradition of valid and accurate cancer registration (confirmed by the inclusion of incidence data in the last seven quinquennial issues of the IARC/WHO series *Cancer Incidence in five Continents*) [12, 13], as well as of systematic examination of all surgically treated lesions, including skin melanomas [11, 31], thus adding validity to the present results.

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Conflict of interest The authors declare that they have no conflict of interest.

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