Personal Medical History, Family History of Cancer, and the Risk of Soft-Tissue Sarcoma

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ABSTRACT

Background: Soft-tissue sarcoma (STS) etiology is largely undefined.

Methods: We analyzed data from an Italian case–control study, including 498 incident, histologically confirmed STS cases and 969 hospital controls. Odds ratios (OR) of STS for self-reported personal medical history and family history of cancer were estimated using Firth penalized logistic regression models.

Results: STS risk was significantly increased with a history of burns [OR, 2.46; 95% confidence interval (CI), 1.10–5.47] and showed a nonsignificant excess with herpes zoster infection (OR, 2.31; 95% CI, 0.65–8.23). Hypertension (OR, 0.71; 95% CI, 0.53–0.94), hypercholesterolemia (OR, 0.66; 95% CI, 0.45–0.96), and tonsillectomy (OR, 0.69; 95% CI, 0.51–0.93) were more frequent among controls. No associations were observed for hepatitis, diabetes, immune-mediated diseases, fractures, surgeries other than tonsillectomy, tooth extraction, or blood transfusion. Family history of cancer showed no major associations, except for STS (0.6% of cases, 0.1% of controls, OR >7) and kidney cancer (OR, 4.69; 95% CI, 1.74–12.7).

Conclusions: Our findings suggest a positive association with family history of STS although based on small numbers. Personal medical history and family history of other cancers had no major role; of interest are the suggestive associations of STS with a history of burns and herpes zoster.

Impact: Further research is needed to replicate our findings and to explore potential underlying mechanisms.

Introduction

Soft-tissue sarcomas (STS) encompass a group of malignant mesenchymal neoplasms, accounting for approximately three quarters of all sarcomas (1, 2), with an unfavorable mortality trend (3). STSs are relatively rare, representing less than 1% of all malignant tumors in adults (4). However, they occur proportionally more frequently in children and young adults (5). A large number of distinct histologic subtypes have been described, each characterized by specific molecular alterations, clinical behavior, therapeutic response, and prognostic features (6). In adults, the most common subtypes, together accounting for more than half of all STS cases, include leiomyosarcoma, liposarcoma, undifferentiated sarcoma, and gastrointestinal stromal tumor (GIST; ref. 7). Anatomically, STSs most frequently arise in the extremities, followed by the trunk and retroperitoneum, whereas occurrences in the head and neck or visceral organs are uncommon (8).

Their rarity and marked heterogeneity in terms of histopathology, anatomic distribution, and molecular pathways hindered understanding of their etiology and pathogenesis (9). A small subset of cases arises in the context of hereditary cancer predisposition syndromes, including Li-Fraumeni syndrome, hereditary retinoblastoma, familial adenomatous polyposis, and neurofibromatosis type 1 (10). Beyond these syndromes, a positive family history of cancer, particularly for sarcomas, breast, and gastrointestinal malignancies, has been associated with an increased risk of selected STSs, reflecting shared genetic susceptibility, epigenetic mechanisms, and gene–environment interactions (11–16).

Ionizing radiation is an established risk factor for secondary sarcomas, typically arising within irradiated fields after long latency periods (17, 18). Other medical conditions may contribute to STS risk through mechanisms involving chronic inflammation, immune dysregulation, or tissue regeneration (19). These include immune-mediated diseases (20), viral infections (21), and prior physical trauma at the tumor site (22). A possible link with medical or surgical procedures, especially those involving repeated tissue disruption or foreign material implantation, has been suggested, but epidemiologic evidence remains sparse (22, 23).

Beyond these, very few other factors have been associated with STS risk, including exposure to selected chemicals, such as phenoxy herbicides, chlorophenols, and dioxins (24, 25), and selected occupational factors (26).

Thus, despite suggestive evidence, epidemiologic data on the role of personal medical history and family history of cancer in STS

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etiology remain scarce and fragmented, largely due to the rarity and heterogeneity of these tumors. In this context, the present study specifically addresses this gap by evaluating the association between selected aspects of personal medical history—including prior diseases, injuries, and medical procedures—and family history of cancer across multiple sites in first-degree relatives, in relation to the risk of STS in a large Italian investigation (27).

Materials and Methods

Study population

The present study is based on an Italian investigation of the epidemiologic, toxicologic, and clinical aspects of STS. The data here considered were collected between 2011 and 2019 within a hospital-based case–control study conducted in Northern Italy. Overall, the study database comprised 498 incident STS cases and 969 controls, recruited from six hospitals in the Metropolitan City of Milan and surrounding areas. Eligible cases and controls were identified from hospital admission records and inpatient wards at the participating centers.

Cases were recruited at the National Cancer Institute ($n = 493$, 99%) and the European Institute of Oncology ($n = 5$, 1%), whereas controls were enrolled at the Niguarda Ca' Granda Hospital ($n = 253$, 26.1%), Gaetano Pini Hospital ($n = 295$, 30.4%), Bollate Hospital ($n = 361$, 37.3%), and Garbagnate Milanese Hospital ($n = 60$, 6.2%). Cases were patients aged 18 to 85 years (median age 57) with incident (i.e., diagnosed within 2 years) histologically confirmed STS [International Classification of Diseases for Oncology, third edition (ICD-O-3) codes as reported in **Table 1**], resident in Italy for at least 15 years at the time of enrollment. Exclusion criteria included patients diagnosed with Kaposi sarcoma, those with a history of any type of neoplasm, those with severe neurologic or psychiatric disorders, and those above the age of 85 years at diagnosis.

Controls were patients aged 18 to 85 years (median age 62) recruited among subjects hospitalized for a wide spectrum of acute nonneoplastic conditions. Of these, 21.8% were admitted for traumas, 16.5% for nontraumatic orthopedic disorders, 53.3% for acute surgical conditions, and 8.4% for miscellaneous other illnesses, such as eye, ear, or skin diseases. Patients whose primary reason for hospital admission was a chronic condition or a disease potentially associated with tobacco use, alcohol consumption, or long-term changes in diet were excluded; however, the presence of such conditions as comorbidities did not constitute an exclusion criterion. During their hospital stay, potential participants were approached in person by trained interviewers introduced by the attending clinical staff and were invited to participate in the study after a detailed explanation of its aims and procedures. All participants provided written informed consent. Less than 10% of either cases or controls approached refused to participate. All individuals who agreed to participate completed the enrollment and the interview-based questionnaire; no withdrawals or dropouts occurred after enrollment.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committees of the NCI, Milan (INT 32/09 of June 11, 2009), and of the Gaetano Pini Hospital (no. 5,752 of June 9, 2010).

Data collection

Cases and controls were interviewed in hospitals by the same centrally trained interviewers using a structured questionnaire (Supplementary Materials S1). Proxy interviews were not permitted; all interviews were conducted directly with study participants. Information was collected on sociodemographic and anthropometric characteristics, lifetime smoking habits (including daily number of cigarettes/cigars and grams of tobacco pipe smoked, age at starting, and age at stopping for former smokers), alcohol consumption (including weekly number of drinks of wine, beer, amari, grappa, whiskey/brandy, age at starting, and age at stopping for former drinkers), and contact with livestock and pets. For female participants, gynecologic and obstetric data, as well as a history of the use of oral contraceptives and hormone replacement therapy, were also recorded. Information on family history included the number of brothers, sisters, sons, and daughters. For each first-degree relative (i.e., parents, siblings, and sons/daughters), we recorded the vital status, current age/age at death, history of cancer (excluding nonmelanoma skin cancer), site of cancer, and age at diagnosis. We collected self-reported information on the history of selected conditions (e.g., chronic infections, chronic inflammatory, cardiometabolic and immune-mediated diseases), injuries (burns and skeletal fractures, with body localization), and medical procedures (e.g., blood transfusions, surgical treatments, and dental extractions). We did not use medical or hospitalization records to validate interview-based data. Habitual diet during the two years before diagnosis or interview was assessed using a validated (28) 65-item food frequency questionnaire.

Blood and adipose tissue samples were collected for a subset of cases and controls and stored at −80°C (27).

Statistical analysis

We estimated the odds ratios (OR) of STS, with the corresponding 95% confidence intervals (CI), according to various aspects of personal medical history and family history of cancer in first-degree relatives using unconditional Firth penalized logistic regression models to address issues related to sparse data. ORs were calculated for factors with at least 10 exposed subjects (cases plus controls). The final model included terms for age (in categories: <40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75 years), sex, years of education (in categories: <7, 7–11, 12–14, ≥15), and area of residence (northern, central, and southern Italy). Models for family history of cancer also included a term for family size (in continuous). The potential confounding effect of body mass index (BMI), tobacco smoking, and alcohol consumption was evaluated; however, as the addition of these variables did not substantially change any of the risk estimates and most exposures were infrequent, these variables were not retained in the final models. Analyses stratified by sex and by major histologic subtype were conducted for factors suggestively associated with STS risk in the main analysis. As a sensitivity analysis, analyses of family history of cancer were repeated after excluding the 28 cases with family histories suggestive of hereditary predisposition (i.e., at least one relative diagnosed with cancer before age 40 years). Statistical analyses were performed with SAS version 9.4 (SAS Institute; RRID: SCR_008567).

Results

Among the 498 STS cases, 288 (57.8%) were males, and 210 (42.2%) were females. The distribution of sarcoma subtypes, overall and by sex, is provided in **Table 1**. Liposarcoma was the most common STS subtype (33.7%) in both sexes, followed by

Table 1. Frequency distribution of sarcoma subtype (International Classification of Diseases for Oncology, third edition, ICD-O-3 codes) for 498 cases of STS, in the overall case sample and by sex. Italy, 2011 to 2019.

STS subtype	ICD-O-3 histology codes	Overall soft tissue sarcomas, 498 *n* (%)	Males, 288 *n* (%)	Females, 210 *n* (%)
Liposarcoma	8850–8858	168 (33.7)	107 (37.2)	61 (29.1)
Fibrosarcoma	8810–8815	69 (13.9)	33 (11.5)	36 (17.1)
Leiomyosarcoma	8890	43 (8.6)	23 (8)	20 (9.5)
Dermatofibrosarcoma	8832	41 (8.2)	22 (7.6)	19 (9.1)
GIST	8936	27 (5.4)	21 (7.3)	6 (2.9)
Synovial	9040–9043	20 (4)	10 (3.5)	10 (4.8)
MPNST	9540–9560	15 (3)	7 (2.4)	8 (3.7)
Chondrosarcoma	9220–9240	12 (2.4)	7 (2.4)	5 (2.4)
Angiosarcoma	9120, 9124, 9130, 9133, 9170	10 (2)	7 (2.4)	3 (1.4)
Sarcoma NOS	8800–8805	57 (11.4)	32 (11.1)	24 (11.4)
Other types[a]		36 (7.2)	19 (6.6)	18 (8.6)

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; PEComa, perivascular epithelioid cell neoplasm.
[a]Including rhabdomyosarcoma ($n = 9$, 1.8%, ICD-O-3 codes: 8900, 8901, 8912), Ewing sarcoma ($n = 7$, 1.4%, ICD-O-3 code: 9260), PEComa ($n = 5$, 1%, ICD-O-3 code: 8714), myofibroblastic sarcoma ($n = 4$, 0.8%, ICD-O-3 code: 8825), chordoma ($n = 4$, 0.8%, ICD-O-3 code: 9370), malignant fibrous histiocytoma ($n = 2$, 0.4%, ICD-O-3 code: 8830), alveolar soft part sarcoma ($n = 2$, 0.4%, ICD-O-3 code: 9581), malignant granular cell soft-tissue tumor ($n = 1$, 0.2%, ICD-O-3 code: 9580), carcinosarcoma ($n = 1$, 0.2%, ICD-O-3 code: 8982), and clear-cell sarcoma NOS ($n = 1$, 0.2%, ICD-O-3 code: 9044).

fibrosarcoma (13.9%), leiomyosarcoma (8.6%), and dermatofibrosarcoma (8.2%); 11.4% of patients had sarcoma not otherwise specified (NOS). Among liposarcoma cases, 61 were well-differentiated liposarcomas, 51 were dedifferentiated liposarcomas, 25 were liposarcomas NOS, 19 were myxoid tumors, 5 were round cell tumors, and 7 were pleomorphic liposarcomas. Liposarcomas (37.2% vs. 29.1%) and GISTs (7.3% vs. 2.9%) were more frequent among males, whereas fibrosarcomas were more frequent among females (17.1% vs. 11.5%). With respect to the anatomic site, STS occurred in the trunk in 241 patients (48.4%, including 112 in the retroperitoneum), in the limbs in 248 (49.8%), and in the head and neck in 9 (1.8%).

Table 2 gives sociodemographic and anthropometric characteristics in cases and controls. STS cases were slightly younger and more educated than controls, whereas the distribution of BMI, tobacco smoking, and alcohol consumption was similar in the two groups.

The distribution of STS cases and controls and the corresponding ORs for selected aspects of personal medical history are shown in **Table 3**. No association was found for a history of any hepatitis (OR, 0.82; 95% CI, 0.49–1.36), diabetes (OR, 1.12; 95% CI, 0.65–1.94), or immune-mediated diseases (OR, 0.64; 95% CI, 0.30–1.34). Hepatitis A, hypertension, and hypercholesterolemia were more frequently reported among controls; the ORs for the three conditions were 0.43 (95% CI, 0.19–0.99), 0.71 (95% CI, 0.53–0.94), and 0.66 (95% CI, 0.45–0.96), respectively. A nonsignificant excess risk was observed for herpes zoster infection (OR, 2.31; 95% CI, 0.65–8.23).

With respect to injuries, previous burns were associated with an increased STS risk (OR, 2.46; 95% CI, 1.10–5.47). No concordance was observed between the site of the prior burn and the location of the STS (Supplementary Table S1), and the association did not seem to be confined to specific histologic STS types (Supplementary Table S2). No association was found with the number of previous fractures (OR, 0.76; 95% CI, 0.51–1.15 for ≥2 fractures vs. none), irrespective of their location. Tonsillectomy was reported more frequently by controls than by cases (25% vs. 17.1%); the OR was 0.69 (95% CI, 0.51–0.93). No other surgical procedures investigated, including tooth extraction and blood transfusion, were associated with STS risk.

Approximately 50% of cases and 48% of controls reported a family history of cancer in first-degree relatives. The mean age at STS diagnosis was 57.9 years among cases with a family history and 52.5 years among those without a family history. The ORs are given in **Table 4**. There was no association with family history of any cancer (OR, 1.04; 95% CI, 0.81–1.33), either overall or by histologic subtype (Supplementary Table S2). However, individuals with three or more affected first-degree relatives had a nonsignificant increase STS risk (OR, 1.49; 95% CI, 0.71–3.15). Three cases (0.6%) and one control (0.1%) reported a family history of STS; the corresponding OR was largely above 1 (7.17). There was a significant association with family history of kidney cancer (OR, 4.69; 95% CI, 1.74–12.7), which did not seem to be limited to a specific histologic subtype (Supplementary Table S2). The OR was nonsignificantly increased for family history of female-specific cancers (uterus: OR, 2.06; 95% CI, 0.62–6.78; ovary: OR, 1.43; 95% CI, 0.31–6.56; breast: OR, 1.40; 95% CI, 0.71–2.75). Family history of cancer at other sites did not show a significant association with STS risk.

After excluding the 28 cases with at least one relative diagnosed with cancer before age 40, the ORs for family history of kidney cancer (OR, 3.82; 95% CI, 1.34–10.90), family history of STS (OR, 5.61; 95% CI, 0.51–61.21), and ≥3 affected relatives (OR, 1.33; 95% CI, 0.61–2.92) were only slightly attenuated.

In analyses by sex, the ORs for burn history were 2.04 (95% CI, 0.61–6.87) in females and 2.37 (95% CI, 0.79–7.12) in males; the ORs for family history of kidney cancer were 4.23 (95% CI, 1.20–14.95) in females and 5.28 (95% CI, 0.99–28.17) in males; and the ORs for ≥3 relatives affected by any cancer were 1.38 (95% CI, 0.50–3.79) in females and 1.50 (95% CI, 0.46–4.88) in males.

Discussion

In the present study, based on one of the largest epidemiologic datasets of STS to date, several aspects of family history of cancer in first-degree relatives and personal medical history, including selected common and rare diseases, surgeries, and bone fractures, were not significantly associated with overall STS risk. Family history of STS was associated with an increased STS risk although this finding was based on small numbers and the effect did not reach

Table 2. Distribution of 498 cases of STS and 969 controls according to selected sociodemographic characteristics. Italy, 2011 to 2019.

Covariates	Cases, *n* (%)	Controls, *n* (%)
Age (years)		
<40	76 (15.3)	139 (14.3)
40–44	55 (11)	66 (6.8)
45–49	40 (8)	66 (6.8)
50–54	54 (10.8)	66 (6.8)
55–59	52 (10.4)	90 (9.3)
60–64	69 (13.9)	120 (12.4)
65–69	59 (11.9)	137 (14.1)
70–74	47 (9.4)	154 (15.9)
≥75	46 (9.2)	131 (13.5)
Sex		
Male	288 (57.8)	529 (54.6)
Female	210 (42.2)	440 (45.4)
Years of education[a]		
<7	88 (17.7)	183 (19)
7–11	158 (31.8)	333 (34.6)
12–14	146 (29.4)	327 (34)
≥15	105 (21.1)	119 (12.4)
BMI[a], kg/m^2		
<25	210 (42.9)	446 (46)
25–29.9	199 (40.6)	379 (39.1)
≥30	81 (16.5)	144 (14.9)
Tobacco smoking[a]		
Never	219 (44)	413 (42.6)
Former	116 (23.3)	288 (29.7)
Current, *n* cigarettes/day		
<10	35 (7)	75 (7.8)
10–19	51 (10.2)	131 (13.5)
≥20	30 (6)	80 (8.3)
Alcohol drinking[a] (drinks/week)		
Never	106 (21.3)	173 (18.0)
<7	146 (29.3)	282 (29.3)
7 to <14	88 (17.7)	173 (18.0)
14 to <21	86 (17.3)	208 (21.6)
≥21	72 (14.5)	126 (13.1)
Family size[b], mean (SD)	3.8 (2.4)	4.0 (2.8)

[a]The sum does not add up to the total because of missing values.
[b]Including siblings and offspring; excluding the proband and partner.

Table 3. Distribution of 498 cases of STS and 969 controls, with ORs[a] and corresponding 95% CI, according to personal medical history. Italy, 2011 to 2019.

Medical history	Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)
Past diseases			
Any hepatitis	29 (5.8)	65 (6.7)	0.82 (0.49–1.36)
Hepatitis A	10 (2.0)	28 (2.9)	0.43 (0.19–0.99)
Hepatitis B	12 (2.4)	16 (1.7)	1.64 (0.72–3.73)
Hepatitis C	4 (0.8)	13 (1.3)	0.79 (0.24–2.64)
Diabetes	27 (5.4)	43 (4.4)	1.12 (0.65–1.94)
Hypertension	146 (29.3)	387 (40)	0.71 (0.53–0.94)
Hypercholesterolemia	52 (10.4)	165 (17.1)	0.66 (0.45–0.96)
Herpes zoster	5 (1)	6 (0.6)	2.31 (0.65–8.23)
Any immune-related disease[b]	11 (2.2)	34 (3.5)	0.64 (0.30–1.34)
Past injuries			
Burns	15 (3)	14 (1.4)	2.46 (1.10–5.47)
No. of fractures			
0	338 (67.9)	612 (63.2)	1
1	115 (23.1)	251 (25.9)	0.81 (0.61–1.08)
2+	45 (9.0)	106 (10.9)	0.76 (0.51–1.15)
Past medical procedures[c]			
Surgeries			
Tonsillectomy	85 (17.1)	242 (25)	0.69 (0.51–0.93)
Discal hernia repair surgery	12 (2.4)	38 (3.9)	0.59 (0.29–1.20)
Abdominal hernia repair surgery	60 (12.0)	113 (11.7)	1.06 (0.73–1.54)
Gallbladder surgery (including removal)	22 (4.4)	65 (6.7)	0.64 (0.37–1.11)
C-section[d]	22 (10.5)	47 (10.7)	0.63 (0.34–1.14)
Musculoskeletal surgery	74 (14.9)	221 (22.8)	0.56 (0.41–0.76)
No. of teeth extracted			
0	99 (20.4)	164 (17.2)	1
<10	255 (52.5)	452 (47.4)	0.92 (0.66–1.28)
≥10	132 (27.2)	338 (35.4)	0.82 (0.55–1.21)
Blood transfusion	18 (3.7)	26 (2.7)	1.13 (0.57–2.22)

[a]Derived from Firth penalized unconditional logistic regression models, including terms for age, sex, area of residence, and years of education. The referent group for each comparison is all other subjects who did not report that condition, injury, or medical condition.
[b]Including: ulcerative colitis, bronchial asthma, allergy/eczema, psoriasis, lichen ruber planus, celiac disease, thyroiditis, lupus, polymyositis, rheumatoid arthritis, rheumatic disease, polyarthritis or other autoimmune vasculitis, myasthenia gravis, multiple sclerosis, thrombocytopenia, agranulocytosis, Sjögren syndrome, Raynaud disease, hemolytic anemia, pernicious anemia, serum sickness, and hypogammaglobulinemia.
[c]The most frequently reported surgeries were considered.
[d]Percentages were calculated among females only.

statistical significance. Significant associations were observed for a family history of kidney cancer and a history of burns, and suggestive, though nonsignificant, increases in risk were observed for herpes zoster infection and family history of female-specific cancers.

A few studies considered the association between family history of cancer and STS risk (11–16). Two US case–control studies, restricted to males and conducted in the late 1970s and early 1980s—one hospital-based and including 217 STS cases (15) and the other population-based and including 133 STS cases (16)—reported similar age-adjusted or age-matched ORs of approximately 1.3, of marginal statistical significance. The latter (16) also assessed the association with family history across multiple sites and observed excess risks for family history of selected hematopoietic cancers (OR, 8.9; 95% CI, 1.7–51.2 for Hodgkin lymphoma; OR, 4.0; 95% CI, 0.5–25.5 for non-Hodgkin lymphoma), pancreatic cancer (OR, 6.1; 95% CI, 0.9–38.9), and, to a lesser extent, prostate (OR, 1.9; 95% CI, 0.7–5.1), brain (OR, 1.8; 95% CI, 0.4–7.1), and skin (OR, 1.4; 95% CI, 0.6–3) cancers. A Canadian population-based case–control study based on 357 male cases reported an age-adjusted OR of 1.3 (95% CI, 1–1.68) for family history of any cancer, which, however, decreased to 1.14 (95% CI, 0.81–1.60) after controlling for family size (14). Additionally, a US hospital-based case–control study based on medical record review, including 425 sarcoma cases (mostly STS cases) and a similar number of controls matched for age, sex, and race, found ORs between ~2 and ~4 for family history of cancer, depending on the type of affected relative (12).

Studies on the familial aggregation of kidney cancer have primarily focused on the risk of renal cell carcinoma among relatives and did not report an increased occurrence of STS. From a biological perspective, there is no established shared etiologic pathway

Table 4. Distribution of 498 cases of STS and 969 controls, with ORs[a] and corresponding 95% CI, according to family history of cancer among first-degree relatives. Italy, 2011 to 2019.

Cancer site[b]	Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)
Head and neck	14 (2.8)	30 (3.1)	1.18 (0.58–2.41)
Esophagus	2 (0.4)	8 (0.8)	0.57 (0.11–2.94)
Stomach	27 (5.4)	53 (5.5)	1.23 (0.73–2.07)
Intestine	36 (7.2)	77 (7.9)	0.84 (0.53–1.33)
Liver	18 (3.6)	48 (5)	0.80 (0.44–1.46)
Pancreas	8 (1.6)	21 (2.2)	1.24 (0.53–2.90)
Lung	42 (8.4)	89 (9.2)	1.24 (0.81–1.90)
Bone	1 (0.2)	11 (1.1)	0.45 (0.08–2.74)
Breast	19 (9)	30 (6.8)	1.40 (0.71–2.75)
Uterus	6 (2.9)	7 (1.6)	2.06 (0.62–6.78)
Ovary	4 (1.9)	5 (1.1)	1.43 (0.31–6.56)
Prostate	34 (6.8)	40 (4.1)	1.21 (0.63–2.35)
Bladder	4 (0.8)	14 (1.4)	0.38 (0.11–1.27)
Kidney	15 (3)	7 (0.7)	4.69 (1.74–12.7)
Brain	7 (1.4)	24 (2.5)	0.33 (0.13–0.85)
Thyroid	4 (0.8)	10 (1)	0.53 (0.15–1.89)
Lymphohematopoietic	20 (4)	28 (2.9)	1.04 (0.53–2.04)
Hodgkin	3 (0.6)	3 (0.3)	1.28 (0.23–7.07)
Non-Hodgkin	3 (0.6)	4 (0.4)	0.61 (0.09–4.04)
Leukemia	12 (2.4)	17 (1.8)	1.25 (0.53–2.91)
Myeloma	3 (0.6)	4 (0.4)	1.26 (0.23–6.97)
STS	3 (0.6)	1 (0.1)	7.17 (0.81–63.7)
All cancers	247 (49.6)	467 (48.2)	1.04 (0.81–1.33)
No. of relatives affected			
0	251 (50.4)	502 (51.8)	1
1	178 (35.7)	333 (34.4)	1 (0.77–1.31)
2	53 (10.6)	108 (11.1)	1.09 (0.73–1.64)
3+	16 (3.2)	26 (2.7)	1.49 (0.71–3.15)

[a]Derived from Firth penalized unconditional logistic regression models, including terms for age, sex, area of residence, years of education, and family size. The referent group for each comparison is all other subjects who did not report family history at that specific site.
[b]Cancer sites are listed in anatomic order.

linking sporadic kidney cancer and STS. Although rare hereditary cancer syndromes may include both sarcomas and renal tumors within their clinical spectrum, these conditions are uncommon and unlikely to largely explain the associations observed in population-based studies of sporadic cases. In line with this interpretation, sensitivity analyses excluding STS cases with family histories suggestive of hereditary cancer syndromes yielded only slightly attenuated ORs. An alternative explanation is diagnostic misclassification among affected relatives, as retroperitoneal STS may present as renal masses and, particularly in historical cases or in the absence of pathologic confirmation, may have been misreported as kidney cancer. A similar mechanism may also apply to other tumor sites, particularly female reproductive cancers such as uterine and ovarian tumors. Pelvic STS can clinically mimic gynecologic malignancies and may therefore have been misreported as cancers of the uterus or ovary. Therefore, any observed association with a family history of kidney cancer or gynecologic cancers should be interpreted with caution.

An association between prior burns and the risk of STS has been reported, although the evidence remains limited and largely based on case reports and case series (29, 30). Malignant transformation may occur in burn scars after long latency periods, likely driven by chronic inflammation, persistent oxidative stress, and repeated cycles of tissue injury and repair. Medical management of burns, including skin grafting or repeated surgical interventions, may also contribute to local alterations in tissue architecture. In our study, STS cases reporting a history of burns were reviewed, with particular attention to the anatomic location of both the burn injury and the tumor. No concordance was observed between the site of the prior burn and the location of the STS, and the association did not seem to be restricted to a specific histologic subtype of STS. These findings suggest that the observed association is unlikely to reflect a direct local malignant transformation of burn scars although it may be related to systemic and long-term effects of chronic tissue injury and repair. Recall bias is possible, whereby patients with sarcoma are more likely to report previous burns at the tumor site. However, 90% of burns were reported >10 years before diagnosis or interview, indicating that reporting bias is unlikely.

An increased STS risk associated with herpes zoster infection has been reported by another Italian study (21), which also suggested potential associations with common childhood infections, particularly mumps and chickenpox. However, other studies did not confirm these associations (16, 31). Although a role of viruses in human sarcoma development has long been hypothesized, the only well-established viral-sarcoma relationship is between human herpesvirus 8 and Kaposi sarcoma. Herpes zoster results from the reactivation of latent varicella-zoster virus and is often accompanied by transient impairment of cell-mediated immunity, which can facilitate oncogenic processes, including the development of mesenchymal tumors (32). Nevertheless, current evidence supporting a causal link between herpes zoster and STS remains limited.

Some of the observed differences in findings across sarcoma studies may be partly explained by variation in case characteristics, particularly in terms of disease histologic subtype composition and sex distribution. Among studies reporting on family history of cancer, the US case–control study based on medical record review by Nabi and colleagues (12) showed a markedly different subtype distribution compared with the present study, with a substantially lower proportion of liposarcomas (~7% vs. 34%), larger proportions of leiomyosarcomas (~15% vs. 9%) and GISTs (~9% vs. 5%), and the inclusion of Kaposi sarcomas and osteosarcomas. With regard to sex distribution, that study also had a higher proportion of female cases (48% vs. 42%), whereas three other studies (14–16) assessing the association between family history and STS risk recruited only male STS cases and did not provide information on disease subtypes. With respect to medical history, the study reporting an association with herpes zoster infection and other selected childhood infections (21) showed a lower proportion of liposarcomas (~16% vs. 34%), a similar proportion of leiomyosarcomas, and higher proportions of fibrosarcomas (~23% vs. 14%) and malignant fibrous histiocytomas (18% vs. < 1%). Large-scale registry-based studies describing the epidemiology of STS in different countries (33–36) indicate a higher incidence of STS in males than in females, with male-to-female ratios ranging from approximately 1.1 to 1.5, in line with the present study. With respect to disease histology, these studies reported highly variable subtype proportions. Substantial heterogeneity in diagnostic criteria, histologic classification systems, and subtype groupings—including the miscellanea category—prevents meaningful quantitative comparisons across studies.

The present study is one of the largest epidemiologic investigations conducted to date on STSs, a group of rare and heterogeneous

malignancies. Major strengths of this study include its large sample size, the high participation rate among both cases and controls, and the availability of detailed, interview-based information on a wide range of sociodemographic, lifestyle, medical, and familial factors. In particular, the availability of comprehensive data on family history of cancer in first-degree relatives, including cancer site and age at diagnosis, allowed for an in-depth evaluation of familial cancer patterns rarely explored in previous STS studies. However, most of the exposures under investigation were rare in the study population, including family history of specific cancer sites, with corresponding estimates likely being unstable and sensitive to small changes in the data. In addition, although the overall study sample was large, the sample size substantially decreased in stratified analyses, such as those conducted by sex and histologic subtype, further limiting statistical power.

To improve comparability between cases and controls and to minimize selection bias, we recruited the control group from major teaching and general hospitals in the study area and excluded patients admitted for chronic conditions from the comparison group. As the large majority of STS cases were enrolled at a specialized sarcoma referral center, a higher proportion of cases than controls originated from outside the Milan area. We therefore adjusted our risk estimates for the area of residence to account for potential geographic variation in sociodemographic and lifestyle characteristics.

With regard to information bias, data on medical and family history were self-reported, collected by questionnaire, and not supplemented by medical chart review. However, the questionnaire was administered by trained interviewers, ensuring standardized data collection. In addition, high agreement between self-reported and health record data was reported for several medical conditions and procedures, including various cardiac conditions (>90%), selected cardiac procedures (>90%), joint replacement (100%), stroke (96%), multiple sclerosis (98%), Crohn disease (96%), thyroid diseases (87%), diabetes (79%), rheumatoid arthritis (87%), and other autoimmune diseases (89%; ref. 37). With regard to family history of cancer, self-reported data were found to be fairly accurate according to a systematic review by the US Agency for Healthcare Research and Quality: specificity across all cancer types ranged from 91% to 99%, whereas sensitivity values showed greater variability, with breast cancer having the highest values (around 85%–90%; ref. 38). Sensitivity ranged from 57% to 65% for colorectal cancer, from 67% to 83% for ovarian cancer, and from 69% to 79% for prostate cancer.

It is possible that patients with cancer recalled their medical history and family cancer history in greater detail than controls (38). Nevertheless, the interviews were conducted in similar hospital settings for cases and controls, and the same trained interviewer administered the questionnaire to both groups, thus improving the comparability of the information collected. Moreover, satisfactory reliability of self-reported medical history and family history of cancer among hospital controls has been shown in our network of studies (39, 40). In particular, k-statistics >0.85 were observed for various comorbidities such as diabetes, thyroid diseases, hepatitis, and benign breast disease, as well as for appendectomy and hysterectomy (39). For family history, kappa values were 0.7 for any cancer, 1 for oesophageal cancer, 0.8 for stomach cancer, 0.7 for liver and pancreatic cancers, 0.6 for intestinal cancer, and 0.5 for lung cancer (40). In addition, any misclassification of self-reported exposures is likely to be nondifferential by case–control status and hence likely to have biased risk estimates toward the null.

The higher proportion of controls reporting selected previous surgical and medical conditions may reflect a greater likelihood of hospitalization among hospital controls (Berkson's bias). As for confounding, cases were older than controls; therefore, age was adjusted for using a granular dummy-variable specification with multiple 5-year age categories and two open-ended classes, allowing flexible control for age, thus controlling for age-related confounding. In addition to age, risk estimates were adjusted for sociodemographic characteristics; BMI, tobacco smoking, and alcohol consumption were evaluated as potential confounders but were not retained in the final models, as they did not materially affect the results. However, some residual confounding cannot be excluded.

Some of the few studies reporting on medical and family history with which our findings are compared were case–control studies that identified STS cases through population-based cancer registries (14–16, 31). These studies benefit from comprehensive case ascertainment and high completeness of incident cases, but they relied on telephone or postal questionnaires to collect exposure information, often with moderate participation rates and frequent inclusion of proxy respondents. Such features may introduce differential accuracy in exposure reporting, particularly for personal medical history and family history variables.

In conclusion, the present analysis contributes to improving the limited knowledge of risk factors for STS. Our results indicate a role of family history of STS but do not support a major contribution of personal medical history or other aspects of family history of cancer in STS development. Of interest are the suggestive findings of an increased risk associated with a history of burns and herpes zoster infection, which provide leads for further investigation. The observed associations with family history of kidney cancer also warrant additional study. Despite the low prevalence of several exposures under investigation in a study of a rare cancer, the present findings help identify potentially relevant etiologic hypotheses and highlight key priorities for future research. These include larger collaborative studies to enable adequately powered subtype-specific analyses, improved characterization of familial aggregation through validated family history data and linkage with cancer registries, and integration of epidemiologic evidence with molecular and biomarker-based investigations.

Data Availability

Data will be made available upon reasonable request to the corresponding author.

Authors' Disclosures

F. Turati reports grants from the European Union–NextGenerationEU–National Recovery and Resilience Plan, Call 2023 (PNRR-TR1-2023-12377497), and the University of Milan, Research Support Plan 2022 to 2023 during the conduct of the study. G. Esposito reports grants from the European Union–NextGenerationEU–Italian National Recovery and Resilience Plan, Call 2023 (PNRR-TR1-2023-12377497), during the conduct of the study. C. Santucci reports the European Union–NextGenerationEU–Italian National Recovery and Resilience Plan, Call 2023 (PNRR-TR1-2023-12377497). I. Milanesi reports grants from the European Union–NextGenerationEU–Italian National Recovery and Resilience Plan, Call 2023 (PNRR-TR1-2023-12377497), during the conduct of the study. P. Lovreglio reports grants from the European Union during the conduct of the study. F. Bravi reports grants from the European Union–NextGenerationEU–Italian National Recovery and Resilience Plan, Call 2023 (PNRR-TR1-2023-12377497), during the conduct of the study. C. La Vecchia reports grants from the European Union–NextGenerationEU (PNRR-TR1-2023-12377497) during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

F. Turati: Data curation, formal analysis, validation, methodology, writing–original draft, writing–review and editing. **M. Pizzato:** Data curation, validation, methodology, writing–original draft, writing–review and editing, review of histologic records and ICD-O coding. **G. Esposito:** Data curation, validation, methodology, writing–review and editing. **P. Bertuccio:** Data curation, validation, writing–review and editing. **C. Galeone:** Conceptualization, investigation, methodology, writing–review and editing. **C. Santucci:** Data curation, validation, writing–review and editing. **I. Milanesi:** Data curation, validation, writing–review and editing. **P. Lovreglio:** Funding acquisition, writing–review and editing. **P. Piscitelli:** Funding acquisition, writing–review and editing. **F. Parazzini:** Funding acquisition, writing–review and editing. **F. Bravi:** Data curation, funding acquisition, validation, methodology, writing–review and editing. **E. Negri:** Conceptualization, investigation, methodology, writing–review and editing. **S. Pavanello:** Funding acquisition, writing–review and editing. **C. La Vecchia:** Conceptualization, investigation, methodology, writing–review and editing.

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Note

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References

1. Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO classification of soft tissue tumours: news and perspectives. Pathologica 2021;113:70–84.
2. Trama A, Badalamenti G, Baldi GG, Brunello A, Caira M, Drove N, et al. Soft tissue sarcoma in Italy: from epidemiological data to clinical networking to improve patient care and outcomes. Cancer Epidemiol 2019;59:258–64.
3. Pizzato M, Collatuzzo G, Santucci C, Malvezzi M, Boffetta P, Comandone A, et al. Mortality patterns of soft-tissue sarcomas worldwide up to 2018, with predictions for 2025. Eur J Cancer Prev 2023;32:71–80.
4. Mastrangelo G, Coindre JM, Ducimetière F, Dei Tos AP, Fadda E, Blay JY, et al. Incidence of soft tissue sarcoma and beyond: a population-based prospective study in 3 European regions. Cancer 2012;118:5339–48.
5. van der Graaf WTA, Orbach D, Judson IR, Ferrari A. Soft tissue sarcomas in adolescents and young adults: a comparison with their paediatric and adult counterparts. Lancet Oncol 2017;18:e166–75.
6. WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. 5th ed. Vol. 3. Lyon (France); International Agency for Research on Cancer; 2020. (WHO Classification of Tumours).
7. Bacon A, Wong K, Fernando MS, Rous B, Hill RJW, Collins SD, et al. Incidence and survival of soft tissue sarcoma in England between 2013 and 2017, an analysis from the national cancer registration and analysis service. Int J Cancer 2023;152:1789–803.
8. Amadeo B, Penel N, Coindre JM, Ray-Coquard I, Ligier K, Delafosse P, et al. Incidence and time trends of sarcoma (2000-2013): results from the French network of cancer registries (FRANCIM). BMC Cancer 2020;20:190.
9. Connolly EA, Boye K, Bonvalot S, Kratz CP, Leithner A, Malkin D, et al. Genetic predisposition in sarcomas: clinical implications and management. EClinicalMedicine 2025;83:103203.
10. Farid M, Ngeow J. Sarcomas associated with genetic cancer predisposition syndromes: a review. Oncologist 2016;21:1002–13.
11. Araki Y, Yamamoto N, Tanzawa Y, Higashi T, Kuchiba A, Hayashi K, et al. Family cancer history and smoking habit associated with sarcoma in a Japanese population study. Sci Rep 2022;12:17129.
12. Nabi S, Kahlon P, Kuriakose P. Analyzing multiple risk factors in patients with sarcomas. A case-control study. Indian J Cancer 2015;52:337–42.
13. Ji J, Eng C, Hemminki K. Familial risk for soft tissue tumors: a nation-wide epidemiological study from Sweden. J Cancer Res Clin Oncol 2008;134:617–24.
14. McDuffie HH, Pahwa P, Karunanayake CP, Spinelli JJ, Dosman JA. Clustering of cancer among families of cases with Hodgkin lymphoma (HL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), soft tissue sarcoma (STS) and control subjects. BMC Cancer 2009;9:70.
15. Kang H, Enzinger FM, Breslin P, Feil M, Lee Y, Shepard B. Soft tissue sarcoma and military service in Vietnam: a case-control study. J Natl Cancer Inst 1987;79:693–9.
16. Zahm SH, Blair A, Holmes FF, Boysen CD, Robel RJ, Fraumeni JF Jr. A case-control study of soft-tissue sarcoma. Am J Epidemiol 1989;130:665–74.
17. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Radiation. Vol. 100D. Lyon (France): IARC; 2012.
18. Veiga LHS, Vo JB, Curtis RE, Mille MM, Lee C, Ramin C, et al. Treatment-related thoracic soft tissue sarcomas in US breast cancer survivors: a retrospective cohort study. Lancet Oncol 2022;23:1451–64.
19. Montgomery C, Park KJ, Gardner JM, Majors I, Nicholas R. Post-traumatic sarcomas: do they exist? Int J Surg Pathol 2019;27:722–8.
20. He MM, Lo CH, Wang K, Polychronidis G, Wang L, Zhong R, et al. Immune-mediated diseases associated with cancer risks. JAMA Oncol 2022;8:209–19.
21. Serraino D, Franceschi S, Talamini R, Frustaci S, La Vecchia C. Non-occupational risk factors for adult soft-tissue sarcoma in northern Italy. Cancer Causes Control 1991;2:157–64.
22. Olsson HL, Wagner P. Tissue trauma and the subsequent risk of soft tissue sarcoma of the extremity: a population based case-control study in Sweden. J Clin Oncol 2017;35:e13088.
23. Keel SB, Jaffe KA, Petur Nielsen G, Rosenberg AE. Orthopaedic implant-related sarcoma: a study of twelve cases. Mod Pathol 2001;14:969–77.
24. IARC monographs on the evaluation of carcinogenic risks to humans. Chemical agents and related occupations. Vol. 100F. Lyon (France): IARC; 2012.
25. Edwards D, Voronina A, Attwood K, Grand'Maison A. Association between occupational exposures and sarcoma incidence and mortality: systematic review and meta-analysis. Syst Rev 2021;10:231.
26. Burningham Z, Hashibe M, Spector L, Schiffman JD. The epidemiology of sarcoma. Clin Sarcoma Res 2012;2:14.
27. Guercio V, Donato F, Pelucchi C, Verga F, Passini V, Galeone C, et al. Plasma levels of polychlorinated biphenyls (PCB) and the risk of soft tissue sarcoma. Med Lav 2019;110:342–52.
28. Decarli A, Franceschi S, Ferraroni M, Gnagnarella P, Parpinel MT, La Vecchia C, et al. Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. Ann Epidemiol 1996;6:110–8.
29. Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. Burns 2005;31:403–13.
30. Choi JY, Cha WJ, Kim J, Jung ER, Jung SN, Seo BF. Undifferentiated pleomorphic sarcoma of a chronic burn scar of the knee with lymph node metastasis. Int J Low Extrem Wounds 2023;22:767–73.
31. Hossain A, McDuffie HH, Bickis MG, Pahwa P, Cross Canada Study of Pesticides and Health Researchers. Case-control study on occupational risk factors for soft-tissue sarcoma. J Occup Environ Med 2007;49:1386–93.
32. Wang YP, Liu CJ, Hu YW, Chen TJ, Lin YT, Fung CP. Risk of cancer among patients with herpes zoster infection: a population-based study. CMAJ 2012;184:E804–809.
33. Yang Z, Zheng R, Zhang S, Zeng H, Li H, Chen W. Incidence, distribution of histological subtypes and primary sites of soft tissue sarcoma in China. Cancer Biol Med 2019;16:565–74.

34. Ogura K, Morizane C, Satake T, Iwata S, Toda Y, Muramatsu S, et al. Soft-tissue sarcoma in Japan: national cancer registry-based analysis from 2016 to 2019. Jpn J Clin Oncol 2024;54:1150–7.
35. Ferrari A, Sultan I, Huang TT, Rodriguez-Galindo C, Shehadeh A, Meazza C, et al. Soft tissue sarcoma across the age spectrum: a population-based study from the Surveillance Epidemiology and End Results database. Pediatr Blood Cancer 2011;57:943–9.
36. Zeissig SR, Emrich K, Reinwald F, Kasper B, Kleihues-van Tole K, Justenhoven C, et al. Sarcoma research with cancer registry data: data and peculiarities of Germany in the light of other countries. Oncol Res Treat 2023;46:370–81.
37. Zozus MN, Walden A, Pieper CF. Comparing the accuracy of health record data and self-reported data. Washington (DC): Patient-Centered Outcomes Research Institute (PCORI); 2023.
38. Qureshi N, Wilson B, Santaguida P, Carroll J, Allanson J, Culebro CR, et al. Collection and use of cancer family history in primary care. Evid Rep Technol Assess (Full Rep) 2007;159:1–84.
39. Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol 2001;54:902–6.
40. Bravi F, Bosetti C, Negri E, Lagiou P, La Vecchia C. Family history of cancer provided by hospital controls was satisfactorily reliable. J Clin Epidemiol 2007;60:171–5.