Smoking and Family Cancer History Are Associated With Sarcomas in A Japanese Population Study

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Abstract

Background: Sarcoma is a rare cancer, and it is also the cause of the development of various kinds of sarcomas, such as gene abnormalities, which has recently becoming evident due to advances of genetic testing. The approach to solve the origin of diseases is essential to elucidate both the external environmental factors and the internal genetic factors. However, the lifestyle habits, lifestyle-related diseases, personal and family cancer history of sarcoma patients remain unclear.

Methods: A total of 1320 sarcoma patients were enrolled in this study. A questionnaire on lifestyle habits, life-style diseases, and the patient's personal and family cancer history was completed at presentation. A total of 1320 controls were selected by propensity score matching for age and gender. Smoking, drinking, obesity, hypertension, dyslipidemia and diabetes mellitus were compared. In addition, we investigated the incidence of a personal and family cancer history in sarcoma patients.

Results: A smoking habit was the only independent risk factor for high-grade soft tissue sarcoma development in adults ≥ 20 years old ($n=952$), excluding low-grade and intermediate malignant soft tissue tumors (Odds ratio [OR], 2.45; 95% confidence interval [CI] 1.88-3.20, $p<0.001$). The ORs of high-grade liposarcoma and undifferentiated pleomorphic sarcoma (UPS) were 2.56 and 3.00, respectively. Eight percent of sarcoma patients had a personal history of another cancer. Thirty percent of soft tissue sarcoma patients had a family history of cancer in a first-degree relatives (malignant peripheral nerve sheath tumor, 52%; leiomyosarcoma, 46%).

Conclusions: We confirmed that a smoking habit were associated with the development of high-grade soft tissue sarcomas. A family history of cancer might be associated with certain soft tissue sarcomas, but a further investigation will be necessary.

Background

Sarcoma is a rare cancer, and it is also the cause of the development of various kinds of sarcomas, such as gene abnormalities, which has recently becoming evident due to advances of genetic testing. The approach to solve the origin of diseases is essential to elucidate both the external environmental factors and the internal genetic factors.

Lifestyle habits of smoking or drinking and lifestyle-related diseases, such as diabetes mellitus (DM) or hypertension are considered to risk factors for various types of cancer [1-15]. Cigarette smoking is reported to be a major risk factor for head and neck, lung, and esophageal cancer through the exposure of the respiratory system and upper digestive tract to carcinogens [1-7]. Alcohol consumption is also associated with the development of liver, breast, upper-aerodigestive tract, and head and neck cancer through ethanol-mediated carcinogenesis in metabolic disorders or immunosuppressive effects [8, 9].

DM patients have a significantly increased risk of liver, pancreas, and kidney cancer due to exposure to multiple molecules that are expanded by metabolic abnormalities [10-12]. Obesity is defined by an

elevated body mass index (BMI) as a consequence of excessive adipose tissue. Adipose tissue is a dynamic endocrine organ that is responsible for constant metabolism and energy homeostasis. Unchecked hyperadiposity usually leads to metabolic disorders such as altered production of steroid hormones, or chronic subclinical inflammation. These pathophysiologic effects have been associated with tumor development and the progression of cancers such as breast or prostate cancer [16, 17]. Dyslipidemia is also associated with the risk of breast or pancreatic cancer [18-20]. Hypertension is linked to kidney, prostate, breast, and colorectal cancer by the damage of vessels flowing through the organs [13-15].

However, there have been few studies on the lifestyle habits or lifestyle-related diseases associated with sarcomas [21-28]. There are more than 50 distinct histologic subtypes of sarcoma in 2013 WHO (World Health Organization) classification [28], and many of the subtypes can occur at any age, and are not limited to a specific location in the body, which was one of the differences from other cancers. The rarity of the disease and the diverse number of subtypes make it difficult to estimate its prevalence. The identification of risk factors for sarcoma among lifestyle habits and lifestyle-related diseases, might be feasible for preventing its occurrence.

In addition, a personal and family cancer history increases the risk of breast, colorectal, gastric, and testicular cancer [29-34]. However, little is known about the personal and family cancer history of sarcoma patients, other than those with Li-Fraumeni syndrome or Lynch syndrome. Li-Fraumeni syndrome is caused by a *p53* gene mutation, and is well known to be associated with a personal and family history of breast cancer and the development of some subtypes of sarcoma: osteosarcoma, rhabdomyosarcoma, leiomyosarcoma and liposarcoma [35, 36]. Lynch syndrome is due to microsatellite instability and/or the deletion of mismatch repair genes of *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and is also associated with a personal and family history of colorectal cancer, in addition to the occurrence of some types of sarcoma, such as UPS and bone tumor [37-39].

We investigated the lifestyle habits and lifestyle-related diseases in bone and soft tissue sarcoma patients, and compared them to healthy controls, using propensity score matching (PSM) methods, and identified a risk factor for the development of sarcoma. In addition, we investigated the personal and family history of cancer in bone and soft tissue sarcoma patients.

Methods

Data sources

We enrolled 1320 patients (male, n=739; female, n=581; median age, 48 years; interquartile range [IQR] 25-73) with bone and soft tissue sarcoma who were identified from a pathological database at National Cancer Center Hospital between 2006 and 2013, which contained all patients who had pathological diagnosis at the hospital. We had included all patients with primary sarcoma confirmed by a histopathological examination. As part of the take-up examination, all patients filled in the questionnaire about lifestyle habits, lifestyle-related diseases, and their personal and family history of cancer as part of

the first visit check-up. The target patients consisted of 274 patients with bone sarcoma and 1046 with soft tissue sarcoma.

The controls were selected from 9127 individuals in the National Health and Nutrition Examination Survey conducted by the Japanese Ministry of Health, Labour and Welfare in 2014 [40]. The samples were chosen by stratified random sampling from the Japanese people who were ≥ 1 year old at the time of the national survey. The objectives for this national survey was to produce a national estimate of the current status of health in Japanese people for use in health policy.

Variables

A case-control study by using propensity score matching (PSM) was conducted for possible risk factors among lifestyle habits and lifestyle-related diseases, including smoking, alcohol consumption, DM, obesity, dyslipidemia and hypertension. To define the lifestyle variables in this study, the same categories were applied to the control group. In both of cases and controls, a smoking habit was defined as a current habit of smoking $\geq 1/2$ pack per day, including cases with a former smoking habit. An alcohol drinking habit was defined as the consumption of ≥ 500 mL of beer on ≥ 3 days per week. An ethanol amount of 500 mL of beer is equivalent to 240 mL of wine, 180 mL of Japanese sake, 80 mL of spirit (30% of ethanol), and 60 mL of whisky. Obesity was defined as BMI ≥ 25 kg/m². DM was defined by taking antidiabetic medicines or insulin injections. Hypertension and dyslipidemia were defined by taking medicines for these conditions. We also performed sub-analyses for differences in lifestyle habit and lifestyle-related diseases, according to disease origin (bone or soft tissue) and histological type [28].

In addition, we investigated the prevalence of a personal and family history of cancer in sarcoma patients from a questionnaire at the first visit check-up. A family history of cancer included first, second, and third-degree relatives with any cancer. The types of cancer the sarcoma patients and their family had had were also investigated. Sub-analyses for differences in family history were performed according to sex, disease origin (bone or soft tissue), and histological type [28]. There were no data on the personal cancer history or family cancer history in the control group; thus, the prevalence of a personal cancer or family cancer history was only investigated in the sarcoma patients.

Statistical analyses

Propensity scores were calculated based on a logistic regression model taking the dependent variable of being sarcoma patients and explanatory variables of age and sex. Each sarcoma patient was matched with control persons based on the propensity scores up to third decimal places. Pairs with close values were adopted for incomplete matching pairs, and all cases were successfully matched with a control. After PSM, a conditional logistic regression analysis was performed to identify independent risk factors for sarcoma, by diminishing the influence of confounding factors. The adjusted odds ratio (OR) was calculated for each factor. *P* values of <0.05 were considered to indicate statistical significance. We also assessed statistical power with a β error level of < 0.10 .

In addition to describing relationship between the prevalence of lifestyle factors, lifestyle-related diseases and sarcoma occurrence, we further described the prevalence of a personal and family history of cancer among sarcoma patient in total and for respective sarcoma histology types.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria) [41].

This study was approved by the ethical committee of National Cancer Central Hospital (Institutional Review Board Research Number: 2017-336) in compliance with the guidelines of the Helsinki Declaration of 1964.

Results

Sample characteristics

All the 1320 patients with sarcomas were matched for the 1320 controls from the National Health and Nutrition Examination Survey conducted by the Japanese Ministry of Health, Labour and Welfare in 2014 [40]. A total of 2640 subjects were analyzed after PSM. The characteristics of the 1320 sarcoma patients were as follows: smoking habit, n=400 (30%); drinking habit, n=303 (23%); obesity, n=258 (20%); DM, n=70 (5%); hypertension, n=183 (14%); and dyslipidemia, n=79 (6%). The characteristics of the 1320 controls were as follow: smoking habit, n=242 (18%); drinking habit, n=276 (21%); obesity, n=229 (17%); DM, n=48 (4%); hypertension, n=154 (12%); and dyslipidemia, n=89 (7%) (Table 1).

In total, 8% (108/1320) of patients with sarcoma in the bone and soft tissue had a personal cancer history. On the other hand, patients with sarcoma in the bone and soft tissue in total had family history of cancers as follows: up to first-degree, n=367 (28%); up to second-degree, n=651 (49%); and up to third-degree relatives, n=730 (55%) (Table 2).

Relationship between life-style /personal cancer history /family history and sarcoma

In the multivariate analysis, a smoking habit increased sarcoma with an OR of 2.03, (95% confidence interval [CI] 1.66-2.48, $p<0.001$). Alcohol drinking habit, obesity, hypertension, and dyslipidemia were not significantly associated with the development of bone and soft tissue sarcoma (Table 1).

The smoking rate was 400/1320 (%) in sarcoma patients, 61/274 (22%) in patients with malignant bone tumors, and 339/1046 (32%) in patients with malignant soft tissue tumors, respectively (Table 3).

Among high-grade malignancies in adults ≥ 20 years old (n=952), excluding low-grade and intermediate malignant tumors (giant cell tumor of bone, atypical lipomatous tumor, desmoid-type fibromatosis, etc.), the OR of a smoking habit in high-grade sarcoma patients was 2.14 (95% CI 1.70-2.69, $p<0.001$), and that in patients with high-grade bone sarcoma was 1.55 (95% CI 0.94-2.56, $p=0.09$) and that in patients with

high-grade soft tissue sarcoma was 2.45 (95% CI 1.88-3.20, $p<0.001$), according to the multivariate analysis after PSM (Table 4).

The rate of a personal cancer history in malignant bone tumor patients was 5% (14/274). The rates of malignant bone tumor patients with a family history of cancer up to the first-, second-, and third-degree relatives were 20% (56/274), 46% (127/274), and 52% (142/274), respectively. The rate of a personal cancer history in malignant soft tissue tumor patients was 9% (94/1046). The rates of the malignant soft tissue tumor patients with a family history of cancer up to the first-, second-, and third-degree relatives were 30% (311/1046), 50% (524/1046), and 55% (578/1046), respectively (Table 5).

Distribution of life-style /personal cancer history /family history in respective sarcoma histology subtypes

In terms of the histological subtypes among adults ≥ 20 years old with high-grade soft tissue sarcoma, the smoking rates in patients with undifferentiated pleomorphic sarcoma (UPS) and liposarcoma were higher than those in controls: 43% (75/175) vs. 20% (35/175), and 44% (65/147) vs. 19% (35/147), respectively. The ORs were 3.00 (95% CI: 1.76-5.11, $p<0.001$) and 2.56 (95% CI: 1.47-4.44, $p<0.001$), respectively (Table 4).

The rate of no significant personal cancer history was $>10\%$ in patients with any type of bone sarcoma. Among cases of soft tissue sarcoma, patients with angiosarcoma (38%; 6/22) and UPS (17%; 31/180) tended to have a personal history of another cancer. The most common types of historical cancer in these patients were breast cancer (16%; 15/94), colorectal cancer (11%; 10/94), and lung cancer (10%; 9/94) (Table 6A).

In bone sarcoma, 41% (7/17) of patients with chordoma had a first-degree relative family history of cancer. In soft tissue sarcoma, 52% (13/25) of the patients with malignant peripheral nerve sheath tumor (MPNST), and 46% (26/57) of the patients with leiomyosarcoma, 42% (5/12) of the patients with extraskeletal myxoid chondrosarcoma (EMC), and 39% (21/54) of the patients with synovial sarcoma, had a family history of cancer up to the first-degree relatives, although the numbers of each histological subtype were comparatively small due to their rarity (Table 5). The common types of family cancer were gastric cancer, lung cancer and colorectal cancer in both bone and soft tissue sarcoma patients. Gastric cancer was most commonly associated with 30% (17/56) of family cancers up to the first-degree relatives of bone sarcoma patients, and 34% (107/311) of family cancers up to the first-degree relatives of soft tissue sarcoma patients. Lung cancer and colorectal cancer were also highly associated with 18% (10/56) and 20% (11/56) of family cancers up to the first-degree relatives of bone sarcoma patients, and 23% (71/311) and 20% (62/311) of family cancers up to the first-degree relatives of soft tissue sarcoma patients, respectively (Table 6B).

Discussion

A large number of carcinogens in cigarette smoke have been implicated as contributors to oncogenesis in various types of cancer [1-7]. However, there have only been a few previous reports about the association

between smoking and sarcoma development [22-26, 42]. Recent genomic studies have expanded our knowledge regarding the basis of carcinogenesis, including sarcoma; however, gene abnormalities, such as fusion genes or driver mutations, in most types of sarcoma remain unclear [43-50]. Understanding the impact of lifestyle habits, lifestyle diseases, and genetic abnormalities would be helpful to advise patients on how to prevent carcinogenetic factors and also how to obtain appropriate genetic counseling.

The monograph in 2004 by the International Agency for Research on Cancer (IARC) in the WHO, never depicted a relationship between smoking and bone sarcomas, and there was no definite conclusion on the correlation between smoking and soft tissue sarcoma [42]. In previous reports, a cohort study with a 26-year follow-up period found an association between smoking and mortality in soft tissue sarcoma patients; the relative risk (RR) was 1.8 (95% CI: 1.1-2.9) (26). On the other hand, an Italian hospital-based case-control study detected no effect of smoking on soft tissue sarcoma [22]. In 2015, smoking was reported as a potential risk factor for sarcoma with an OR of 2.67 [23]. (Table 7).

Our results suggested that a smoking habit was associated with the development of high-grade soft tissue sarcomas with an OR of 2.45. Patients with liposarcoma and UPS showed higher ORs of 2.56 and 3.00, respectively. The ORs for lymphoma was reported to be 2.47 [5] (Table 8). The OR for high-grade soft tissue sarcoma, especially for liposarcoma and UPS, in smokers, might be close to or higher than the risk of developing for these cancers which the association of smoking were reported previously. Recently, SMARCA4-deficient thoracic sarcoma was reported to be highly associated with smoking (78%, 11/13) [51, 52]. To the best of our knowledge, there have been no studies on the association between smoking exposure and the development of other types of sarcoma. Our results newly indicated that the development of liposarcoma or UPS were comparatively associated with a smoking habit.

In this study, the rate of a personal cancer history in sarcoma patients was not very high overall, but patients with certain histological types of sarcoma tended to have a similar personal cancer history. Among the 6 patients with a history of breast cancer (40%; 6/15), 4 had angiosarcoma, and 2 had UPS. Their history of radiation therapy was not obtained from the first-visit take-up examination, but standard treatment for breast cancer often includes postoperative radiotherapy, in addition to chemotherapy and surgical treatment (tumor excision and lymphadenectomy), as breast cancer is likely to metastasize to lymph nodes. Angiosarcoma and UPS are also the most common radiation-induced sarcomas, so these might be cases of secondary sarcoma [53]. However, the number of these cases was relatively few, and it was impossible to discriminate between primary and radiation-induced sarcoma based on the pathological findings alone. In addition, no sarcoma patients in this study had affected head and neck cancer, which is often treated with radiation therapy.

Some sarcoma patients had a family history of cancer [23, 54, 55]. McDuffie et al. stated that 37% (133/357) of soft tissue sarcoma patients had a first-degree relative with a history of cancer [54]. Nabi et al. reported that 35% (147/425) sarcoma patients had a first-degree relative with a history of cancer [23]. In our study, 30% (311/1046) of the soft tissue sarcoma patients had a first-degree relative with a history of cancer, which was close to the rate of a previous report (Table 9).

The more common histological types in sarcoma patients with a first-degree relatives with a history of cancer were MPNST (52% [13/25]), leiomyosarcoma (46% [26/57]), EMC (42% [5/12]), chordoma (41% [7/17]), and synovial sarcoma (39% [21/54]) (Table 5.). All these histological types are well known to be associated with genetic abnormalities. MPNST was associated with *NF1* gene mutations [44]. Leiomyosarcoma was associated with deletion of *TP53* and *RB1* gene and *BRCA1/2* gene rearrangement [48]. EMC was correlated with *NR4A3* gene rearrangement [46]. Chordoma was associated with T-box-family transcription factor; brachyury [49, 50]. The *SS18-SSX* fusion gene was involved in synovial sarcoma [45]. The inheritance of these genes might have contributed to occurrence of some kinds of sarcoma. A basic study in genes will be needed in order to clarify the mechanism underlying the occurrence of these sarcomas.

Lung cancer and breast cancer are commonly reported as types of family cancer associated with sarcoma in previous reports [23, 55]. However, in our study, gastric cancer was the most common type of family cancer in both bone and soft tissue sarcoma (Table 6B, 9).

The higher incidence of gastric cancer in comparison to U.S. or European populations may be because the population of this study was entirely Japanese, an Asian population that is particularly susceptible to gastric cancer. However, research on the gene expression or the hereditary form of gastric cancer, might lead to the discovery of a new mechanism for the development of sarcoma.

The present study was associated with some limitations. First, the case has been derived from high-volume hospital. The patient characteristics may not be representative of whole Japanese patients with sarcoma. Second, a recall bias in the sarcoma patients might be present in detecting lifestyle habit and family cancer history because of the lack of any validation of the self-reported findings. Patients may be reporting more life-style risk factors than the representative survey conducted nationwide. But the contrast that smoking is related to sarcoma while alcohol is not may not indicate that the recall is not the only explanation of the observed relationship. Third, we could not obtain the personal or family history of cancer in control cases; thus, we could not include a personal or family cancer history in a case-control analysis. However, it would be helpful to know the incidence of other cancers in Japanese sarcoma patients and their relatives in order to provide them with useful information and also to encourage them to undergo genetic counseling.

Conclusions

We confirmed that a smoking habit was associated with the development of soft tissue sarcomas, especially liposarcoma and UPS. A first-degree relative with a history of gastric, lung or colorectal cancer, was suggested to be associated with the development of bone and soft tissue sarcomas, although further investigation is needed to support this association as this study had no data regarding the family history of cancer from the control group.

List Of Abbreviations

IQR, Interquartile range; PSM, Propensity score matching; OR, Odds ratio; RR, Relative risk; DM, Diabetes mellitus; BMI, Body mass index; MPNST, Malignant peripheral nerve sheath tumor; EMC, Extraskeletal myxoid chondrosarcoma; UPS, Undifferentiated pleomorphic sarcoma; CI, Confidence interval; IARC, International Agency for Research on Cancer; WHO, World health organization

Declarations

Ethics approval and consent to participate

This study was approved by the ethical committee of National Cancer Central Hospital (Institutional Review Board Research Number: 2017-336) in compliance with the guidelines of the Helsinki Declaration of 1964, and written informed consent was obtained from all study participants and/or their parents (in case of children).

Consent for publication

The consent for publication of the manuscript from the patients and/or their parents (in case of children) was obtained by the National Cancer Central Hospital.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Competing interests

The authors declare no conflicts of interest in association with the present study.

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Authors' contributions

KA, TH, YN, TY, HT, and AY contributed to the concept and design of the study. HK, TA, MS, IK, EM, and KE contributed to the acquisition, analysis or interpretation of working data. TY, EM and KE assisted the data collection. AY analyzed all the patient's data and was involved in drafting the manuscript. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, table 1,2,3,4,5,6,7,8,9 is only available as a download in the Supplemental Files section.

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