A CASE-CONTROL STUDY OF SOFT-TISSUE SARCOMA

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The roles of nonagricultural occupations, tobacco use, beverage consumption, medical history, and other factors in the development of soft-tissue sarcoma were examined in a population-based case-control study in Kansas. Based on 133 cases diagnosed between 1976–1982 and 948 controls, there were significant excesses associated with use of the drug chloramphenicol (odds ratio (OR) = 5.4, 95% confidence interval (CI) 1.2–23.9) and chewing tobacco or snuff (OR = 1.8, 95% CI 1.1–2.9). The risk associated with smokeless tobacco varied with the location of the tumors; greater risks were observed for tumors of the upper gastrointestinal tract (OR = 3.3), the lung, pleura, and thorax (OR = 3.1), and the head, neck, and face region (OR = 2.4) than other regions of the body (OR = 1.4). A nonsignificant excess was seen with the use of cholesterol-lowering drugs, such as clofibrate (OR = 1.7). Four cases reported histories of prior radiation treatment to the same area of their bodies as their tumors. Soft-tissue sarcoma was also associated with employment in woodworking occupations (OR = 1.7, 95% CI 0.9–3.2) and risk increased with increasing duration of employment. Persons with first-degree blood relatives with a history of Hodgkin’s disease, lymphoma, or cancers of the pancreas, prostate, brain, or skin were at increased risk. Many of the associations observed in this study, notably the risk of soft-tissue sarcoma with smokeless tobacco and medications such as chloramphenicol, deserve further evaluation.

A population-based case-control study in Kansas was initiated to investigate the environmental etiology of soft-tissue sarcoma, non-Hodgkin’s lymphoma, and Hodgkin’s disease. The results pertaining to agricultural factors have been presented elsewhere (1, 2). This report will focus on the effects of nonagricultural occupations, tobacco use, medical history, beverage consumption, and other factors on the inci-

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Abbreviations: CI, confidence interval; ICDO, International Classification of Diseases for Oncology; OR, odds ratio.

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idence of soft-tissue sarcoma. The etiology of soft-tissue sarcoma is largely unknown (3), with little epidemiologic research, other than case reports, having been carried out on nonagricultural factors.

**MATERIALS AND METHODS**

**Cases**

All newly diagnosed cases of soft-tissue sarcoma (*International Classification of Diseases for Oncology* (ICDO) (4) histology codes (all topographical codes examined): 8800–8811, 8813, 8830–8855, 8860, 8890–8891, 8894–8902, 8910–8920, 8930–8981, 8990–8991, 9040–9044, 9120, 9130, 9140, 9150, 9170, 9540, 9540, 9550, 9560, 9581) among white male Kansas residents, aged 21 years or older, during 1976–1982, were identified through the University of Kansas Cancer Data Service, a population-based registry that covers the state of Kansas. Although the registry is a passive system, reporting is mandated by Kansas law and is considered over 90 percent complete. The Kansas registry reports a higher annual incidence rate for soft-tissue sarcoma (4.1/100,000) than reported by the nearby Iowa National Cancer Institute-sponsored Surveillance, Epidemiology, and End Results Registry (3.4/100,000). Methods have been presented in detail elsewhere (1, 2). There were 139 soft-tissue sarcoma histologically confirmed cases, as determined by a review panel of three pathologists.

**Controls**

The controls (*n* = 1,005) were white men from the general population of Kansas. Three controls per case were frequency matched by age (± two years) and vital status to the combined age distribution of the study’s original three cancer case series (non-Hodgkin’s lymphoma, Hodgkin’s disease, and soft-tissue sarcoma). For living cases, controls aged 65 years or older were selected from the Health Care Financing Administration file (the Medicare file), whereas, controls aged 64 years or younger were selected by telephone using a two-staged random digit dialing technique (5). For deceased cases, the controls were selected from Kansas state mortality files with the additional matching factor of year of death. Persons with a cause of death of soft-tissue sarcoma, Hodgkin’s disease, non-Hodgkin’s lymphoma, a malignancy of an ill-defined site (ICDO code 195), homicide, or suicide were excluded.

**Interviews**

Telephone interviews were obtained from 133 soft-tissue sarcoma cases and 948 controls, or, if deceased, from their next-of-kin, between December 1982 and January 1984 (table 1). The overall response rate, a weighted average accounting for the refusals in the household census phase of the random digit dialing procedure and the refusals of randomly selected eligible controls to provide interviews (5), was 93 percent. Approximately one-half of the persons interviewed were study subjects themselves (cases: 50 percent; controls: 51 percent) with the remaining interviews supplied by next-of-kin proxy respondents. The distribution of proxy type was similar among the cases and controls (spouse: 31 percent cases, 27 percent controls; child: 9 percent cases, 10 percent controls; sibling: 5 percent cases, 6 percent controls; parent: 2 percent cases, 3 percent controls; other: 4 percent cases, 4 percent controls).

Information collected included demographic characteristics; usual adult height and weight; a priori suspect nonfarming occupations (3); cigarette, cigar, and pipe smoking; use of chewing tobacco or snuff; consumption of coffee, alcohol, and raw milk products; present and past medical conditions and treatments; trauma; and familial cancer. Subjects were asked for exposure histories until a key date which was five years prior to the cancer diagnosis for the cases (key date range: 1971–1977) and was 1977 for all controls. Because of the difference in key dates for the two groups, the controls had slightly more opportunity to sustain “reportable” exposures than the
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667 cases, meaning the odds ratios obtained in this study may underestimate the true risks.

Risk measurements

The measure of association used was the odds ratio. All risk estimates were adjusted for the effects of age by stratification (20-39, 40-59, 60-79, and >79 years). Maximum likelihood estimates of the overall risk and 95 percent confidence intervals were computed by Gart’s method (6). For duration-response relations, significance was assessed by means of Mantel’s one-tailed linear trend test (7).

RESULTS

Tobacco use

A lifetime history of smoking at least 100 cigarettes was associated with an odds ratio of 0.9 (95 percent CI 0.6-1.4) for soft-tissue sarcoma. Subjects who usually smoked nonfilter cigarettes had an odds ratio of 1.1 (95 percent CI 0.7-1.9), while usual smokers of filter cigarettes had an odds ratio of 0.8 (95 percent CI 0.4-1.3). No trends were observed for age started smoking, total years, number of cigarettes smoked per day, or pack-years. Cigar and pipe smokers had an odds ratio of 1.1 (95 percent CI 0.7-1.7). Tobacco chewers and snuff users had a significantly elevated risk (table 2). Risk associated with smokeless tobacco varied by location of the tumor. Greater risks were seen for tumors of the upper gastrointestinal tract, the lung, pleura, and thorax, and the head, face, or neck region than other areas of the body. The soft-tissue sarcoma cell types, fibromatous (ICDO codes: 8810-8811, 8813, 8830-8832), myxomatous (ICDO codes: 8890-8891, 8894-8902, 8910-8920), and other (ICDO codes: 8800-8804, 8840, 8860-8881, 8890-8891, 9040-9044, 9120, 9130, 9140, 9150, 9170, 9540, 9560, 9581), all showed about a two-fold excess risk, and only sarcomas of adipose tissue (ICDO codes: 8850-8855, 8860) were not associated with use of smokeless tobacco. One of the 28 exposed cases (malignant schwannoma) and six of the 105 unexposed cases (three neurofibrosarcomas and three malignant schwannomas) had neurogenic sarcomas (odds ratio (OR) = 1.1). No data on amounts or duration of chewing tobacco or snuff use were available.

Beverage consumption

Lifetime consumption of at least 100 cups of coffee was not associated with excess risk of soft-tissue sarcoma (OR = 0.9, 95 percent CI 0.5-1.7). Risk was not affected by age started drinking coffee regularly, the total number of years of coffee drinking, or by the number of cups per day of either decaffeinated or regular coffee. Consumption of beer (OR = 0.6), wine (OR = 0.7), or hard liquor (OR = 0.9) were also not related to the development of soft-tissue sarcoma. There was a slight non-significant excess of soft-tissue sarcoma among consumers of raw, unpasteurized milk products (OR = 1.2, 95 percent CI 0.8-1.9), which appeared to be limited to fibromatous (OR = 1.5, 95 percent CI 0.6-3.5) and “other” (OR = 1.3, 95 percent CI 0.7-2.5) sarcoma cell types; however, the excesses are small and not statistically significant.

Medical history

Table 3 presents the odds ratios for selected medical conditions and treatments as reported by the study subjects; we did not verify the data by contacting medical care providers. A significant excess of soft-
### Table 2

**Numbers of soft tissue sarcoma cases diagnosed in Kansas, 1976–1982, and controls, giving odds ratios (ORs) (with 95 percent confidence intervals (CIs)), by tumor characteristics among smokeless tobacco users**

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonuser</strong></td>
<td>105</td>
<td>819</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever used smokeless tobacco, i.e., chewing tobacco or snuff</td>
<td>28</td>
<td>127</td>
<td>1.8</td>
<td>1.1-2.9</td>
</tr>
<tr>
<td><strong>Location of tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper gastrointestinal tract</td>
<td>4</td>
<td>3.3</td>
<td>0.8-12.6</td>
<td></td>
</tr>
<tr>
<td>Lung, pleura, thorax</td>
<td>5</td>
<td>3.1</td>
<td>0.9-10.5</td>
<td></td>
</tr>
<tr>
<td>Head, neck, face</td>
<td>3</td>
<td>2.4</td>
<td>0.5-10.2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>1.4</td>
<td>0.7-2.5</td>
<td></td>
</tr>
<tr>
<td><strong>Soft-tissue sarcoma cell type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromatous</td>
<td>7</td>
<td>1.8</td>
<td>0.7-4.7</td>
<td></td>
</tr>
<tr>
<td>Adipose</td>
<td>3</td>
<td>1.1</td>
<td>0.2-4.2</td>
<td></td>
</tr>
<tr>
<td>Myomatous</td>
<td>7</td>
<td>2.1</td>
<td>0.8-5.3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>1.9</td>
<td>0.9-3.9</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years) at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>4</td>
<td>22</td>
<td>2.3</td>
<td>0.6-8.2</td>
</tr>
<tr>
<td>40–59</td>
<td>6</td>
<td>20</td>
<td>1.7</td>
<td>0.6-4.9</td>
</tr>
<tr>
<td>60–79</td>
<td>9</td>
<td>50</td>
<td>1.3</td>
<td>0.5-2.9</td>
</tr>
<tr>
<td>80+</td>
<td>9</td>
<td>35</td>
<td>3.2</td>
<td>1.0-10.1</td>
</tr>
</tbody>
</table>

### Table 3

**Numbers of soft tissue sarcoma cases diagnosed in Kansas, 1976–1982, and controls, giving odds ratios (ORs) (with 95 percent confidence intervals (CIs)), for selected self-reported medical treatments or conditions and family history of cancer**

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol-lowering drugs</td>
<td>5</td>
<td>20</td>
<td>1.7</td>
<td>0.5-5.0</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>4</td>
<td>5</td>
<td>5.4</td>
<td>1.2-23.9</td>
</tr>
<tr>
<td>Epilepsy or seizure medication</td>
<td>1</td>
<td>13</td>
<td>0.5</td>
<td>0.03-4.0</td>
</tr>
<tr>
<td>Radiation treatment, prior to soft-tissue sarcoma</td>
<td>7</td>
<td>39</td>
<td>1.2</td>
<td>0.5-3.0</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>46</td>
<td>310</td>
<td>1.0</td>
<td>0.7-1.5</td>
</tr>
<tr>
<td><strong>Medical conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergies</td>
<td>21</td>
<td>169</td>
<td>0.8</td>
<td>0.5-1.4</td>
</tr>
<tr>
<td>Chicken pox</td>
<td>87</td>
<td>609</td>
<td>1.1</td>
<td>0.7-1.8</td>
</tr>
<tr>
<td>Chloracne</td>
<td>2</td>
<td>7</td>
<td>1.8</td>
<td>0.3-10.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8</td>
<td>67</td>
<td>0.8</td>
<td>0.3-1.7</td>
</tr>
<tr>
<td>Eczema</td>
<td>4</td>
<td>27</td>
<td>1.1</td>
<td>0.3-3.3</td>
</tr>
<tr>
<td>Heart disease</td>
<td>21</td>
<td>256</td>
<td>0.5</td>
<td>0.3-0.8</td>
</tr>
<tr>
<td>Hepatitis, jaundice, cirrhosis</td>
<td>4</td>
<td>21</td>
<td>1.2</td>
<td>0.3-3.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>176</td>
<td>0.6</td>
<td>0.3-1.1</td>
</tr>
<tr>
<td>Kidney stones or other urinary problem</td>
<td>5</td>
<td>46</td>
<td>0.8</td>
<td>0.3-2.1</td>
</tr>
<tr>
<td>Trauma</td>
<td>46</td>
<td>301</td>
<td>1.1</td>
<td>0.8-1.7</td>
</tr>
<tr>
<td><strong>Family history of cancer</strong></td>
<td>66</td>
<td>397</td>
<td>1.3</td>
<td>0.9-1.9</td>
</tr>
</tbody>
</table>

* The referent group for each comparison is all other subjects who did not report that medical treatment, condition, or family history.
tissue sarcoma was seen among users of the drug chloramphenicol. The four exposed cases had varied cell types: myxoid liposarcoma, giant cell sarcoma (pleomorphic cell sarcoma), carcinosarcoma, not otherwise specified, and sarcoma, not otherwise specified. Excess risks were reported by living subjects (three cases, two controls: OR = 8.4, 95 percent CI 1.1–74.0) and by next-of-kin (one case, three controls: OR = 2.7, 95 percent CI 0.1–30.7). Five cases and 20 controls reported taking cholesterol-lowering drugs, for example, clofibrate (OR = 1.7, 95 percent CI 0.5–5.0). Two cases were myomatous sarcomas (OR = 3.1, 95 percent CI 0.5–15.2) and three were “other” sarcoma cases (OR = 2.9, 95 percent CI 0.6–10.9). The risks were lower among living subjects (one case, five controls: OR = 1.1, 95 percent CI 0.05–10.5) than among deceased subjects (four cases, 15 controls: OR = 1.9, 95 percent CI 0.5–6.4).

There was no significant increase in the risk of soft-tissue sarcoma among persons who had received radiation as part of a medical treatment prior to the diagnosis of the soft-tissue sarcoma. However, six of the seven sarcoma cases reported irradiation in the same area of the body as their tumors. Review of Cancer Data Service records revealed that two cases appeared to be reporting treatment received for their current sarcoma. Of the remaining four cases, two had histories of radiation treatment six and eight years earlier for prior malignancies (malignant lymphoma and squamous cell carcinoma of the glottis, respectively) in the same body region as the subsequent soft-tissue sarcoma. The remaining two cases had no mention of radiation treatment for any prior or current cancer diagnosis in the Cancer Data Service records; their self-reported prior radiation treatment may have been for nonmalignant conditions (e.g., enlarged thymus) or for cancers unknown to the Cancer Data Service. The soft-tissue sarcoma cases were twice as likely to report prior radiation to the head and neck region (OR = 1.81, 95 percent CI 0.6–5.4) and the thoracic or abdominal cavities (OR = 2.2, 95 percent CI 0.6–7.4) as the controls. In addition, the sarcoma cases who reported prior radiation were more likely to have tumors in the head and neck area (25 percent) than sarcoma cases who did not report prior radiation (8 percent).

History of tonsillectomy was not associated with increased risk for all soft-tissue sarcoma cases combined or for any cell type except adipose tumors (10 exposed cases, OR = 2.2, 95 percent CI 0.8–6.2).

No soft-tissue sarcoma cases reported a history of any immunodeficiency syndrome, neurofibromatosis, Gardner’s syndrome, or retinoblastoma—heritable disorders suspected of causing a small proportion of soft-tissue sarcoma cases (3). There was no excess of soft-tissue sarcoma associated with eczema, allergies, or previous trauma (“injuries from accidents”). Chickenpox was associated only with adipose sarcomas (15 exposed cases, OR = 5.6, 95 percent CI 0.8–114.3).

The significant decrease in risk of soft-tissue sarcoma among persons with a history of heart disease may have been due in part to the inclusion of deceased controls who have a higher rate of heart disease in comparison to the general population. Among living subjects with a history of heart disease, the odds ratio was 0.8 (95 percent CI 0.3–2.0) while among deceased subjects the odds ratio was 0.4 (95 percent CI 0.2–0.7). Likewise, the low risk associated with a history of hypertension differed by vital status (living: OR = 0.9, 95 percent CI 0.4–1.7; deceased: OR = 0.4, 95 percent CI 0.2–1.1).

Subjects reporting a history of cancer of any site among their first-degree blood relatives had an odds ratio of 1.3 for soft-tissue sarcoma. Risk was increased for myomatous (OR = 2.1, 95 percent CI 0.9–4.7) and fibromatous (OR = 1.7, 95 percent CI 0.8–3.8) sarcomas, but not adipose (OR = 0.9) or other (OR = 1.0) sarcomas. Excesses of specific cancer sites among relatives were noted as follows (ORs (and 95 percent CIs
in parentheses): Hodgkin's disease, 8.9 (1.7–51.2); lymphoma, 4.0 (0.5–25.8); and cancers of the pancreas, 6.1 (0.9–38.9), prostate, 1.9 (0.7–5.1), brain, 1.8 (0.4–7.1), and skin, 1.4 (0.6–3.0). Four cases reported bone tumors among family members (OR = 1.2, 95 percent CI 0.3–3.8); however, three of the four cases had fibrous sarcomas (OR = 4.2, 95 percent CI 0.9–16.3). No cases reported soft-tissue sarcoma or adrenocortical cancers among relatives.

Nonagricultural occupations

Soft-tissue sarcoma showed nonsignificant associations with employment on a highway, railroad, or utility right-of-way crew, in a woodworking occupation, and in a sawmill (table 4). Among woodworkers, the risk rose from 1.4 among men employed less than six years to 2.1 for men employed six or more years.

**Demographic and other factors**

Risk for soft-tissue sarcoma did not differ significantly by education, marital status, or religion in which the subject was raised. Using European ancestry as the referent group, Scandinavian (OR = 1.5, 95 percent CI 0.7–2.8), Russian and eastern European (OR = 1.3, 95 percent CI 0.6–2.8), and American Indian (OR = 1.4, 95 percent CI 0.6–2.9) ancestries were related to soft-tissue sarcoma. Risk did not vary with height (χ for trend = 1.040, p = 0.149) but rose with increasing body weight (χ for trend = 1.920, p = 0.027). Persons whose usual adult weight was <141, 141–180, 181–200, or >200 lbs had odds ratios of 1.0, 1.3, 1.4, and 2.0, respectively.

**DISCUSSION**

The etiology of soft-tissue sarcoma is largely unknown (3). A small fraction of

**Table 4**

**Numbers of soft tissue sarcoma cases diagnosed in Kansas, 1976–1982, and controls, giving odds ratios (ORs) (with 95 percent confidence intervals (CIs)) by employment in a priori suspect occupations**

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Ever employed</th>
<th>Employed ≤5 years†</th>
<th>Employed 6+ years†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>No. of controls</td>
<td>OR* 95% CI</td>
</tr>
<tr>
<td>Highway, railroad, or utility right-of-way crews</td>
<td>36</td>
<td>207</td>
<td>1.3 0.8–2.0</td>
</tr>
<tr>
<td>Gardener, florist, or landscaper</td>
<td>3</td>
<td>62</td>
<td>0.3 0.1–1.1</td>
</tr>
<tr>
<td>Woodworking</td>
<td>16</td>
<td>74</td>
<td>1.7 0.9–3.2</td>
</tr>
<tr>
<td>Sawmill</td>
<td>5</td>
<td>31</td>
<td>1.2 0.4–3.2</td>
</tr>
<tr>
<td>Paper and pulp mills</td>
<td>1</td>
<td>8</td>
<td>0.9 0.04–7.1</td>
</tr>
<tr>
<td>Construction</td>
<td>38</td>
<td>255</td>
<td>1.2 0.7–1.8</td>
</tr>
<tr>
<td>Metal machining or refining</td>
<td>11</td>
<td>131</td>
<td>0.6 0.3–1.1</td>
</tr>
<tr>
<td>Job with exposure to radiation</td>
<td>3</td>
<td>25</td>
<td>0.8 0.2–3.0</td>
</tr>
<tr>
<td>Chemical industry</td>
<td>5</td>
<td>42</td>
<td>0.9 0.3–2.4</td>
</tr>
<tr>
<td>Veterinarian</td>
<td>2</td>
<td>8</td>
<td>1.8 0.3–9.2</td>
</tr>
<tr>
<td>Manufacturing or replacing electrical transformers or capacitors</td>
<td>4</td>
<td>28</td>
<td>1.1 0.3–3.4</td>
</tr>
</tbody>
</table>

* Odds ratios are relative to persons never employed in that occupation.
† Some cases and controls had unknown duration of employment in the suspect occupations and were excluded from the ≤5 years and 6+ years columns.
cases seem to be due to high doses of ionizing radiation (3, 8–13), genetic susceptibility (3, 14–17), and immunosuppression (18–20). In addition, angiosarcomas of the liver have been attributed to exposure to thorotrast (9, 10), vinyl chloride (10, 21), inorganic arsenic (21), and androgenic steroids (10). Our study provides leads to some host and environmental factors that might influence the development of soft-tissue sarcoma. We evaluated agricultural exposures in earlier reports, which found associations with use of insecticide on animals (2) but not with the use of herbicides (1). The present report examines the association of tobacco use, beverage consumption, medical history, nonagricultural occupations, and other factors with soft-tissue sarcoma.

Tobacco use and beverage consumption

To our knowledge, this is the first report of an association between soft-tissue sarcoma and use of chewing tobacco or snuff. Greater risk was seen at body sites likely to be in direct contact with the tobacco or the juice occasionally swallowed by the user (i.e., upper gastrointestinal tract, lung, oral cavity). Use of smokeless tobacco has been linked previously to carcinomas of the buccal cavity and pharynx, and possibly other sites such as the esophagus (22, 23). Of particular concern is the presence of N-nitrosonornicotine and other nitrosamines in snuff and finely cut chewing tobacco, which are carcinogenic in laboratory animals (23–25). Risk among smokeless tobacco users was not elevated for malignant schwannomas, neurofibrosarcomas, or other neurogenic sarcomas, a target site for nitrosamines in animal studies (26). An association with soft-tissue sarcoma is important to evaluate in light of the 52 percent increase in sales of smokeless tobacco, particularly among young people, in recent years (22). More detailed data on duration, amount, and age started use of smokeless tobacco would be valuable in further studies.

No associations between soft-tissue sarcoma and cigarette smoking, coffee drinking, or use of alcohol were found, which is consistent with the results of a study in western Washington state (27) and a study with cases identified through the Armed Forces Institute of Pathology (28).

Medical history

A fivefold excess of soft-tissue sarcoma was found among persons reporting use of chloramphenicol, an antibiotic. The drug has been linked previously to acute leukemia and aplastic anemia based on clinical surveys (29–32) and a recent epidemiologic study (33) and to osteogenic sarcoma by a case report (34). The striking association with soft-tissue sarcoma should be further investigated in studies in which the exposure histories can be confirmed through records that precede the cancer diagnosis to eliminate recall bias and possible confusion by the subjects with drugs with similar sounding names. For example, one case had received chemotherapy for his soft-tissue sarcoma and may have confused chloramphenicol with chlorambucil, a chemotherapeutic agent sometimes used in the treatment of sarcoma. Attempts to review the hospital records for subjects who reported chloramphenicol use were unsuccessful due to the impossibility of retrieving the records from long-term storage.

There was also a nonsignificant association between soft-tissue sarcoma and hypolipidemic drugs. Clofibrate, the most commonly used cholesterol-lowering drug in the United States and Europe (35), is a potent inducer of peroxisome proliferation in Chinese hamsters (36) and causes hepatocellular carcinoma in rats (35, 37). Of note are a large dermatofibrosarcoma (37) and sarcomas of the lung and parotid gland (35) that occurred in the exposed rats but not in the controls. Clofibrate is also a suspect carcinogen because it contains a chlorinated phenoxy moiety, similar to the phenoxyacetic acid herbicides (38, 39) which have been linked to the development
of soft-tissue sarcoma in studies in Sweden (40, 41), Denmark (42), and Italy (43). However, we saw no association between soft-tissue sarcoma and these herbicides in Kansas (1), nor did the association occur in similar studies in Washington state (27) or New Zealand (44,45). The World Health Organization cooperative trial of clofibrate reported excess mortality due to cancers of the lung, bronchus, and larynx and of the liver, gallbladder, and intestines in the treated group (46). A randomized trial conducted in the United States, the Coronary Drug Project, has not seen any excess cancers among men with myocardial infarctions treated with clofibrate with mean follow-up of 15 years (personal communication, P. Canner, Maryland Medical Research Institute, 1986). The widespread use of this drug makes imperative further evaluation of its possible neoplastic effects. The risks observed in the present study may underestimate the true risk because of the inclusion of deceased controls, some of whom died from cardiovascular disease. Compared with the true “general population,” these controls overrepresent the prevalence of use of cholesterol-lowering drugs, resulting in an underestimate of risk.

The present study found a greater than expected proportion of cases reporting prior medical irradiation to the same body areas as their subsequent sarcomas. No association between risk of soft-tissue sarcoma and employment in a job involving exposure to radiation was observed. Neither medical nor occupational exposure to radiation was associated with soft-tissue sarcoma in western Washington state (27) or in the study using data from the Armed Forces Institute of Pathology (28).

No cases of soft-tissue sarcoma in this study were known to be associated with the Mendelian syndromes previously linked to soft-tissue sarcoma, such as neurofibromatosis or retinoblastoma (3). There rare syndromes, however, could easily be missed in a case-control study. Soft-tissue sarcoma was associated with a nonsignificant 30 percent excess among persons reporting cancer of any site in members of the immediate family. However, only one of the excess cancer sites (brain) has been prominent in the constellation of neoplasms that comprise the Li-Fraumeni cancer family syndrome featuring sarcomas of the soft-tissues or bone, breast cancer, brain tumors, leukemia, and adrenocortical tumors (14–17, 47). Breast cancer and leukemia, often noted in the family members with this syndrome (15,17, 48,49), did not occur more often than expected among the relatives of the Kansas soft-tissue sarcoma cases.

Kaposi’s sarcoma, a malignancy of the blood vessels, has historically occurred primarily among older men of Eastern European and Mediterranean origin and been indolent in clinical course (50). However, Kaposi’s sarcoma has recently been reported among younger persons with acquired immunodeficiency syndrome (50–52) and other immunologically-suppressed states (3). The present study included only one Kaposi’s case, who was diagnosed at age 76 years, consistent with the classical pattern.

Nonagricultural occupations

The risk for soft-tissue sarcoma was elevated among woodworkers and rose with increasing duration of employment in the job. A case-control study in New Zealand, however, found no association with the occupations of cabinetmaker or related woodworkers (44). Employment in a sawmill, of interest because of the use of pentachlorophenol as a wood preservative (53), was associated with a nonsignificant 20–30 percent excess risk in the present study in Kansas and in New Zealand (45), based on lifetime occupational histories. No association was seen between soft-tissue sarcoma and sawmill work in a study based on death certificate data from Washington state (54).

Demographic and other factors

The risk of soft-tissue sarcoma was found to increase with usual adult body weight.
To our knowledge, there are no previous reports of this association, although many other malignancies have been associated with body weight, high relative body weight, or high caloric intake (55). Osteogenic sarcoma, but not soft-tissue sarcoma, has been associated with increased height (56).  

Summary  
In summary, this case-control study evaluated the role of nonfarming occupations and other potential risk factors for soft-tissue sarcoma. It is worth noting that the power of the study for many of the variables examined was low, which prohibited multivariate analyses and which makes some of the negative findings difficult to interpret. However, some previously reported associations were confirmed and others were detected that provide leads for further investigation. Of interest are the suggestive findings of an increased risk of soft-tissue sarcoma with clofibrate use and woodwork-ings occupations and the stronger associations with chloramphenicol and use of smokeless tobacco.

REFERENCES  

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