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# An updated review of the epidemiology of soft tissue sarcoma

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## Incidence

Soft tissue sarcoma (SST) represents a heterogeneous group of tumor diseases originating from connective tissue accounting for less than 1 % of all malignant tumors in Sweden. With increasing age there is an increase in incidence (National Board of Health). Comprehensive reviews of the epidemiology of soft tissue sarcoma have previously been published (Tucker et al. 1982, Zahm and Fraumeni 1997 and Olsson 1999). The heterogeneity of sarcoma types and the rarity of cases have hampered etiologically oriented studies. When excluding Kaposi sarcoma the incidence of other soft tissue sarcomas have not dramatically increased in developed western countries. Because of the inherent difficulty in classifying SST international variations and geographic patterns have not been evaluated in a meaningful way.

Risk factors of SST are thus only partly known. Risk factors include a family history of cancer/soft tissue sarcoma, certain genetic syndromes, exposure to ionizing irradiation, and exposure to certain chemicals such as vinyl chloride. Other factors associated with SST development include longstanding lymphedema, exposure to Thorotrast, arsenical pesticides and medications, herbicides, immunosuppressive drugs, alkylating agents, androgen-anabolic steroids, human immunodeficiency virus, and exposure to human herpes virus type 8 (Zahm and Fraumeni 1997 and Olsson 1999). Further a tissue trauma has been discussed as a possible risk factor. Studies from our own group has suggested that oral contraceptive use is partly protective for STS in women (Olsson et al. 2001).

The etiologic role of herbicide exposure including dioxin exposure and chlorophenol exposure is still controversial and studies and reviews have reached contradictory results (Lyng 1985, Wiklund and Holm 1986, Wiklund et al. 1988, IARC monographs 1987, Ibrahim et al. 1991, Bueno-de-Mesquita et al. 1993, Lyng 1993, Dich et al. 1997, Froehner and Wirth 2001, Garabrant and Philbert 2002, Tuomisto et al. 2004, Eriksson et al. 1990). In this article, I review epidemiological studies that have been published within the last 5 years in order to possibly provide new etiological clues for further studies.

## Genetic factors

In a bleomycin assay sarcoma patients were found to have a 6 times higher mutagen sensitivity of lymphocytes compared with healthy controls (Berwick et al. 2001). The authors suggest that this could be a marker of susceptibility of SST.

Diamond-Blackfan anemia (DBA) is a congenital pure red cell aplasia and in a registry study (Lipton et al. 2001) encompassing 354 individuals having the syndrome, 6 individuals had developed malignancies (3 osteosarcomas, 1 myelodysplastic syndrome, 1 colon cancer and 1 STS). The authors suggest that sarcoma risk is elevated in the gene carriers.

As synovial sarcomas are characterized by a translocation between (X;18) it was hypothesized in a study (Bu et al. 2002) that the translocation of the X-chromosome only affects the active X-chromosome, and as women have one chromosome inactivated, this should lead to a lower

incidence of synovial sarcoma in women than in men. This hypothesis was corroborated with data from the SEER (Surveillance, Epidemiology and End Results) (SEER, 2003) program where a lower incidence of synovial sarcoma was found in women.

Li-Fraumeni syndrome is a cancer syndrome where young individuals carry a substantial risk of developing sarcoma, leukemia, breast cancer, lung cancer, and adrenal tumors. Cancer incidence was studied in p53 mutation carriers >20 years of age (Hwang et al. 2003). The calculated SIRs showed a >100-fold higher risk of sarcoma, female breast cancer, and hematologic malignancies for the p53 mutation carriers. Interestingly a significantly higher cancer risk was found in female carriers than in male carriers, a difference not explained by an excess of sex-specific cancer. There was no difference in cancer risk between individuals belonging to families with missense mutations or truncating mutations.

The possibility that pesticide exposure may increase the cancer risk in the offspring was studied in Sweden by linking records of male pesticide applicators to the Multigeneration Register and to the Cancer Registry (Rodvall et al. 2003). None of the *a priori* hypotheses of increased risk of tumors of the nervous system, kidney cancer, leukaemia, lymphoma, soft tissue sarcoma, and testicular cancer in children of male pesticide applicators could be confirmed.

### Childhood sarcoma

Among 13,500 children ( $\leq 21$  years of age) diagnosed with soft tissue sarcoma in 25 US and Canadian institutions (Neglia et al. 2001) and who survived for at least 5 years the highest excess risk for a second tumor was seen for bone cancer (SIR=19.1) and breast cancer (SIR=16.1). In multivariate regression models, adjusted for therapeutic radiation exposure, second malignant neoplasms of any type were independently associated with female sex, childhood cancer at a younger age, childhood Hodgkin's disease or soft-tissue sarcoma, and exposure to alkylating agents.

In a review of non-AIDS-defining cancers (Wisnub et al. 1999) an increased incidence in HIV

infected individuals of anal, skin, oral mucosa, head and neck and lung carcinomas, testicular tumors, and pediatric soft-tissue sarcoma was highlighted. There appears to be an emerging role for various concurrent viral infections in the HIV-infected host that are likely implicated in the pathogenesis of some nondefining-AIDS neoplasms including STS.

### Occupational factors

In a study (Briggs et al. 2003) comparing occupational risk factors for selected cancers among African American and White men in the United States significantly increased risks were seen for exposures only in African American men; chromium exposure was associated with non-Hodgkin's lymphoma (OR=3.9, 95% CI 1.2–13), while wood dust exposure was associated with Hodgkin's disease (OR=4.6, 95% CI 1.6–13) and STS (OR=3.7, 95% CI 1.6–9). The results could imply that racial disparities in levels of exposure to occupational carcinogens exist or alternatively be chance findings as confidence intervals still are broad.

Another case-control study from Canada (Pahwa et al. 2003) addressing whether exposure to farm animals was associated with an increased risk for either Hodgkin's disease, multiple myeloma and STS did not reveal a risk association for either disease. Also farm residence or work was not more common than among controls. The only independent risk factor for STS was a family history of cancer.

Sarcoma subtypes and skeletal sarcoma was related to occupational risk factors in a case control study conducted among US men 1984–1988 (Hoppin et al. 1999). In the analysis 251 living sarcoma cases (48 dermatofibrosarcoma protuberans, 32 malignant fibrous histiocytoma (MFH), 67 leiomyosarcoma, 53 liposarcoma, and 51 skeletal sarcoma) and 1908 living controls were included. Self-reported herbicide use was associated with MFH (OR=2.9, 95% CI = 1.1–7.3). Elevated risks for chlorophenol exposure and cutting oil exposure and MFH and leiomyosarcoma were found. These data suggest that sarcoma subtype is important to evaluate in relation to specific risk factors and calls for collection of large study bases.

A follow up study (Bertazzi et al. 2001) of dioxin exposed individuals after the accident in Seveso, Italy 1976 demonstrated an increased all cancer mortality (RR=1.3, 95% CI 1.0-1.7). Individual cancer types showing an increased mortality included lungcancer, rectal carcinoma and non-Hodgkin's lymphoma and Hodgkin's disease. No case of STS was noted.

In a Finnish case-control study comparing STS cases (N=110) with controls (appendicitis patients, N=227) the level of dioxin was measured in subcutaneous fat (Tuomisto et al. 2004). No increased risk associated with increased dioxin concentration was observed. In contrast, the highest risk of sarcoma was found at low levels of dioxin.

A meta-analysis of 6 mortality studies (Boffetta et al. 2003) looking at occupational vinyl chloride exposure and cancer mortality showed an increased risk of liver cancer in all studies with SMR values ranging from 1.6-57. In 4 of the studies the excess risk of liver cancer persisted even after excluding the known relationship between angiosarcoma and vinyl chloride exposure. There was an increased mortality from STS (SMR 2.5, 95% CI 1.6-4.1). Also an increased mortality from lung and brain tumors, blood and lymphatic tumors could not be excluded. The relationship between STS and vinyl chloride exposure could partly be due to an under-diagnosis of angiosarcomas.

In a cohort of Icelandic male deck officers followed between 1966- 1998 an increased risk of STS was found (SIR=2.7, 95% CI 1.2-5.1), but not an increase in total cancer incidence (Sulem and Rafnsson 2003). The possible etiologic factor responsible for this finding is unknown.

The cancer incidence was studied in world class athletes in Finland (Pukkala et al. 2002). Smoking related cancers were less frequent while incidence of other cancers was not reduced. Hurdlers had an increased risk of bone and soft tissue sarcoma. The authors speculated if injuries during their active sport period may predispose for their sarcomas.

### Constitutional factors and medical conditions

Concern has been raised that use of arthroplasties and the operative trauma may increase STS risk.

Cancer incidence was therefore followed in a Finnish cohort of 31 651 patients and 6 Nordic cohorts of 73 000 patients who had undergone total hip or knee arthroplasty (Paavolainen et al. 1999, Visuri et al. 2003). Cancer incidence was not increased and for some sites as the lung, larynx, stomach, colon, and rectum a lower incidence was seen. No increased risk of sarcoma was seen and there was no sarcoma case presenting at the site of operation.

Patients with Dupuytren's contracture have an increased risk of developing STS. To study the association 18 patients with the contracture who later (+5 years ) developed a sarcoma were compared with other patients who did not develop a sarcoma (Wilbrand et al. 2002). No difference in patient characteristics was noted.

Hormonal factors may influence the risk of STS. In both a case-control study and a cohort study in Southern Sweden use of oral contraceptives strongly reduced the risk of STS in women (Olsson et al. 2001).

In a hospital based case-control study from Italy (Tavani et al. 1999) a high BMI (>30 kg/m<sup>2</sup>) was related to an increased risk for STS. These data need confirmation in population based studies avoiding a possible bias with hospital controls.

### Conclusion

The knowledge of risk factors of STS is scattered and incomplete and studies are hampered by the rarity and heterogenous nature of the disease. Several possible risk factors need to be further assessed in STS such as herbicide exposure, constitutional and hormonal factors during childhood, puberty and adulthood. Especially risk studies stratified on STS subtype should have priority as the risk association with herbicide exposure still is controversial. Some medical condition linked to STS development should be deeper studied in order to find out disease mechanisms such as the relationship with Dupuytren's contracture, Diamond-Blackfan anemia, AIDS and a possible inherent mutagen sensitivity and STS risk. Preventing STS is a further challenge. Except for preventing infections to HIV and herpes virus type 8 and exposure to ionizing irradiation and thorotrast

it is unclear if reduction of other exposures could be expected to reduce the incidence of SST. The possibility that oral contraceptive use reduces the risk of STS in females should further be explored in prospective studies.

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