Identification of Soft Tissue Sarcoma Deaths in Cohorts Exposed to Dioxin and to Chlorinated Naphthalenes

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Identification of soft tissue sarcomas (STSs) in epidemiologic mortality studies is complicated by nosologic coding rules that require that STSs arising in a visceral organ must be coded in the International Classification of Diseases (ICD) category for that organ, rather than in the ICD category for malignant neoplasms of connective tissue. Moreover, prior studies have shown poor agreement between diagnoses recorded on death certificates compared with those in hospital records for these tumors. We reviewed deaths from STS among workers in a registry of 6,716 dioxin-exposed workers at the National Institute for Occupational Safety and Health (NIOSH) and in a NIOSH cohort mortality study of 10,240 workers exposed to chlorinated naphthalenes. We identified 19 subjects with STSs. Of these, 17 (89%) were identifiable by reading the entries on selected death certificates, and two (11%) were found only by reviewing medical records of cases coded to ICD categories likely to have contained STS. Of the 17 STSs identified from death certificates, only nine (53%) had been coded as underlying cause of death to the ICD category "malignant neoplasms of soft and connective tissue." Medical records were obtained for 14 of the 17 cases (82%), and in each case, the STS diagnosis was verified. Tissue blocks from tumors were available for review in nine of the 17 cases identified from death certificates, and the diagnosis of STS was verified in seven (78%). Nosologic rules reduce the sensitivity of cohort mortality studies to detect excesses of STS. Development of referent rates based on histologic coding, such as the International Classification of Diseases for Oncology (ICD-O) system, would allow better study of tumors such as STS. (Epidemiology 1993;4:14–19)

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Sarcomas are fleshy tumors that have been recognized as different from carcinomas, or "crab-like" tumors, since the time of Hippocrates.[1] Soft tissue sarcomas (STSs) are primarily those that arise in tissues of mesodermal origin, such as muscle, fat, and connective tissue. They also include tumors of ectodermal origin, such as neurogenic sarcomas, but do not include osteosarcomas[2] (Table 1). As a cause of death, these tumors are rare, accounting for less than 1% of all fatal cancers.[3] A recent study found an excess of STSs in U.S. chemical workers who were exposed to products contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD; dioxin).[4] STSs have been also associated in several case-control studies with exposure to various phenoxy acid herbicides and chlorophenols, some of which did not contain 2,3,7,8-TCDD.[5-7]

Identification of STSs in epidemiologic studies may be clouded by misclassification of deaths due to STS that are coded from death certificate information. In cohort mortality studies, life table analysis of STS is based upon nosologic coding of the underlying cause of death from death certificates. The coding rules for the World Health Organization International Classification of Diseases (ICD) are based on the anatomic site where the tumor originates and require that STSs arising in visceral organs such as the stomach or heart be coded to the ICD category for neoplasms of that organ, rather than to the ICD category for neoplasms of connective tissue.[8] Additionally, STSs occurring in the retroperitoneal space are coded to an ICD category for malignant neoplasms of the peritoneum and retroperitoneum that includes other types of tumors. Consequently, a life table analysis based on death certificates counts as STSs only those deaths coded to the ICD category for malignant tumors of connective tissue (ICD-8 and ICD-9, Category 171; ICD-6 and

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TABLE 1. Soft Tissue Sarcomas*

Source or Class	Morphology
Fibrous tissue	Fibrosarcoma
Fibrohistiocytic	Malignant fibrous histiocytoma
Adipose tissue	Liposarcoma
Muscle	Leiomyosarcoma
	Rhabdomyosarcoma
Blood vessels	Angiosarcoma
Synovial tissue	Synovial sarcoma
Nervous tissue	Malignant schwannoma
	Myxoid neurogenic sarcoma
Unclassified	Other soft tissue sarcomas

* Adapted from Enzinger and Weiss.[2]

ICD-7, Category 197; ICD-5, Category 55E).[8] As an example of how few STSs are coded to this ICD category, a Swedish case-control study that used cases of STS reported to a cancer registry in the period 1978–1986 found that only 60% were coded as connective tissue tumors.[5] In Denmark in 1978–1982, only 33% of incident STSs were coded to ICD (7th revision) Category 197.[9] The ICD category to which connective tissue tumors are coded appears to be influenced by histologic type. Percy found (Table 2) that among incident cases of STS in U.S. whites reported to the Surveillance, Epidemiology and End Results (SEER) Program, 1973–1982, the percentage of incident STSs coded to the ICD category of connective tissue tumors ranged from 6% for dermatofibrosarcoma, which is commonly coded to skin, to 70% for liposarcoma (Constance Percy, National Cancer Institute, personal communication, March 1989).

The accuracy of death certificate and medical record diagnoses of STS may be low. A review of 252 deaths in 1970–1971 included in the U.S. Third National Cancer Survey showed that only 55% of STSs coded in ICD (8th revision) Category 171 on death certificates were confirmed when hospital records were examined.[10] In an analysis of four deaths among U.S. workers exposed to 2,3,7,8-TCDD, Fingerhut *et al*[11] reported that the hospital records for all four individuals confirmed the diagnosis, but only two were further confirmed as STSs when slides of the tumors were reviewed independently by two pathologists with expertise in sarcomas. Hoar *et al*[12] reported that only 81% of incident cases were verified upon tissue review by two expert pathologists. Leyvraz and Costa[13] suggested that the accuracy of pathologists' diagnosis of STS should improve in future years as newer classification schemes[2] and immunochemical staining techniques become better known.

Purpose of the Study

The National Institute for Occupational Safety and Health (NIOSH) has assembled a dioxin registry that includes 6,716 former and current workers at 14 U.S. chemical plants who were assigned to the production of chemicals contaminated with various isomers of dioxin.[14] The data in the registry are being used to conduct several studies, including a recently completed mortality study.[4] About 875 of the workers in the dioxin registry have medical histories of chloracne, a condition associated with 2,3,7,8-TCDD exposure.[15] NIOSH is also conducting a mortality study of 10,240 workers employed at a plant that used chlorinated naphthalenes (known under the trade name of Halowax) to manufacture "navy cable" during World War II. Although chlorinated naphthalenes have not been reported to be contaminated with 2,3,7,8-TCDD, workers exposed to them have developed chloracne.[16] These cohorts were chosen as likely sources from which to evaluate the adequacy of methods used to identify STS, because STS was an *a priori* hypothesis in each of the mortality studies.

One aim of this study was to evaluate the impact of nosologic rules on the ICD categories to which STSs mentioned on death certificates were coded. Another aim was to evaluate the agreement between death certificate diagnoses and medical records by reviewing medical records for all cases of STS and all tumors in organs likely to contain STS. Verification of the diagnosis from tissue specimens was of interest, and slides and tissue blocks were sought for all cases of STS. A final aim was to evaluate whether these attempts to verify death certificate diagnoses by obtaining medical

TABLE 2. Number and Percentage of Incident Cases of Soft Tissue Sarcoma in U.S. Whites Coded to ICD Category 171 by Histologic Type, SEER Program, 1977–1982*

Cases Coded to Connective Tissue (ICD-171)	Sarcoma, Nonosteogenic	Fibrosarcoma	Fibrous Histiocytoma	Liposarcoma	Leiomyosarcoma	Dermatofibrosarcoma
%	47	69	67	70	16	6
Number	626	485	772	965	1,775	431

* Personal communication, Constance Percy, National Cancer Institute, March 1989.

records and tissue specimens yielded enough new information to justify the effort in future studies.

Materials and Methods

Two trained nosologists independently coded all death certificates for the workers in the dioxin registry. Where there was disagreement between the two nosologists, a senior nosologist at the National Center for Health Statistics provided the final opinion. The two nosologists disagreed on the ICD coding for one STS case, but the third nosologist coded it as STS. All death certificates in the Halowax cohort were initially coded by one nosologist. Those death certificates selected for review (as described below) were recoded by a second nosologist, and disagreements were resolved in the same manner as for the dioxin registry.

Cases of STS were initially identified for both cohorts from death certificates on which underlying or contributing causes were coded, according to the ICD version in effect at the time of death, as ICD (8th and 9th revisions) Category 171, ICD (6th and 7th revisions) Category 197, and ICD (5th revision) Category 55E. Additionally, we used a computer search to identify additional death certificates in each cohort likely to mention STS. The search selected death certificates for review if: (1) the underlying or contributory cause of death was a cancer arising in organs in which 2% or more of incident histologic types were found to be STSs in the Third National Cancer Survey.[17] These cancers were those of the stomach, small intestine, retroperitoneum, omentum, mesentery, bones and joints, soft tissues, vagina, uterus, and "other respiratory system." (2) The deaths were coded to "malignant neoplasm without specification of site" [ICD (5th revision) Category 55E; ICD (6th to 9th revisions) Category 199.0] as an underlying or contributory cause of death, unless a primary tumor was also coded for the same death and this tumor was not in the group of sites listed above.

A total of 119 death certificates for members of the dioxin registry and 360 death certificates for members of the Halowax cohort met these selection criteria. We reviewed each certificate manually for mention of an STS in any of the certifier's diagnoses. To identify any STSs missed in the computer search, we manually reviewed each of the approximately 5,000 death certificates in the Halowax cohort and the approximately 1,500 death certificates in the dioxin registry, and we read the certifier's actual diagnoses to identify mention of an STS.

To verify the cause of death, medical records were requested for all cases of STS identified as described above and for all other deaths that had been selected for death certificate review by the computer search. We requested tissue blocks and pathology slides of specimens for each case of STS, and these were reviewed by consulting pathologists at the Armed Forces Institute of Pathology.

Results

Death Certificate Review

Review of information written on the death certificates successfully identified 17 of 19 STS deaths found in the two cohorts combined. For the dioxin registry, five of seven cases of STS were identified from death certificates. Fingerhut *et al*[4,11] have reported six of the cases. Four cases were identified from nosologic coding to ICD Category 171 as the underlying cause of death (Table 3, Cases 1–4). The fifth case (Table 3, Case 5) was identified during the reading of contributory causes of death on 119 death certificates for which records had been requested.

In the Halowax cohort, we identified 12 of 12 cases of STS from death certificates. We identified five cases of nosologic coding to ICD Category 171 (Table 3, Cases 8–12). We identified seven additional cases by reading the causes of death on the 328 death certificates for which records had been requested. Of the seven additional STSs, one was coded to lung (Table 3, Case 13) and one to liver (Table 3, Case 14) as the underlying cause of death. Four STSs occurred in the retroperitoneum and were coded as underlying cause of death to ICD Category 158 "malignant neoplasm of peritoneum and retroperitoneum" (Table 3, Cases 15–18). One STS death (Table 3, Case 19) was coded to ICD Category 199.1, "malignant neoplasm without specification of site."

Of the 19 cases of STS that we identified, one occurred in a white female, one in a black male, and 17 in white males. We found no additional mention of STS after manual review of the approximately 6,000 remaining death certificates in both cohorts.

Medical Record Review

We obtained medical records for 99 of 119 (83%) requested for individuals in the dioxin group and 227 of 360 (63%) requested for persons in the Halowax group. The average time since death was 12.5 years for the 119 workers from the dioxin registry and 26 years for the 360 workers in the Halowax cohort.

For the dioxin registry group, we obtained medical records for all seven STS deaths identified in Table 3, and the diagnosis of STS was confirmed in each case. In Case 5, the medical records indicated that the

TABLE 3. Identification of Soft Tissue Sarcomas from Death Certificates and Verification from Medical Records

Case No.	Year Died	ICD Code: Underlying	ICD Code: Contributing	Underlying Cause*	Contributing Causes	Identified by ICD Codes	Identified on Death Certificate	Diagnosis from Medical Records*	Diagnosis after Tissue Review by Consultant Pathologist*†
Dioxin registry									
1	1978	171.9		MFH		Y	Y	MFH	MFH
2	1972	171.9		Liposarcoma		Y	Y	Liposarcoma	Carcinoma poorly differentiated‡
3	1975	171.9		Malignant fibrosarcoma		Y	Y	Fibrosarcoma	Clear cell carcinoma‡
4	1983	171.9		MFH		Y	Y	MFH	MFH
5	1986	188.9	198.8, 199.0	Carcinoma of bladder	Carcinomatosis; liposarcoma	N	Y	Liposarcoma	Liposarcoma
6	1980	199.0		Carcinomatosis		N	N	MNS	Leiomyosarcoma
7	1965	196.4	199.2	Metastatic osteosarcoma, generalized originating from left arm		N	N	Fibrosarcoma	No tissue available
Halowax cohort									
8	1981	171.2	197.0, 197.7	Sarcoma right arm with metastases to lung		Y	Y	Liposarcoma	Liposarcoma
9	1970	171.3		Fibrosarcoma		Y	Y	No record available	No tissue available
10	1982	171.3		MFH		Y	Y	MFH	MFH
11	1985	171.5		Abdominal wall sarcoma		Y	Y	Rhabdomyosarcoma	No tissue available
12	1975	171.9		Fibrosarcoma		Y	Y	Fibrosarcoma	No tissue available
13	1945	047D	055E	Sarcoma of right leg	Metastatic sarcoma, lungs and spine	N	Y	No record available	No tissue available
14	1979	155.0		Primary hepatic sarcoma		N	Y	Fibrous histiocytoma	No tissue available
15	1966	158		Retroperitoneal sarcoma		N	Y	Liposarcoma§	No tissue available
16	1957	158	199.2	Sarcoma, retroperitoneal	Sarcomatosis	N	Y	Sarcoma	No tissue available
17	1977	158.0		Retroperitoneal sarcoma		N	Y	Sarcoma	No tissue available
18	1985	158.0	199.0	Sarcoma, retroperitoneal space	Sarcomatosis	N	Y	Sarcoma	Carcinosarcoma
19	1953	199.1	165	Sarcoma of right leg	Metastases to lung	N	Y	No record available	No tissue available

* MFH = malignant fibrous histiocytoma; MNS = myxoid neurogenic sarcoma.
† Armed Forces Institute of Pathology.
‡ Not a soft tissue sarcoma.
§ Pathologist's diagnosis stated, "most likely a liposarcoma, but may be an adrenal carcinoma."

metastatic tumor which caused death was an STS rather than a bladder cancer, as noted on the death certificate. The medical record search identified two additional STS deaths (Table 3, Cases 6 and 7) that were not found by reviewing the wording on death certificates. One death (Table 3, Case 6), described as "carcinomatosis" on the death certificate, was found on review of medical records to be due to a myxoid neurogenic sarcoma. The other death (Table 3, Case 7) listed as "metastatic osteosarcoma" on the death certificate was found to be due to a fibrosarcoma of the arm in the medical records.

For the Halowax group, we obtained medical records for nine of the 12 cases of STS identified from death certificates and listed in Table 3 (75%). The diagnosis of STS was verified in all nine cases. No additional STS was identified from the medical record search for the Halowax cohort.

Tissue Review

We obtained tissue blocks or slides from tumors for six of seven cases in the dioxin group and three of 12 cases in the Halowax group. They were reviewed by consulting pathologists from the Armed Forces Institute of Pathology with expertise in the diagnosis of STS. Five of the cases in the dioxin group had been reviewed previously by an independent pathologist with expertise in sarcomas.[11] For the dioxin group, the diagnosis of STS was confirmed in four of six deaths (67%). The remaining two tissue specimens were found to be poorly differentiated carcinomas (Table 3, Cases 2 and 3). Tissue was available for three cases in the Halowax group, and all were confirmed as STSs (Table 4).

Discussion

Cohort mortality studies rely on nosologic coding of

underlying cause of death from death certificate information. This review indicates that the ability to analyze STSs recorded on death certificates can be greatly affected by nosologic rules. For both the dioxin registry and Halowax groups combined, there were 17 STSs identified on death certificates, and 16 of the certificates indicated that the underlying cause of death was STS. Only nine of the 16 (56%) cases were coded to ICD Category 171, "malignant neoplasms of soft and connective tissue." Two cases (12%) were coded to visceral organs, and five (26%) to retroperitoneum. This distribution is comparable with that reported by Eriksson and colleagues,[5] who found that 60% of STSs selected on the basis of histologic type for a case-control study were coded to connective tissue neoplasms.

NIOSH support staff expended considerable effort over a 3-year period to locate and request copies of 479 medical records. The success rate was good for the dioxin registry (83%) but was somewhat lower for the Halowax cohort (63%), owing to the longer time since death of many of the subjects and the closing of several hospitals in the vicinity of the main study plant. For both the dioxin and Halowax groups combined, of the 17 cases of STS identified from death certificates, we obtained medical records for 14 cases, and the diagnosis of STS was verified in each case (82%), a higher rate than the 55% reported by Percy *et al.*[10] We identified only two additional cases of STS solely from medical records (Table 4). There was clearly a greater yield in identifying STSs by reading death certificate diagnoses for selected records than from the long and expensive medical record search.

Verification of the diagnosis of STS by review of slides or tissue blocks for the Halowax cohort was limited because the closing of several hospitals near the study plant severely reduced access to records and specimens. Of the seven tissue specimens sought for the dioxin group, review of tissue specimens for Cases 1–4, 6, and 7 has been described by Fingerhut *et al.*[4,11] Case 5 (Table 3) in the dioxin registry was verified by the consulting pathologists at the Armed Forces Institute of Pathology, as were Cases 1, 3, and 11 (Table 3) in the Halowax cohort.

Although the number of deaths due to STS was small, this study confirms the points made by others[5,9,11] that death certificates, as presently coded, are relatively insensitive for detecting STS. In addition, because ICD coding of cancers on death certificates for the U.S. population is based upon tumor site rather than morphology, STSs occurring in organs or in anatomic sites such as the retroperitoneal space will not be adequately evaluated by cohort mortality studies.

The methods described here increased the number of STSs detected in the cohorts, but the results of the cohort mortality studies were not changed, because the analysis must use the same ICD categories that are used to code death certificates for the U.S. comparison population. Thus, the power of a life table analysis to detect excesses of STS may be reduced when compared with its ability to detect excesses of other tumors such as colon or rectal cancer. If population-based mortality rates for cancer based upon histologic types rather than anatomic sites were developed, they would assist the study of STS and perhaps other rare tumors in cohort studies. The coding scheme developed by the World Health Organization, International Classification of Diseases for Oncology[18] (ICD-O), might be used as the basis for generating mortality rates from population-based tumor registries that would make use of histologic classification. A life table analysis of cancer using ICD-O codes should allow better identification of those at risk for malignancies such as STS.

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TABLE 4. Identification of Soft Tissue Sarcomas

	Coded to Neoplasms of Connective Tissue*	Coded to Other ICD Categories	Additional Cases Identified Only from Medical Records	Total
Dioxin registry	4	1	2	7
Halowax cohort	5	7	0	12
Total	9	8	2	19

* ICD (8th and 9th revisions) Category 171; ICD (6th and 7th revisions) Category 197; ICD (5th revision) Category 55E.

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