

A Cohort Study on Cancer Incidence Among Danish Gardeners

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This study was performed to examine the cancer risk of Danish gardeners having been highly exposed to pesticides. We have followed a cohort of 4,015 employed gardeners (859 females and 3,156 males) from May 1975 until the end of 1984 with regard to cancer incidence. The observed incidence was compared with expected numbers calculated from national incidence rates. For all cancer sites combined, the standardized morbidity ratio (SMR) was 104. Among male gardeners a significantly increased incidence was seen for soft tissue sarcoma (SMR = 526, 95% confidence interval (CI): 109-1,538), and chronic lymphatic leukemia (SMR = 275, 95% CI: 101-599). The incidence of non-Hodgkin's lymphoma was twice that which was expected (SMR = 200, 95% CI: 86-393). We suggest that some of the pesticides to which the gardeners have been exposed are capable of initiating or promoting the development of malignant neoplasms in tissues of mesenchymal origin. © 1992 Wiley-Liss, Inc.

Key words: lymphatic leukemia, non-Hodgkin's lymphoma, occupational cancer, pesticides, soft tissue sarcoma, agricultural exposures, gardeners

INTRODUCTION

Gardeners are exposed to many different substances including insecticides, herbicides, fungicides, disinfectants, growth regulating substances, and fertilizers. The International Agency for Research on Cancer (IARC) has reviewed the evidence for the carcinogenicity of several of these agents and has concluded that the following pesticides may be carcinogenic to humans (IARC-group 2B): amitrole, chlordane, chlorophenoxy acetic compounds, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), 1,2-dibromo-3-chloropropane (DBCP), hexachlorobenzene, hexachlorocyclohexane (including lindane), mirex, toxaphene, and 2,3,7,8-trichloro-dibenzodioxin (TCDD) [International Agency for Research on Cancer, 1974, 1976, 1977, 1979, 1983, 1986, 1987]. In addition, the cancer risk associated with exposure to arsenical-containing pesticides is well documented [International Agency for Research on Cancer, 1980].

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Accepted for publication September 5, 1991.

Only a few epidemiological studies have focused on gardeners' health. A study from the United Kingdom reported an increased risk of soft tissue sarcoma among market gardeners [Balarajan and Acheson, 1984]. A Swedish registry study on persons working in horticulture found no increase in either soft tissue sarcoma or malignant lymphoma [Wiklund and Holm, 1986; Wiklund et al., 1988a], whereas a case-control study on soft tissue sarcoma in the southeast of Sweden revealed a fourfold increase among gardeners [Wingren et al., 1990].

Other occupational groups which may be exposed to pesticides include forestry workers, flour industry workers, farmers, pesticide applicators, and workers employed in pesticide manufacturing plants. Several studies on these groups or on persons living in pesticide contaminated communities have indicated an increased risk of lung cancer [Ott et al., 1974; Barthel, 1976; Barthel, 1981; Lyng, 1985], malignant neoplasms of lymphatic and hematopoietic tissue [Hardell et al., 1981; Burmeister et al., 1982, 1983; Cantor, 1982; Pearce et al., 1985, 1986a,b, 1987; Schumacher, 1985; Hoar et al., 1986; Woods et al., 1987; Dubrow et al., 1988; Flodin et al., 1988; McLaughlin et al., 1988; Corrao et al., 1989; Godon et al., 1989; La Vecchia et al., 1989; Persson et al., 1989; Alavanja et al., 1990; Weisenburger, 1990; Wigle et al., 1990; Zahm et al., 1990; Coggon et al., 1991; Vineis et al., 1991], and soft tissue sarcomas [Hardell and Sandström, 1979; Eriksson et al., 1981, 1990; Lyng, 1985; Vineis et al., 1986; Zahm et al., 1988; Fingerhut et al., 1991].

This study was set up to investigate further the possible relationship between occupational exposure to pesticides and the risk of malignant neoplasms, primarily those of mesenchymal origin. The study considered cancer incidence among employed gardeners throughout a 10-year period.

PERSONS AND METHODS

A historical cohort of employed gardeners was followed from May 1, 1975 through January 1, 1985, with regard to cancer incidence. The observed incidence was compared with that which would have been expected had the sex-, age-, and period-specific cancer incidence rates of the total Danish population applied to the study cohort.

The Study Cohort

The cohort was defined to include every person who, on May 1, 1975, was a member of one of the ten local trade unions of gardeners, associated with the Danish Union of General Workers. The members of the study cohort were identified by using an old version of the membership file, which by coincidence had been kept on a magnetic tape, containing the members' civil registration number and the code of the local trade union to which the person in question was affiliated. The cohort comprised 4,015 persons, of whom 859 were women and 3,156 men.

Follow-Up Procedures

The study cohort was followed until January 1, 1985, with regard to vital status and emigration. The follow-up was performed by our searching for the individual civil registration number of each of the cohort members in the Danish Central Population Register; this procedure enabled us to trace everybody. Each person accumulated person-years at risk from May 1, 1975, until the date of death, the date of

TABLE 1. Number of Person-Years at Risk in the Danish Gardener Cohort, 1975 Through 1984

Age (years)	Males	Females	Total
15-29	4,743	1,315	6,058
30-44	9,069	2,484	11,554
45-54	4,580	1,980	6,560
55-64	6,469	1,806	8,275
65-74	4,288	431	4,719
75-79	310	10	320
80-84	8	1	9
15-84	29,368	8,025	37,393

emigration, or January 1, 1985, whichever occurred first. The study covered a total of 37,393 person-years at risk (Table 1).

Information on the cancer incidence in the cohort was obtained from the Danish Cancer Registry, which is a nationwide register that has been in operation since 1943 [Clemmesen, 1974]. For each member of the study cohort, the individual civil registration number was searched for in the files of the Danish Cancer Registry covering the period from the study start on May 1, 1975 until the most recent updating of the registry, January 1, 1985.

Following the identification of cancer cases, we attempted to get additional exposure data for those study persons who had developed soft tissue sarcoma or malignant neoplasms of the blood- and lymph-forming tissues. For most of these persons, the local unions were able to provide data on work area and/or duration of union membership.

Data-Analysis

The site-specific cancer incidence observed in the study cohort was compared with the expected incidence based on the national incidence rates, specific for 5 year age groups, sex, and periods. To allow for an induction/latency time of 10-15 years, we curtailed the analyses to cover only persons aged 30 years or more, as almost all gardeners start in the trade when they are young (personal communication, head of the gardeners' section of the Danish Union of General Workers). Albeit a crude substitute, analysis by age was the only alternative to ignoring induction/latency time. We also disregarded the data for the oldest age group (i.e., 80-84 years of age) because of the extremely small number (nine) of person-years at risk in this group.

The statistical evaluation was based on the assumption that the observed number follows a Poisson-distribution. Confidence intervals (CI) for the estimated standardized morbidity ratio (SMbR) were based on exact Poisson-limits [Bailar and Ederer, 1964; Ciba-Geigy, 1975].

Exposure

Employed Danish gardeners constitute three fairly separate groups according to work area, namely workers in 1) greenhouses, 2) nursery gardens, and 3) public parks, gardens, and cemeteries. In general, the gardeners display a low job-turnover and a pronounced stability of employment.

According to information obtained from the head of the gardeners' section of the Danish Union of General Workers, almost all of the female members and 10-20%

of the male members were greenhouse workers at the time the cohort was established. Reportedly, the major part of the rest of the gardeners—almost exclusively males—were working in public parks, gardens, and cemeteries. Only a few percent were working in nursery gardens. Both the greenhouse workers and the outdoor gardeners have been regularly exposed to a mixture of pesticides during their active work life. The union people estimate that about one-third of the gardeners, almost exclusively males, have been directly exposed by spraying pesticides, whereas the remainder of the group have been indirectly exposed, primarily by skin contact when handling newly sprayed plants or growing medium mixed with pesticides, and by inhalation when working in newly sprayed areas (personal communication, head of the gardeners' section of the Danish Union of General Workers).

Workers in greenhouses have primarily been exposed to fungicides and insecticides, including the various chlorinated compounds (e.g., DDT, chlordane, and lindane), organophosphorous compounds, and nicotine. Gardeners holding outdoor jobs have primarily been exposed to herbicides, including the phenoxy acetic acids (e.g., 2,4-D, 2,4,5-T, and MCPA) and amitrole. This exposure has taken place regularly throughout the growing season, i.e., from April through October. In addition, the outdoor jobs have involved some exposure to insecticides and fungicides. It is worth noting that DDT had been extensively used in Denmark until the late 1970s. On the other hand, the arsenical insecticides have never been used on a large scale in Denmark.

In this cohort study, data on individual job histories have not been obtained except for a subset of the cancer cases (see above). However, in the main, gender may be taken as a rough substitute of type of exposure, with a predominance of indirect exposure to insecticides among female gardeners, and of direct or indirect exposure to herbicides among male gardeners.

RESULTS

A total of 219 cancer cases was observed in the study cohort. Of these, 217 cases occurred among persons aged 30 to 79 years. The SMRs for the main groups of diagnoses are shown in Table II. None of these ratios differed significantly from unity. Separate analyses for malignancies of mesenchymal origin showed a significantly increased incidence of soft tissue sarcoma and chronic lymphatic leukemia among males, and a non-significant increase of non-Hodgkin's lymphomas in both males and females (Tables III, IV). For those study subjects who developed soft tissue sarcoma, non-Hodgkin's lymphoma, or chronic lymphatic leukemia, the available exposure data are shown in Table V.

DISCUSSION

The results of this 10-year follow-up of employed gardeners seem to indicate that, on the whole, the cancer incidence among gardeners does not differ much from that of the total population. However, significant increases were recorded for soft tissue sarcoma and lymphatic leukemia along with a non-significant increase of non-Hodgkin's lymphoma.

As regards the potential bias in this study, the cohort of gardeners represents a healthy subset of the total Danish population, as the study persons were all occupa-

TABLE II. Cancer Incidence Among Danish Gardeners Aged 30 to 79 Years*

Cancer site ^b	Males		Females		Total	
	Obs/ exp	SMbR (95%CI)	Obs/ exp	SMbR (95%CI)	Obs/ exp	SMbR (95%CI)
Total (140-205)	184/172.05	107 (92-124)	33/35.66	93 (64-130)	217/207.71	104 (91-120)
Buccal cavity and pharynx (140-148)	6/5.28	114 (42-247)	0/0.40	0 (0-922)	6/5.68	106 (39-230)
Digestive organs and peritoneum (150-159)	42/40.78	103 (74-139)	7/5.72	122 (49-252)	49/46.50	105 (78-139)
Respiratory system (160-165)	41/42.58	96 (69-131)	2/2.82	71 (9-256)	43/45.40	94 (69-128)
Breast (170)	0/0.29	0 (0-1272)	10/9.33	107 (51-211)	10/9.62	104 (50-205)
Female genital organs (171-176)	—	—	7/7.75	90 (36-186)	7/7.75	90 (36-186)
Male genital organs (177-179)	20/17.38	115 (70-178)	—	—	20/17.38	115 (70-178)
Urinary system (180-181)	18/20.67	87 (52-136)	2/1.54	130 (16-469)	20/22.21	90 (55-139)
Skin (190-191)	31/24.37	127 (86-181)	1/2.45	22 (1-125)	32/26.82	111 (76-157)
Other specified sites (192-197)	6/6.43	93 (34-203)	1/1.48	68 (2-376)	7/7.91	88 (36-182)
Unspecified sites (198-199)	5/4.11	122 (40-284)	1/0.71	141 (4-785)	6/4.82	124 (46-271)
Lymphatic and hematopoietic tissue (200-205)	15/10.45	144 (80-237)	2/1.46	137 (17-495)	17/11.91	143 (83-229)

*Observed no. (Obs), expected no. (exp), standardized morbidity ratio (SMbR), and 95% confidence interval (95% CI) for the SMbR.

^bThe code of the International Classification of Diseases (ICD), 7th revision, in parentheses.

TABLE III. Incidence of Soft Tissue Sarcoma Among Danish Gardeners^{a,b}

	Obs	Exp	SMbR	(95% CI)
Males	3	57	526	(109-1,538)
Females	0	0	0	(0-4,099)
Total	3	57	455	(94-1,328)

^aObserved no. (Obs), standardized morbidity ratio (SMbR), and 95% confidence interval (95% CI) for the SMbR.

^bCode No. 197 in the ICD, 7th revision.

nationally active at the time of enrollment into the study. The cohort constitutes—also with respect to urbanization—a non-representative sample of the total Danish population as only a few city-dwellers are included. Generally, the cancer incidence rates are higher in cities than the national average. This difference is most pronounced for tobacco-related neoplasms [Clemmesen, 1974; Danish Cancer Registry, 1982]. According to the unpublished results of Lander, gardeners generally smoke less than the average population. This feature would create a negative confounding as far as tobacco-related cancers are concerned. As regards the diagnoses that were seen in excess among the gardeners, i.e., soft tissue sarcoma, chronic lymphatic leukemia,

TABLE IV. Incidence of Malignant Neoplasms of Lymphatic and Hematopoietic Tissue Among Danish Gardeners^a

Diagnosis	Males			Females			Total		
	Obs	SMbR	(95% CI)	Obs	SMbR	(95% CI)	Obs	SMbR	(95% CI)
Total ^b	15	144	(80-237)	2	137	(17-495)	17	143	(83-229)
Non-Hodgkin's lymphoma ^b	6	173	(63-376)	2	364	(44-1,314)	8	200	(86-393)
Chronic lymphatic leukemia ^c	6	275	(101-599)	0	0	(0-1,677)	6	251	(92-546)
Other leukemias ^d	3	144	(30-419)	0	0	(0-1,118)	3	123	(25-361)

^aObserved no. (Obs), standardized morbidity ratio (SMbR), and 95% confidence interval (95% CI) for the SMbR.

^bICD, 7th revision, nos. 200-205.

^cICD, 7th revision, nos. 200, 202, and 205.

^dICD, 7th revision, no. 204.0. National incidence rates for chronic lymphatic leukemia have not been available, but have been estimated from the incidence rates for all leukemias and the proportion of chronic lymphatic leukemia among the incident cases of leukemia, 1973 through 1977, stratified by age and sex.

^eICD, 7th revision, nos. 204.1-204.4.

TABLE V. Duration of Exposure Prior to Diagnosis for Those Gardeners Who Developed Soft Tissue Sarcoma (STS), Non-Hodgkin's Lymphoma (NHL), or Chronic Lymphatic Leukemia (CLL)

Diagnosis (ICD-7) ^a	Age (years) at diagnosis	Sex	Duration of exposure (years)
STS (197)	31	Male	9
STS (197)	60	Male	13
STS (197)	71	Male	42
NHL (200)	38	Female	5
NHL (200)	75	Female	10
NHL (200)	71	Male	10
NHL (200)	54	Male	17
NHL (200)	54	Male	28
NHL (200)	65	Male	35
NHL (200)	64	Male	45
NHL (205)	70	Male	Unknown
CLL (204.0)	56	Male	32
CLL (204.0)	69	Male	35
CLL (204.0)	66	Male	44
CLL (204.0)	56	Male	Unknown
CLL (204.0)	68	Male	Unknown
CLL (204.0)	68	Male	Unknown

^aThe code of the ICD, 7th revision, in parentheses.

and non-Hodgkin's lymphoma, the national incidence rates have not displayed any regional trends within the period studied [Danish Cancer Registry, 1982], and there is no reason to suspect that the observed increase among the gardeners has been due to confounding by urbanization. As regards the quality of diagnosis, this has not differed between the two groups compared, because access to medical care was free and equal throughout the period studied. All in all, the estimated SMbR for soft tissue

sarcoma, chronic lymphatic leukemia, and non-Hodgkin's lymphoma seem to be reasonably free from bias. On the other hand, the SMR-estimates for tobacco-related cancers are certainly biased in a negative direction.

The diagnostic category soft tissue sarcoma (International Classification of Diseases, 7th revision (ICD-7), code number 197) includes all extraskeletal sarcomas excluding lympho- and reticulosarcomas. However, some of the cases of soft tissue sarcoma may have been coded according to their topographic localization rather than according to their histology. The extent of this type of misclassification has been the topic of a validation study performed by the Danish Cancer Registry. This examination revealed that, during the years 1978 through 1982, the registered incidence of extraskeletal sarcomas excluding lympho- and reticulosarcomas had been 3.4 times the registered incidence of ICD-7 code No. 197 [Lyngé et al., 1987]. Nevertheless, the national incidence rates for soft tissue sarcoma are based on the cases given code No. 197, and the comparison of observed and expected numbers (Table III) have to be restricted to the cases given this code. For completeness, however, we checked the list of gardener cancer cases for extraskeletal sarcomas. For this purpose, we made use of a special sarcoma code, which the Danish Cancer Registry has employed since it started registration procedures in 1942 [Clemmesen, 1965]. By this procedure, we found no additional cases of soft tissue sarcoma among the gardeners.

We found a fivefold increased incidence of soft tissue sarcoma among Danish gardeners. This observation is consistent with the findings in several studies of occupational groups exposed to herbicides [Hardell and Sandström, 1979; Eriksson et al., 1981, 1990; Lyngé, 1985; Vineis et al., 1986; Zahm et al., 1988; Wingreen et al., 1990; Fingerhut et al., 1991]. Other studies have failed to demonstrate an association with herbicide exposure [Hoar et al., 1986; Wiklund and Holm, 1986; Wiklund et al., 1988b; Green, 1991; Vineis et al., 1991]. This inconsistency may reflect methodological differences affecting study sensitivity or differences between the populations studied as to the type and the level of occupational exposure.

Our observation of an increased incidence of chronic lymphatic leukemia and of non-Hodgkin's lymphoma is in agreement with the results of several other studies, which have pointed to chlorinated pesticides such as the phenoxy acetic compounds and DDT as being possible risk factors for lymphopoietic neoplasms [Hardell et al., 1981; Hoar et al., 1986; Pearce et al., 1986a,b; Woods et al., 1987; Flodin et al., 1988; Persson et al., 1989; Alavanja et al., 1990; Weisenburger, 1990; Wigle et al., 1990; Zahm et al., 1990; Coggon et al., 1991; Vineis et al., 1991]. In this context, it seems worth mentioning the evidence for a cytological relationship between chronic lymphatic leukemia and the various types of non-Hodgkin's lymphoma as the majority of cases in both diagnostic categories are of B-cell origin [DeVita et al., 1989]. The fact that most cases of chronic lymphatic leukemia and of non-Hodgkin's lymphoma represent manifestations of a malignant transformation in a B-lymphocyte progenitor cell could imply a common etiology for the diseases in question.

CONCLUSIONS

Our finding of an increased incidence of soft tissue sarcoma and lymphatic neoplasms in the pesticide exposed cohort agreed with our expectations based on the scientific literature relating to this topic. Our results indicate that some pesticides may be capable of initiating or promoting the development of malignant neoplasms orig-

inating in mesenchymal tissues. It is tempting to suggest that some of the carcinogenic substances such as amitrole or the halogenated compounds have played a part.

ACKNOWLEDGMENTS

The authors thank Mr. Knud Ove Pedersen and Mr. Jesper Lund Larsen for collecting data on individual job histories as well as providing information about the changes over the years in the gardening trade, and of typical exposure situations. We also want to thank Ms. Marianne Fur Poulsen, Ms. Lotte Jørgensen, and Ms. Inge Olsen for their assistance in the preparation and linguistic correction of the manuscript.

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