

Time trends in cancer risk and pesticide exposure, a long-term follow-up of Danish gardeners

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Objectives Occupational exposure to petrochemical pesticides was high during the first 10–15 years after their introduction in the late 1940s, and, during these years, many cases of intoxication occurred. In the 1960s, the use and marketing of pesticides was regulated to reduce exposure to these substances, and, since 1970, substantial exposure has been rare in Denmark. The present study aimed at investigating the extent to which these alterations have influenced the cancer risk of gardeners.

Methods A historical cohort of 3156 male gardeners was followed from May 1975 until 2002 with regard to cancer incidence.

Results The cancer incidence was significantly below the national average [standardized incidence ratio (SIR) 0.86, 95% confidence interval (95% CI) 0.79–0.94], but an analysis by birth cohort indicated marked differences with a downward tendency for younger birth cohorts. Among the gardeners born prior to 1915, significant increases were found for leukemia (12 cases, SIR 2.33, 95% CI 1.32–4.10) and soft tissue sarcoma (3 cases, SIR 5.87, 95% CI 1.89–18.20).

Conclusions Gardeners constitute a healthy worker group, but an increased risk of soft tissue sarcoma and leukemia is indicated for people born prior to 1915, a finding that may reflect substantial pesticide exposure during the late 1940s and the 1950s. Among the gardeners born in 1915 or later, no excess cancer risk was found. The latter finding suggests a cancer-preventive effect for safety recommendations and improved technical devices with respect to pesticide application, along with legislative control measures to reduce pesticide exposure.

Key terms leukemia; soft tissue sarcoma.

Starting shortly after World War II, and culminating in the late 1950s, an epidemic of pesticide intoxication was recorded by the Danish National Board of Health. At the top of the epidemic, the annual figure for accidental pesticide intoxication was around 100, the typical victim being a male aged 40–60 years (1).

The first petrochemical pesticides were introduced in Denmark shortly after World War II, and, during their first 10–15 years on the market, these compounds were generally used with little or no consideration of their potential toxicity. Around 1960, the hazards related to the use of pesticides had become obvious, and control measures were implemented in all types of professional forestry, agriculture, and gardening. Once control measures were introduced, the exposure dropped sharply within a few years, after which a slower, but steady reduction has taken place. During the 1960s, the incidence

of severe pesticide intoxications became substantially reduced, and, since 1975, only sporadic cases have been notified.

Pesticides do not only cause acute intoxication, some of them may also act as carcinogens or as cancer promoters. These issues have been addressed in several epidemiologic studies on pesticide-exposed populations, the cancer types most often found in excess being leukemia, lymphoma, multiple myeloma, prostate cancer, and soft tissue sarcoma (2–4).

In 1992, we reported cancer incidence data for a national gardener cohort followed in 1975–1984. This study indicated a significantly increased incidence of soft tissue sarcoma and leukemia (5). Because Danish gardeners' exposure to pesticides changed substantially during the period 1945–1975, we wanted to study whether a parallel pattern could be seen in the incidence

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of certain types of cancer. We therefore decided to extend the follow-up to the end of 2001, since, by then, most members of the cohort would have reached an age at which cancer incidence is substantial.

Study population and methods

We followed a cohort of male union members from 1 May 1975 until 31 December 2001. The men studied were identified from an old cross-sectional union file covering all members of the Danish Union of General Workers. In 1973, the Union copied their membership file in order to provide personal identification data for a study on disability pensioning among its members (6), and the researcher responsible for that study saved the copy. We drew our study cohort from this copy of the 1973 Union membership file.

In the Union, gardeners were organized separately into local gardeners' sections, and we used the membership files of these sections to identify the men to be included in the cohort. The study cohort comprised every male who could be identified by a valid civil registration number in the membership file for one of the gardener sections of the Union as of 1 April 1973 and who was still alive and living in Denmark on 1 May 1975.

Altogether 3156 male gardeners were enrolled in the gardener cohort and followed with regard to survival, emigration, disappearance, and cancer incidence from

1 May 1975 until 31 December 2001. Follow-up information was obtained from the Central Person Register and the Danish Cancer Registry. Using the civil registration number as the key, we searched for each man in both registers. The Danish Cancer Registry, which was set up in 1942, codes all diagnoses according to the seventh revision of the International Classification of Diseases (ICD-7). By the time of the study, the Cancer Registry had been updated to 31 December 2001 with regard to cancer incidence. The Central Person Register is currently being updated within 1 week with regard to deaths, emigrations, and disappearances.

For each man, we calculated the person-years at risk from 1 May 1975 until the date of death, emigration, disappearance (according to the Central Person Register), or 31 December 2001, whichever came first. The observed cancer incidence was compared with the expected incidence on the basis of national cancer incidence rates for males combined with the number of person-years at risk accumulated by the cohort. All of the comparisons were standardized for age and calendar time. The computations made use of the facilities in the Stata programming package, version 8.2 (www.stata.com). For the statistical evaluation, we assumed that the observed numbers followed a Poisson distribution.

Because exposure had changed over time, we subdivided the cohort by year of birth, taking this parameter as a proxy of exposure level. On the basis of prior knowledge about the use of pesticides in our country, we decided to consider the following three subcohorts: (i) an early, high-exposure cohort, (ii) a late, low-exposure cohort, and (iii) an intermediate, or medium-exposure cohort. The early subcohort covered people born prior to 1915; therefore the men included in this cohort would all have been at least 30 years old when the era of heavy pesticide exposure started shortly after World War II. The late subcohort covered people born in 1935 or later, and all the men included in this cohort would, therefore, at the most, have been 25 years of age in 1960, when the heavy exposure period was coming to an end. The remaining men (ie, those born in 1915–1934) made up the intermediate subcohort.

The distribution of the study cohort is shown in table 1, which also provides basic follow-up data.

Table 1. Distribution of the study cohort, person-years at risk, and observed and expected cancer incidence for 1975–2001, by age and birth cohort.

Birth cohort	Person-years at risk	Observed cancer incidence	Expected cancer incidence
≤69 years			
Early ^a	2 924	33	44.93
Intermediate ^b	20 190	161	204.12
Late ^c	33 548	28	70.75
Total ^d	56 661	222	319.81
≥70 years			
Early ^a	4 989	176	148.30
Intermediate ^b	4 704	123	138.62
Late ^c	—	—	—
Total ^d	9 693	299	286.91
All ages combined			
Early ^a	7 913	209	193.23
Intermediate ^b	24 894	284	342.74
Late ^c	33 548	28	70.75
Total ^d	66 354	521	606.72

^a People born before 1915, high exposure group (N=512).

^b People born in 1915–1934, medium exposure group (N=1409).

^c People born in 1935 or later, low exposure group (N=1235).

^d N=3156.

Results

Overall, 521 cancer cases occurred in 1975–2001, an incidence figure significantly below the national average. Marked deficits were found for skin cancer and urinary cancer (table 2). This study added 17 years of follow-up to the previous 10-year study (5) by including the period 1985–2001 (inclusive), during which 335 new

cancer cases occurred, including 10 leukemia cases and 1 case of soft tissue sarcoma. An analysis by birth cohort (table 3) revealed that the cancer incidence in the early subcohort equaled the national average, while the incidence was low or very low in the later subcohorts. Within the early subcohort, we found a significant excess of leukemia and soft tissue sarcoma, the latter finding being based on three cases only (table 3). In addition, in the early subcohort, we found a nonsignificant excess of prostate cancer [standardized incidence ratio 1.33, 95% confidence interval (95% CI) 0.97–1.83].

Discussion

Our study shows a significantly reduced cancer incidence among Danish gardeners when compared with the national average, with marked deficits for skin cancer and cancer of the urinary tract. Compared with the first 10 years of follow-up (1975–1984), for which a standardized incidence ratio equal to 1.07 (95% CI 0.92–1.24) was recorded, our findings indicate a significant reduction in cancer incidence during the subsequent 17 years of follow-up (1985–2001, inclusive). The birth-cohort analysis indicated that this difference reflects a cohort effect in that later birth cohorts display incidence ratios much lower than that of the early birth cohort of gardeners.

Regarding sources of potential bias, the present cohort represents a healthy subset of the total population. The men in the study were occupationally active at baseline, and it is well known that such people are generally of better health than the average population. Furthermore, the rural-to-urban distribution of our

cohort was unbalanced when compared with that of the total Danish population, city-dwellers being underrepresented among the gardeners. A marked rural-to-urban gradient is well known for unhealthy lifestyle habits, including smoking, alcohol consumption, poor dietary habits, and pernicious leisure-time activity. A parallel rural-to-urban gradient has been found for most cancer sites, the incidence being lower in rural areas than in provincial towns and cities, a trend that also applies to Danish male data on skin cancer, urinary cancer, soft tissue sarcoma, and leukemia (7). All in all, it seems likely that our study has been biased in a negative direction by lifestyle habits and baseline health status.

Table 2. Cancer incidence in 1975–2001 by cancer site. (SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Cancer site ^a	Observed (N)	SIR	95% CI
Buccal cavity and pharynx (140–8)	9	0.53	0.24–1.01
Digestive organs and peritoneum (150–9)	133	0.97	0.80–1.18
Respiratory system (160–5)	114	0.94	0.78–1.13
Breast (170)	–	0.00	0.00–3.76
Male genital organs (177–9)	77	1.01	0.80–1.27
Urinary system (180–1)	49	0.67	0.50–0.89
Skin (190–1)	69	0.65	0.50–0.82
Other specified sites (192–7)	17	0.83	0.52–1.34
Soft tissue sarcoma (197)	4	1.96	0.53–5.02
Unspecified sites (198–9)	11	0.72	0.36–1.29
Lymphatic and hematopoietic tissue (200–5)	42	1.07	0.77–1.44
Leukemia (204)	22	1.39	0.87–2.10
Total (140–205)	521	0.86	0.79–0.94

^a The code number of the International Classification of Diseases, seventh revision, is shown in parentheses.

Table 3. Cancer incidence in 1975–2001 by birth cohort and cancer site. (SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Cancer site ^a	Early birth cohort (–1914)			Intermediate birth cohort (1915–34)			Late birth cohort (1935–)		
	Observed (N)	SIR	95% CI	Observed (N)	SIR	95% CI	Observed (N)	SIR	95% CI
Buccal cavity and pharynx (140–8)	3	0.74	0.24–2.29	6	0.65	0.29–1.44	–	0.00	0.00–1.02
Digestive organs and peritoneum (150–9)	54	1.13	0.86–1.47	73	0.94	0.75–1.19	6	0.50	0.23–1.12
Respiratory system (160–5)	34	0.90	0.64–1.26	72	0.98	0.78–1.23	8	0.84	0.42–1.69
Male genital organs (177–9)	39	1.34	0.97–1.81	35	0.89	0.64–1.23	3	0.43	0.14–1.33
Urinary system (180–1)	25	1.07	0.72–1.59	23	0.53	0.36–0.80	1	0.16	0.02–1.11
Skin (190–1)	28	0.93	0.64–1.35	36	0.61	0.44–0.85	5	0.28	0.12–0.67
Other specified sites (170, 192–7)	7	1.74	0.83–3.64	6	0.57	0.25–1.26	4	0.68	0.26–1.82
Soft tissue sarcoma (197)	3	5.87	1.89–18.20	–	0.00	0.00–3.77	1	1.82	0.26–12.89
Unspecified sites (198–9)	3	0.64	0.21–1.97	8	0.90	0.45–1.79	–	0.00	0.00–2.13
Lymphatic & hematopoietic tissue (200–5)	16	1.40	0.86–2.28	25	1.19	0.80–1.75	1	0.15	0.02–1.04
Leukemia (204)	12	2.33	1.32–4.10	9	1.04	0.54–2.01	1	0.48	0.07–3.44
Total (140–205)	209	1.08	0.94–1.24	284	0.83	0.74–0.93	28	0.40	0.27–0.57

^a The code number of the International Classification of Diseases, seventh revision, is shown in parentheses.

Compared with other occupational groups in Denmark, gardeners stand out as the single group that has experienced the most frequent and intense exposure to pesticides. Professional gardening includes work in greenhouses, nurseries, public parks and cemeteries, and garden construction, and, for example, greenhouse gardening involves pesticide application several times a month all year round. Exposure can not only occur during spraying operations, but also during re-entry into newly sprayed areas (8, 9)

Regarding time trends in pesticide exposure, marked changes have taken place within the period relevant for the present cohort. In particular, no carcinogenic pesticides—except arsenical compounds—were used in Denmark before the end of World War II, the first petrochemical pesticides being introduced in the late 1940s.

The Danish National Environmental Board recently published a comprehensive mapping of historical pesticide use in gardening, a mapping that is based on pesticide registry data (www.mst.dk, 2004). According to these data, which date back to the late 1940s, the pesticides introduced during the period 1945–1965 include DDT (dichlorodiphenyltrichloroethane), lindane, 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), amitrol, and atrazine, together with organochlorine pesticides such as the cyclodienes (aldrin, dieldrin, endosulfan), dicofol, metoxychlor, 2,4-D (2,4-dichlorophenoxyacetic acid) and other chlorophenoxy acids. Any pesticide classified as a suspected carcinogen became banned (eg, the arsenical pesticides were banned in the early 1950s). Many compounds, including, for example, chlordecone, heptachlor, chlordane, mirex, toxaphene, hexachlorobenzene, nitrofen, and DBCP (dibromochloropropane), have never been legally introduced in Denmark.

The 1940s and 1950s were characterized by insufficient legislation on pesticide handling and the absence of cautious safety procedures, a situation that seems to have been similar in other countries in western

Europe (1, 10–11), but, during the 1950s, the intoxication epidemic raised public concern about the hazards associated with these new chemical compounds. As a consequence, the Danish authorities put limitations on commercial pesticide transactions and regulated the use of pesticides (eg, by compulsory certification for professional pesticide application). In addition, recommendations on safe handling practices were spread. These control measures were undertaken around 1960, and, at about the same time, new and safer technology for pesticide application gradually gained a footing in Denmark, as well as in other developed countries (10). For example, the back-pack sprayer equipment, which often involved extensive dermal exposure, was replaced by handgun spraying, and also tractor ramp application became increasingly prevalent. Furthermore, pesticide users adopted a more cautious and safe way of handling these chemicals.

Compared with 1945–1959, during which the exposure level was high, the level dropped sharply within the first years of the 1960s. Since the mid-1960s, the exposure level has decreased more slowly, but steadily. Figure 1 shows the period of legal use for several pesticides suspected to be carcinogenic.

We used the time of birth as a proxy for exposure level. Danish male gardeners have been extremely job-stable, most of them staying in the trade from a young age until retirement; therefore, we believe that time of birth is a good proxy for exposure history. During the 1940s and 1950s, the new pesticides were expensive, and pesticide application was left to experienced gardeners, not to the young ones. Therefore, we selected 1915 and 1935 as cut points for the birth-cohort analysis.

In our study, we found a significantly increased incidence of leukemia (12 cases) and soft tissue sarcoma (3 cases) in the early birth cohort, findings that were not replicated in the two later birth cohorts (born in 1915 or later). Members of the early birth cohort were likely to have been substantially exposed during the first decades after World War II, the exposure comprising arsenical compounds, in addition to organochlorine pesticides, organophosphorous insecticides, and fungicides.

Some studies have found an excess risk of soft tissue sarcoma and leukemia in occupational groups exposed to pesticides (12–19). Associations have been described between soft tissue sarcoma and exposure to phenoxy acid herbicides, while leukemia has been found to occur in excess among people exposed to insecticides such as DDT and organophosphorous compounds (3).

In conclusion, our findings indicate an increased risk of leukemia and soft tissue sarcoma among gardeners born in the early years of the 20th century. These people are likely to have been engaged in pesticide application during the first 10–15 years after World War II, a period of substantial pesticide exposure. No association was

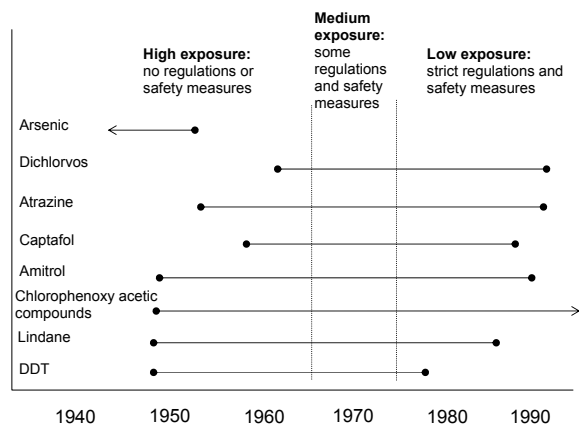


Figure 1. Availability and control of potentially carcinogenic pesticides in Denmark after World War II. (DDT = dichlorodiphenyltrichloroethane)

found for the younger birth cohorts, a finding indicating that technical improvement of the application devices, combined with pesticide control measures adopted around 1960, have reduced or eliminated the excess cancer risk among Danish gardeners.

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