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Cancer morbidity among Danish female pharmacy technicians

by Johnni Hansen, PhD, Jørgen H Olsen, MD¹

HANSEN J, OLSEN JH. Cancer morbidity among Danish female pharmacy technicians. *Scand J Work Environ Health* 1994;20:22-6. **OBJECTIVES** — Pharmacy technicians maintain a substantial production and packing of pharmaceuticals and other chemicals, many of which are carcinogens. This study reports on cancer incidence among Danish female pharmacy assistants and dispensers. **METHODS** — Altogether, 8499 compulsory members were identified in the archives of the Association of Danish Pharmacy Technicians and followed through the files of the Danish Cancer Registry (1970-1990); observed figures were compared with those expected on the basis of national cancer incidence rates. **RESULTS** — The overall standardized incidence ratio [SIR] for cancer was 1.0 [N = 219, 95% confidence interval (95% CI) 0.8-1.1]. A 1.5-fold (N = 34; 95% CI 1.1-2.1) elevated risk of nonmelanoma skin cancer was found, especially for long-term pharmacy assistants (N = 15, SIR 2.8, 95% CI 1.6-4.6). An increased risk for non-Hodgkin's lymphoma appeared among long-term pharmacy dispensers (N = 5, SIR 3.7, 95% CI 1.2-8.9). In the entire group, the risk of tobacco-related tumors was significantly reduced (N = 8, SIR 0.4, 95% CI 0.2-0.9), together with the probably socioeconomic-associated cervical cancer risk (N = 18, SIR 0.6, 95% CI 0.4-0.9). **CONCLUSIONS** — Sunlight is usually the dominant cause of nonmelanoma and melanoma skin cancer, but occupational factors may have contributed in this study in view of the uncommon localization observed for many of these cancers and the unelevated melanoma risk. In addition to the increased risk of non-Hodgkin's lymphomas, which may have been associated with exposure to organic solvents, the results do not indicate any other notable cancer risks during the follow-up.

Key terms: cohort study, drugs, non-Hodgkin's lymphoma, nonmelanoma skin cancer, pharmaceutical workers, women.

A substantial number of known and suspected carcinogens are pharmaceuticals and related chemicals (1). Although the main source of human exposure to pharmaceuticals is their use in medical therapy, people involved in manufacturing and packing such agents are also exposed during long periods (2). The approximately 320 Danish pharmacies have a 100-year tradition of compounding pharmaceuticals, and they account for about one-quarter of all the drugs used in Denmark (3). Extemporaneous preparations and a large number of reagents and chemical mixtures are also prepared for technical purposes at pharmacies. This work is normally maintained by pharmacy assistants and dispensers. The aim of this study was to evaluate the cancer risk among a historical cohort of pharmacy technicians.

Subjects and methods

Pharmacy technicians undergo three years of formal training as apprentices at a pharmacy before they are licensed as a pharmacy assistant or dispenser. The

training of pharmacy dispensers began around the time of the Second World War. The first pharmacy assistants were licensed in 1962. Pharmacy assistants follow courses in chemistry, pharmacology, and human biology, whereas the dispensers are especially qualified in bookkeeping and business-related subjects. Both groups receive training in the low-scale compounding of pharmaceuticals. After training, particularly the dispensers are occupied in the packing and bottling of tablets, mixtures, and ointments, while the assistants normally compound pharmaceuticals and related agents. Since 1970, all trained technicians working in Danish pharmacies have been compulsory members of the Association of Danish Pharmacy Technicians. Only about 1% of its members are men, who have not been included in this study. About 90% of the members work in pharmacies, and the remainder are employed mainly in pharmaceutical and related industries.

The study population was intended to include all female pharmacy technicians licensed as of 1 January 1970 or later. Individual files for active and retired members were obtained from one of two registers, kept by the Union. The first, which was computerized, covered all members active in 1985 and all subsequent new members (N = 6415). The second, a manual register based on paper cards, comprised information on persons who had either died or were withdrawn before data were transferred to

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computer files in 1985 ($N = 2645$). Each record included the name and either a unique 10-digit personal identity number (including six digits for date of birth) or solely date of birth, along with date of license, type of final education (ie, pharmacy assistant or dispenser), date of membership, and eventual withdrawal from the Union. Present job activity was categorized as working at a pharmacy, in the pharmaceutical industry, or in nonpharmaceutical jobs. An additional 39 persons were found in both the paper and computer records. The reasons for exclusion of a total of 555 individuals are shown in table 1. The major reasons were training unfinished by the end of 1990 (the end of follow-up) ($N = 317$) and male gender ($N = 117$). The identities of all except 360 women (4.0%) were verified in the Central Population Register on the basis of their identity number. Each of the 360 women whose identification number was invalid or missing was searched for manually in the files of the Central Population Register on the basis of date of birth, and the record was checked visually taking into account gender and present and historic names according to a previously described procedure (4). Only 45 women (0.5%) remained unidentified and were consequently excluded from the study. The 8499 identified women were searched for in the Register for date of death or emigration.

Subsequently, each woman was searched for in the files of the Danish Cancer Registry during the period 1 January 1970 to the end of 1990. The cancer register contains all new cases of malignant disease diagnosed in Denmark since 1943 (5). A modified version of the International Classification of Diseases, seventh revision (ICD—7) was used for classifying the diagnosis (5); from 1978 on, cancers were also classified according to ICD—O (6), which also specifies tumor morphology. Only one skin cancer of each morphological type was recorded per person; thus, if one person was diagnosed as having two or more skin tumors of identical histological types, the person was classified as having one primary skin tumor, multiple sites.

Since all of the women in the cohort had had three years of training in a pharmacy before obtaining their license, the period of risk was considered to begin three years before that date or on 1 January 1970, whichever occurred later. The end of follow-up was taken as date of death, date of emigration, or 31 January 1990, for those known to be living in Denmark at the closing date.

The expected number of site-specific cancers in the cohort was calculated by multiplying the person-years at risk during the follow-up period in each five-year age and calendar-year group by the corresponding site-specific incidence rates in the general Danish female population. The standardized incidence ratio (SIR) was taken as the ratio between the total number of observed and the total number of expected cases (7). Their corresponding exact 95% confidence intervals (95% CI) were calculated (8).

Table 1. Individuals identified from the files of the Association of Danish Pharmacy Technicians and reasons for exclusion.

	N
Records identified	
Computer files	6415
Paper cards	2645
Duplicates ^a	39
Total	9099
Exclusions	
Training not terminated ^b	317
Men	117
Inhabitants of Greenland or the Faroe Islands ^c	79
No formal training in a pharmacy	26
No known entry into union	10
Emigrated before start of follow-up	6
Total number of excluded members	555
Lost to follow-up ^d	45
Women finally included in the study	8499

^a Records from both paper and computer files.

^b Trainees are not compulsory members of the union.

^c Present address.

^d Identification number unobtainable.

The distributions of histological types and anatomic sites of the nonmelanoma skin cancers observed in the cohort were compared with those of a random sample of 680 nonmelanoma skin cancer cases in the general female population with a corresponding distribution of year of birth and diagnosis from the files of the Danish Cancer Registry.

Results

The characteristics of the cohort are given in table 2. It can be seen that about 90% of the women obtained their license in the 1960s or later and that 73% of the entire group was followed-up for more than 15 years. The cancer morbidity experience of more than 143 000 female person-years (95 135 for pharmacy assistants and 48 669 for dispensers) was available. Of the 8499 women included, 214 developed cancer, of whom five had two tumors, yielding a total of 219 malignant neoplasms, with 86 among pharmacy assistants and 133 among dispensers, in the 21-year period of follow-up. The overall cancer risk was uniform (SIR 1.0). Table 3 shows the site-specific risks of the entire cohort. The risk for nonmelanoma skin cancer was significantly elevated. Exclusion of this generally nonfatal cancer gave a relative risk of 0.9 (95% CI 0.8—1.0) for all other sites combined. In the subgroups of pharmacy assistants and dispensers, the risk for nonmelanoma skin cancer was 2.0 ($N = 16$, 95% CI 1.2—3.1) and 1.2 ($N = 18$, 95% CI 0.7—2.0), respectively. No significant change in the risk for these skin cancers was seen according to 20 years' duration of union membership, or for the equivalent time since first employment at a pharmacy (table 4). For women being sole-

Table 2. Descriptive characteristics (as percentage) of the cohort of female members of the Association of Danish Pharmacy Technicians, 1970–1990.

Characteristic	Assistant (N = 6070)	Dispenser (N = 2429)	Both groups (N = 8499)
Year license obtained			
< 1950	0.0	6.5	1.9
1950–1959	0.7 ^a	19.9	6.2
1960–1969	16.4	48.0	25.4
1970–1979	49.3	19.0	40.5
1980–1990	33.4	0	23.9
Unknown	0.2	6.7	2.1
Age at licensing (years)			
< 20	0.9	16.2	5.3
20–24	89.4	74.2	85.1
25–29	5.9	1.6	4.7
≥ 30	3.6	1.5	1.8
Unknown	0.2	6.7	2.1
Length of follow-up ^b (years)			
0–4	4.1	0.5	3.0
5–9	15.2	0.7	11.1
10–14	17.1	1.2	12.5
15–19	25.3	10.4	20.9
20–24	25.6	36.1	28.6
≥ 25	12.7	50.1	23.9

^a These women had previous training as pharmacy dispensers.

^b Calculated from three years before licensing to date of emigration, disappearance or end of follow-up (31 December 1990) after 1 January 1970. For 2.1% of the members with an unknown date of license, date of entry into the union was used instead of date of licensing.

Table 3. Risk of cancer (1970–1990) among female members of the Association of Danish Pharmacy Technicians. (O = observed number, E = expected number, SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Site (ICD-7)	O	E	SIR	95% CI
Buccal cavity and pharynx (140–148)	1	2.4	0.4	0.01–2.6
Digestive organs (150–159)	20	23.4	0.9	0.5–1.3
Liver (155)	2	1.5	1.4	0.2–4.9
Pancreas (157)	3	2.6	1.2	0.2–3.4
Respiratory organs (160–164)	6	12.4	0.5	0.2–1.0
Lung (162)	6	11.0	0.5	0.2–1.2
Breast (170)	70	65.2	1.1	0.8–1.4
Cervix uteri (171)	18	29.0	0.6	0.4–0.9
Corpus uteri (172)	9	8.3	1.1	0.5–2.1
Ovary (175)	14	12.1	1.2	0.6–1.9
Kidney (180)	3	3.0	1.0	0.2–2.9
Bladder (181)	1	3.1	0.3	0.01–1.8
Melanoma of skin (190)	14	14.7	0.9	0.5–1.6
Other skin (191)	34	22.2	1.5	1.1–2.1
Brain and nervous system (193)	9	10.3	0.9	0.4–1.7
Lymphatic and hematopoietic tissues (200–205)	16	12.4	1.3	0.7–2.1
Non-Hodgkin's lymphoma (200, 202)	5	4.0	1.3	0.4–3.0
Hodgkin's disease (201)	5	3.3	1.5	0.9–3.4
Multiple myeloma (203)	2	0.8	2.8	0.3–10.2
Leukemia (204)	4	4.2	1.0	0.3–2.4
Other	4	10.0	0.40	0.1–1.0
Total (140–205)	219	228.7	1.0	0.8–1.1

ly employed at pharmacies over the whole period from the date of starting training to the end of follow-up or date of death, the SIR was 2.8 (N = 15, 95% CI 1.6–4.6) for pharmacy assistants and 1.6 (N = 11, 95% CI, 0.8–2.8) for dispensers. A non-significant higher proportion of squamous-cell car-

cinomas (N = 3) was observed for pharmacy technicians than for the random sample of cases in the general population (table 5), and 27% of the nonmelanoma skin cancers among the union members were multiple, compared with only 16% among the population sample. For the specified sites, a significant lower proportion of nonmelanoma skin cancers appeared for the head locality than in the population sample.

Nonsignificantly elevated risks were found for Hodgkin's disease among the pharmacy assistants (SIR 1.7, N = 4) and for non-Hodgkin's lymphoma among the pharmacy dispensers (SIR 2.4, N = 5). When a duration of at least 15 years of work as a pharmacy dispenser was taken into account, the SIR for non-Hodgkin's lymphoma was 3.7 (N = 5, 95% CI 1.2–8.9). A significant deficit was observed for cervical cancer in the combined group (SIR 0.6, N = 5), on the basis of equally low risks in the two groups of members. The risk for cancers (of the buccal cavity, pharynx, larynx, lung and bladder) related to tobacco smoking was also significantly decreased (N = 8, SIR 0.4, 95% CI 0.2–0.9).

Discussion

The pharmacy technicians had a 53% significantly higher risk for nonmelanoma skin cancer than the general population. The risk appeared to be concentrated in the subgroup of pharmacy assistants (SIR 2.0, N = 18), especially among those with stable employment at a pharmacy (SIR 2.8, N = 15). Exposure to sunlight is the major risk factor for both melanoma and nonmelanoma skin cancer (9), but the topographical and morphological patterns in our group indicate that other factors may also be involved. First, the risk for malignant melanoma was not elevated, indicating that exposure to sunlight had not been much more frequent for the pharmacy technicians than for the general population. Second, the nonmelanoma skin cancers among the pharmacy technicians were not more frequently distributed for sites habitually exposed to sunlight (ie, face, scalp, and neck). Although we observed a higher relative frequency of squamous-cell carcinomas, which are more strongly associated with sun exposure than basal-cell carcinomas (10), it was nonsignificant and based on only three cases. Furthermore, nonmelanoma skin cancer is one of the major occupational cancers, and the International Agency for Research on Cancer has recently reported that 17 pharmaceuticals may cause skin cancer in humans (1). Among these, especially arsenic salts and coal tars were widely used in Danish pharmacies up until the 1980s (3). An elevated risk of nonmelanoma skin cancer has, to our knowledge, not previously been described among employees handling pharmaceuticals. Most occupational cancer studies are, however, based on mortality data, and, since this disease in general is

Table 4. Risk of nonmelanoma skin cancer (1970–1990), according to duration and time since start of membership in the Association of Danish Pharmacy Technicians. (O = observed, SIR = standardized incidence ratio, 95% CI = 95% confidence interval)

Time since start of membership	Duration of membership								
	< 20 years			≥ 20 years			All		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
< 20 years	13	1.7	0.9–2.9	0	—	—	13	1.6	0.9–2.9
≥ 20 years	2	0.7	0.1–2.6	19	1.6	1.0–2.5	21	1.5	0.9–2.2
All	15	1.4	0.8–2.4	19	1.6	1.0–2.5	34	1.5	1.1–2.1

Table 5. Distribution of nonmelanoma skin cancer by morphology and topography among the members of the Association of Danish Pharmacy Technicians (ADPT) and age and calendar time-matched sample from the Danish Cancer Register.

	Percentage distribution		
	ADPT members (N = 34)	Population sample (N = 680)	ADPT:population
Tumor morphology			
Missing ^a	9	9.0	1.0
Squamous-cell carcinoma	9	5.3	1.7
Basal-cell carcinoma	73	83.7	0.9
Other and unspecified	9	1.9	4.6
All morphological types	100	100	1
Tumor topography			
All topographical sites	100	100.0	1
Multiple sites	27	16.4	1.7
Specified sites	73	83.6	0.9
	(N = 25)	(N = 568)	
All specified sites	100	100	1
Face, scalp and neck ^b	40	60.6	0.6
Upper limb	12	3.4	3.5
Trunk	36	27.9	1.3
Anus	8	3.2	2.5
Other specified	4	4.9	0.8

^a Morphological classification of tumors was available only after 1977.

^b Inclusive lip, external ear, and eyelid.

nonfatal, it might have been overlooked. Finally, the topographical distribution of nonmelanoma skin cancers in our study was similar to that among Danish patients with psoriasis treated with various carcinogenic pharmaceuticals (11), which may indicate common causal factors (eg, coal tars and arsenic compounds).

The five cases of non-Hodgkin's lymphoma were all found in the subgroup of pharmacy dispensers, who had a significant, almost fourfold increase in their standardized incidence ratio when a latency of at least 20 years of work was considered. This risk is in accordance with the results of studies of workers exposed to organic solvents, health professionals, and patients exposed to pharmaceuticals (12–16). The fact that none of the cases was found among pharmacy assistants might be due to fact that the latency of around 20 years had not yet been achieved for about two-thirds of this group.

Follow-up was completed for 99.5% of the cohort members; therefore the selection bias was reduced to a minimum. It has been estimated that the Dan-

ish Cancer Register covers about 98% of all malignant neoplasms (17). However, some general underreporting of nonmelanoma skin cancer may exist, owing to the normally nonlethal character of the disease (18), but the interpretation of the relative distribution of topography and morphology would not be affected.

National rates were used as reference in this study because the numbers of employees in Danish pharmacies are similar to local population densities and therefore bias caused by geographic variations in risks may have been diminished. Social differences may exist between pharmacy technicians and the general population, but skin cancer is, in general, unaffected by social class (19). However, a slight overreporting of skin cancer may have occurred among the pharmacy technicians, since health professionals may pay more attention to skin diseases. Risk was considered to begin three years before licensing. Since person-years before the cohort-defining event generally tends to be rather free of risk, some minor dilution of the risk may have occurred.

More appropriate health care in this occupational group than in the general population may also have reduced cancer risks. For instance a lower smoking frequency in this population has been reported previously (20) and has been further corroborated by the finding of a significantly decreased risk for smoking-related tumors; a correspondingly low risk for lung cancer has previously been reported for similar groups of health care personnel (21). The significantly reduced cervical cancer risk observed in this study is also found among women with similar jobs (22) and may likewise reflect a more healthy life-style.

The fact that pharmacy dispensers and assistants have different tasks and are consequently exposed to different levels of various carcinogens may explain their different levels of risk. Although work as a pharmacy technician implies possible exposures to carcinogenic chemicals, no information about specific jobs or exposures was available. However, some pharmacy technicians mainly have counter and administrative tasks and are therefore not usually exposed to carcinogens. This fraction may have diluted the risk of cancer for the truly exposed. Finally, most of the cohort members, especially the pharmacy assistants, were relatively young at the end of the follow-up. Since most cancers occur in older people, any tumors already initiated in the pharmacy technicians will not be observed until some time in the future. Further follow-up and individual exposure assessments are needed to clarify the cancer risks of this group.

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