Original article

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Brain tumors and occupational exposures in a cohort of female textile workers in Shanghai, China

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Objectives This study assessed the associations between brain tumors and specific processes and exposures among female textile workers in Shanghai, China.

Methods A case–cohort study was conducted that was nested in a cohort of textile workers originally included in a randomized trial of breast self-examination. Incident brain tumor cases (N=114) were identified from 1989 to 1998 from a tumor and death registry operated by the Shanghai Textile Industry Bureau. A subcohort (N=3188), representing an age-stratified random sample of the entire cohort, was selected as a comparison group. Job-exposure matrices were created to assess historical exposures to specific agents, including quantitative assessments for cotton dust and endotoxin exposure. Cox proportional hazards modeling, modified according to a case–cohort design, was used to analyze associations between jobs and exposures and the risk of brain tumors.

Results Employment in maintenance workshops was associated with an increased brain tumor incidence (ever-never exposed hazard ratio 2.36, 95% confidence interval 1.12–4.97), with increasing hazard ratios by duration of employment in maintenance jobs. Handling or processing wool fibers was associated with an increased risk of brain tumors, as was specific exposure to wool fibers; however, estimates did not increase with duration of employment.

Conclusions These results provide some preliminary suggestion that employment in textile industry maintenance jobs and exposure to wool products may be associated with an increased risk of brain tumors.

Key terms case–cohort study; maintenance; textile industry; wool.

Although brain tumors are rarely diagnosed, the 5-year survival rates of adults are low (less than 25% for people diagnosed after 45 years of age), and, therefore, the importance of identifying risk factors is high (1). The etiologies of brain tumors are not well understood, although associations with some occupations and occupational exposures have been reported. Several studies have observed an increased risk of brain tumors in association with work in the textile industry (2–7), although no specific causative agents have been identified. Studies of other industries have found associations between brain tumors and several exposures commonly encountered in the textile industry, including electromagnetic fields (EMF) [see Kheifets (8) and Ahlbom (9) for reviews], solvents (10–12), metals (10, 13, 14), and lubricants (15–17).

While past studies focused on a broad array of industries, our research focused solely on the textile industry. By linking job histories with cancer registry data in a large, previously established cohort of female

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textile workers in Shanghai, China, we were able to examine specific textile industry processes and exposures and evaluate their relation to brain tumors.

Study population and methods

The study population was derived from 267 400 women employed in 526 factories of the Shanghai Textile Industry Bureau (STIB) who were originally enrolled in a randomized trial of breast self-examination in 1989–1991 in Shanghai, China (18, 19). At enrollment, the women were administered a questionnaire eliciting data on demographic characteristics, smoking and alcohol habits, and reproductive history. The study was approved by the institutional review boards of the Station for Prevention and Treatment of Cancer of the STIB and the Fred Hutchinson Cancer Research Center.

For this study of textile industry exposures and brain tumors, we used a case–cohort design nested within the original randomized trial. A subcohort of 3188 workers was selected. This number was chosen because it was about twice as many persons as the largest group of cancer cases (1507 cases of breast cancer), and it allowed us to have adequate statistical power to perform analyses for multiple cancer sites. The subcohort was selected after the case status was known, but without regard to case status. Members of the subcohort formed a randomized sample of the whole cohort, stratified into 5-year age groups, with the sampling fraction for each age group such that the age distribution of the subcohort approximated the age distribution of all of the cases combined.

Current and retired workers received routine health care through their factory health clinics. Tumor incidence was determined from 1989 to 1998 from medical reports submitted by individual factories to a tumor and death registry operated by the STIB. Case finding was supplemented by manual review of the records of the Shanghai Cancer Registry (SCR) (19). As further verification of identified cases, STIB records were reviewed to determine the basis for diagnosis, and brain cancers occurring following metastases from other sites (N=8) were excluded. Fifty cases were not matched in the SCR, but 27 (54%) of them were confirmed by STIB medical staff. A basis for diagnosis was not available for 15 cases. Following these reviews, all primary brain tumors [International Classification of Diseases (ICD), 9th revision codes 191, 192.2, 194.3, 225, 348.0, 348.8; N=114] identified in the cohort were selected for the present case–cohort study; four of the cases were coincidentally also selected for the subcohort.

Data on employment period, workplace, task descriptions, and changes in jobs for each woman were abstracted from factory personnel records by trained field workers, and women whose data were not available for abstraction (9%) were interviewed directly. Most (85%) of the women in the subcohort had worked in only one or two factories over their entire careers (18).

In addition, information on the primary fibers used in the factories, manufacturing processes, and the occurrence of hazardous exposures (chemical uses, biological and physical exposures) were assessed in China by trained industrial hygienists. Nine sectors of fiber type were defined [cotton, cotton-synthetic, cotton-other fiber (not synthetic), wool, silk, synthetic fibers, mineral, other mixed fiber, and none] and specific processes that occurred in each sector were grouped by a team of occupational hygiene experts. Each woman's work history was linked by process groupings to a specially developed job-exposure matrix (JEM) that classified likely exposures in jobs and processes according to the following agents: electromagnetic fields, cotton dusts, synthetic fiber dusts, lubricants, wool, solvents, acids, bases, and caustics, metals, and endotoxin (Wernli et al, in submission). Textile industry processes and specific exposures were coded as ever (≥1 year) versus never (<1 year) exposed and were also categorized by number of years of exposure (never, <10 years, 10–20 years, ≥20 years).

Quantitative estimates of exposures to cotton dust and bacterial endotoxin were estimated for specific jobs from historical cotton dust measurements available from factory inspection reports. The cumulative exposure to endotoxin for the case–cohort study participants was approximated on the basis of the estimated cotton dust levels and previously published data regarding specific endotoxin per unit dust in textile processes (20–24). Cumulative exposure was then categorized into quartiles among those who were ever exposed, on the basis of the subcohort's exposure distribution. The cotton dust estimates for six specific processes in two factories over four time periods were validated using independently collected measurement data (24). Women who worked as machinists, in wool production, or as sanitation workers were excluded from the endotoxin analyses because these processes may have entailed exposures to endotoxin from sources other than cotton.

The risk of brain tumor associated with each job process in the textile industry and specific exposure was estimated using a weighting scheme for the stratified case–cohort design (25), using Stata version 8.0 (Stata Corporation, College Station, TX, USA). Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazard methods with robust variance estimates (26). The cases and subcohort members contributed person-time to the analysis beginning with their dates of enrollment into the study until the dates of diagnosis (all cases, including cases from the subcohort) or the end of follow-up (subcohort

noncase members). The participants who were selected for the subcohort but also developed brain tumors contributed person-time to the subcohort group until immediately preceding the diagnosis date, at which time they were censored. The participants who died (N=181, 5.6%) or left the STIB (N=96, 3.0%) prior to 31 December 1998 were censored at date of death or departure from the industry. All cases received a one-unit weight, and the controls were weighted by the inverse of their sampling probabilities. Therefore, this weighting scheme mimicked the analysis that would have taken place had data for the whole cohort been available, and it was consistent with the sampling plan of the study design. Additional analyses were conducted when exposures were lagged by 10 and 20 years to account for the potential latency of carcinogenesis. All of the analyses were adjusted for age. We also compared frequencies of various demographic and lifestyle factors between the cases and noncases to evaluate possible confounding of textile industry exposure–brain tumor associations and further examined whether such factors were confounders by adjustment in multivariable models. Finally, to assess the consistency of our results, we performed analyses excluding the 15 brain tumor cases for which a basis for diagnosis was not available. Because these analyses did not differ from those that included all of the cases, we present results from analyses on all 114 brain tumor cases.

Table 1. Distribution of the cases and a subcohort of noncases according to demographic factors, smoking, alcohol use, and reproductive history.

Characteristic	Cases (N=114)		Noncases (N=3184)	
	N	%	N	%
Age				
30–34 years	8	7.0	177	5.6
35–39 years	16	14.0	302	9.5
40–44 years	4	3.5	297	9.3
45–49 years	6	5.3	166	5.2
50–54 years	14	12.3	317	10.0
55–59 years	31	27.2	863	27.1
60–64 years	28	24.6	964	30.3
65–69 years	7	6.1	98	3.1
Marital status				
Never married	0	0	29	0.9
Ever married	114	100	3155	99.1
Smoking status				
Never	108	94.7	3039	95.5
Ever	6	5.3	145	4.5
Alcohol consumption				
Never	92	80.7	2608	81.9
<1 drink/month	15	13.2	433	13.6
≥1 drink/month	7	6.1	143	4.5
Live births				
0	0	0	124	3.9
1	32	29.6	750	23.6
2	20	18.5	572	18.0
>2	56	51.8	1738	54.6
Postmenopausal				
Yes	78	68.4	2196	69.1
No	36	31.6	984	30.9
Hysterectomy				
Yes	10	8.8	127	4.0
No	104	91.2	3053	96.0

Results

The cases and noncases were similar in age distribution, marital status, smoking, alcohol consumption, parity, and menopausal status (table 1). Proportionately more cases (9%) than noncases (4%) had a history of hysterectomy (P=0.01). None of the demographic factors listed in table 1 importantly affected the hazard ratios for the occupational processes and exposures; therefore, all of the models were adjusted only for age (design variable). A comparison of demographic factors between the subcohort and the entire cohort revealed that they were similar in terms of smoking status and alcohol consumption (27).

Risks associated with involvement in a variety of textile industry processes are shown in table 2. Employment in maintenance jobs was positively associated with brain tumor incidence, and the association increased with greater time involved with the process (P-trend=0.04). The risk estimate was statistically significant when all of the participants who were ever employed in maintenance workshops were compared with those who were not (data not shown in tables: HR 2.36, 95% CI 1.12–4.97). Increased risks were found for handling, processing, or spinning wool fibers for less than 10 years and 10 to 20 years, but the risk did not increase by duration of work with wool fibers, and few cases were exposed in high-duration categories. An analysis comparing ever to never handling, processing, or spinning wool fibers indicated an elevated but not significant relative risk (data not shown in tables: HR 2.00, 95% CI 0.90–4.46). Analyses of exposures with 10- and 20-year lag times revealed no meaningful changes in the risk estimates for any of the textile industry processes.

The associations of specific exposures incurred from textile industry processes with brain tumors are presented in table 3. Exposure to wool for 10–20 years was associated with brain tumors, whereas exposure for <10 or >20 years was not, and no significant association was observed for having ever been exposed to wool (data not shown in tables: HR 1.32, 95% CI 0.80–2.17). Analyses of exposures with 10- and 20-year lag times revealed inverse associations for women exposed to lubricants, electromagnetic fields, or synthetic fiber dust for at least 20 years, the statistically significant risk

Table 2. Age-adjusted hazard ratios (HR) with 95% confidence intervals (95% CI) for the association between brain tumors and textile industry processes according to the duration of involvement in the processes.

Job process [a]	Cases (N=114)	Noncases (N=3184)	HR	95% CI	P-trend
Cotton fibers—material handling, fiber processing, spinning					
Never	94	2588	1	.	.
<10 years	5	122	1.12	0.45–2.78	.
10–20 years	1	154	0.17	0.02–1.25	.
>20 years	14	320	1.15	0.65–2.03	0.92
Mixed fibers—material handling, fiber processing, spinning					
Never	98	2741	1	.	.
<10 years	4	126	0.90	0.32–2.50	.
10–20 years	4	115	0.99	0.36–2.74	.
>20 years	8	202	1.12	0.54–2.34	0.80
Wool fibers—material handling, fiber processing, spinning					
Never	107	3082	1	.	.
<10 years	3	20	4.16	1.21–14.3	.
10–20 years	2	28	2.05	0.48–8.76	.
>20 years	2	54	1.06	0.25–4.43	0.57
Weaving					
Never	77	2065	1	.	.
<10 years	12	231	1.47	0.79–2.74	.
10–20 years	7	295	0.63	0.29–1.39	.
>20 years	18	593	0.83	0.49–1.41	0.31
Cutting or sewing					
Never	101	2889	1	.	.
<10 years	5	87	1.66	0.66–4.18	.
10–20 years	4	96	1.22	0.44–3.39	.
>20 years	4	112	1.05	0.38–2.92	0.71
Warehouse packing and quality control					
Never	97	2664	1	.	.
<10 years	7	182	1.06	0.48–2.31	.
10–20 years	7	148	1.29	0.59–2.84	.
>20 years	3	190	0.44	0.14–1.40	0.30
Maintenance					
Never	106	3078	1	.	.
<10 years	3	48	1.87	0.57–6.10	.
10–20 years	2	27	2.12	0.50–9.00	.
>20 years	3	31	2.79	0.84–9.30	0.04
Administration or nonproduction					
Never	79	2277	1	.	.
<10 years	12	339	1.05	0.55–1.97	.
10–20 years	13	266	1.40	0.76–2.58	.
>20 years	10	302	0.96	0.49–1.88	0.75

[a] Only processes with at least five exposed cases are presented.

Table 3. Age-adjusted hazard ratios (HR) with the 95% confidence intervals (95% CI) for the association between brain tumors and textile industry exposures according to the duration of the exposures. (EMF = electromagnetic fields)

Exposure [a]	Cases (N=114)	Noncases (N=3184)	HR	95% CI	P-trend
EMF					
Never	38	1016	1	.	.
<10 years	14	344	1.12	0.60–2.10	.
10–20 years	18	576	0.84	0.47–1.48	.
>20 years	44	1248	0.95	0.61–1.49	0.71
Lubricants					
Never	47	1210	1	.	.
<10 years	11	331	0.89	0.46–1.74	.
10–20 years	16	495	0.82	0.46–1.47	.
>20 years	40	1148	0.89	0.58–1.38	0.62
Synthetic fiber dust					
Never	69	1919	1	.	.
<10 years	10	238	1.21	0.61–2.37	.
10–20 years	14	362	1.04	0.58–1.86	.
>20 years	21	665	0.91	0.55–1.49	0.71
Wool					
Never	94	2734	1	.	.
<10 years	3	94	0.92	0.28–2.97	.
10–20 years	9	111	2.36	1.16–4.80	.
>20 years	8	245	0.96	0.46–2.00	0.42
Solvents					
Never	98	2726	1	.	.
<10 years	5	169	0.81	0.32–2.04	.
10–20 years	7	139	1.31	0.59–2.91	.
>20 years	4	150	0.73	0.27–2.03	0.80
Acids, bases & caustics					
Never	107	2921	1	.	.
<10 years	1	90	0.28	0.04–2.10	.
10–20 years	4	86	1.17	0.42–3.29	.
>20 years	2	87	0.63	0.15–2.60	0.57
Metals					
Never	104	2958	1	.	.
<10 years	3	87	0.98	0.30–3.17	.
10–20 years	4	57	1.86	0.66–5.23	.
>20 years	3	82	1.06	0.33–3.42	0.56

[a] Only agents with at least five exposed cases are presented.

estimates ranging from 0.4 to 0.5 (results not shown in tables).

The quantitative estimates of exposures to cotton dust and endotoxin were not consistently associated with brain tumors (table 4). Somewhat inverse risk gradients were observed for cumulative exposures to cotton dust and to endotoxin with a 20-year lag, but neither the risk estimates nor the tests of trend were statistically significant.

Discussion

The duration of employment in maintenance jobs was related to an increased risk of brain tumors. Exposure to wool fibers was also associated with brain tumors, but the risk did not increase by duration of employment.

According to our job process groupings, the women employed in maintenance workshops in this study were involved in electrical welding, metal works, carpentry, painting, and waste water processing. These jobs potentially entailed exposures to metals, lubricants, solvents, or natural fibers. In an examination of these specific exposures, as assigned by the job-exposure matrix, only exposure to metals showed a somewhat positive association with brain tumors. Lead, included in our metals category of exposure, has been implicated as a risk factor for brain cancer (13), and other studies have found an increased risk of brain cancer for machinists, precision metal workers, welders, and metal cutters (10, 14, 15, 28). Our findings should be interpreted with caution,

Table 4. Age-adjusted hazard ratios (HR) with the 95% confidence intervals (95% CI) for the associations between brain tumors and estimated cumulative quantitative cotton dust and endotoxin exposures. [a]

Dust exposure	Cases (N=114)	Non-cases (N=3184)	HR	95% CI	P-trend [b]
Endotoxin[a] (EU/m^3 × years) – no lag					
0	30	916	1.00	reference	
>0 to 1517.35	25	530	1.38	0.80–2.39	
>1517.35 to 2429.97	16	529	0.90	0.49–1.67	
>2429.97 to 3530.63	19	530	1.08	0.60–1.93	
>3530.63	17	530	0.95	0.52–1.72	0.65
Endotoxin[a] (EU/m^3 × years) – 10 years lag					
0	31	926	1.00	reference	
>0 to 1517.35	27	628	1.22	0.70–2.11	
>1517.35 to 2429.97	16	500	0.94	0.51–1.72	
>2429.97 to 3530.63	17	480	1.04	0.57–1.88	
>3530.63	16	501	0.92	0.50–1.68	0.65
Endotoxin (EU/m^3 × years) – 20 years lag					
0	39	1093	1.00	reference	
>0 to 1517.35	29	665	1.17	0.72–1.91	
>1517.35 to 2429.97	14	462	0.83	0.45–1.54	
>2429.97 to 3530.63	14	401	0.94	0.50–1.75	
>3530.63	11	414	0.69	0.35–1.36	0.22
Cotton dust (mg/m^3 × years) – no lag					
0	33	1016	1.00	reference	
>0 to 55.85	26	541	1.43	0.84–2.43	
>55.85 to 96.98	11	543	0.61	0.30–1.21	
>96.98 to 143.42	21	542	1.20	0.76–2.23	
>143.42	23	542	1.30	0.76–2.23	0.62
Cotton dust (mg/m^3 × years) – 10 years lag					
0	34	1026	1.00	reference	
>0 to 55.85	29	611	1.36	0.80–2.31	
>55.85 to 96.98	10	520	0.57	0.28–1.16	
>96.98 to 143.42	20	511	1.18	0.67–2.06	
>143.42	21	516	1.21	0.70–2.10	0.70
Cotton dust (mg/m^3 × years) – 20 years lag					
0	43	1198	1.00	reference	
>0 to 55.85	27	638	1.13	0.69–1.85	
>55.85 to 96.98	15	456	0.92	0.50–1.68	
>96.98 to 143.42	15	457	0.90	0.49–1.65	
>143.42	14	435	0.87	0.47–1.60	0.53

[a] Women with jobs in sanitation or wool production and machinists were not included in the analysis.
[b] Trend test across the median of fourths, among the exposed only.

however, since they are based on small numbers of exposed cases, and an increasing time of exposure to metals was not related to a greater risk of brain tumors in our data.

We observed increases in brain tumor risk when we analyzed employment processes involving wool, as well as for wool exposure as assigned by the job-exposure matrix; however, no positive trend was observed for increasing lengths of time exposed to wool products. Several previous studies have identified associations between brain tumors and exposure to wool products, although the evidence is somewhat inconsistent. McLaughlin et al (28) found that women employed in the wool industry in Sweden were at a significantly increased risk of brain tumors. Preston-Martin et al (29) reported that working with sheep (and thereby presumed to be exposed to wool) was significantly associated with brain tumors among men in New Zealand. In contrast, Menegoz (30) did not detect an association between contact with sheep and the risk of brain tumors. Possible explanations for a relation with wool exposure are unclear, although employment in wool processing has been shown to cause infectious disease (31–33), and infectious etiologies for brain tumors have been hypothesized (34, 35).

Exposure to endotoxin has been hypothesized to be related to a decreased risk of lung cancer (36–39), perhaps by activation of the immune system with macrophage surveillance and increased secretion of cytokines such as TNF-α (tumor necrosis factor) (40). However, to our knowledge, an apparently protective effect of endotoxin with a relation to brain tumor risk has not been previously reported. Our observation of a slightly decreased risk with increasing endotoxin exposure was only observed when exposures were lagged by 20 years, and it was not statistically significant. Future studies investigating this relationship should be conducted.

When exposures to textile industry processes were lagged for 10 and 20 years, the women exposed to lubricants, electromagnetic fields, or synthetic fiber dusts for at least 20 years were at decreased risk of brain tumors. We did not have a priori biological reasons for suspecting protective effects of these exposures for brain tumors. We hypothesize that these observations may be the result of a healthy worker survivor effect, as women in the 20-year exposure categories lagged by 20 years had longer total employment in the industry than women of similar ages in the lower-duration exposure categories, possibly indicating that they were in better overall health (41).

Previous studies of textile employment and brain tumors were population-based case–control studies that were not designed specifically to investigate exposures in the textile industry (2, 4–7). Our study had the advantage of focusing on specific exposures and job processes, and compared textile workers to each other, rather than to workers employed in other occupations. In addition, since we assigned exposures based on factory records of each woman's work history, the exposure status was not prone to recall bias.

This study did have several limitations, however. Many exposures and processes had small numbers of exposed persons and, therefore, led to statistically imprecise risk estimates. The possibility of our findings being due to chance cannot be ruled out. Although all of the brain tumor cases in our study were verified through a cancer registry or medical records, information on tumor histology was not readily available for most of the cases. Because the causes of brain tumors

may differ by type (42–44), exposure–disease associations that are specific to certain tumor types may have been obscured in our analyses. Finally, it is possible that we did not observe positive associations by increasing the duration of exposure because the less healthy workers may have left jobs with harmful exposures before they had time to develop brain tumors.

Our findings indicate that future investigations on brain tumors should examine exposures involved in maintenance work, such as lubricants, solvents, and metals. Our findings also support prior evidence that exposures to wool products increase the risk of brain tumors, despite the absence of clear pathogenic mechanisms.

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