ORIGINAL ARTICLE

Occupational risk factors for pancreatic cancer among female textile workers in Shanghai, China

W Li, R M Ray, D L Gao, E D Fitzgibbons, N S Seixas, J E Camp, K J Wernli, G Astrakianakis, Z Feng, D B Thomas, H Checkoway

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See end of article for authors' affiliations

Correspondence to:
Dr W Li, Epidemiology
Program, Public Health
Sciences, Fred Hutch
Cancer Research Center,
1100 Fairview Avenue
North, Building M4-A402,
PO Box 19024, Seattle
WA, 98109, USA; wli@
fhcrc.org

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Objectives: To investigate whether occupational exposures to dusts and chemicals in the Shanghai textile industry are associated with risk of pancreatic cancer.

Methods: A case cohort study nested in a cohort of 267 400 female textile workers in Shanghai, China was conducted among 180 incident pancreatic cancer cases and an age stratified randomly selected comparison subcohort (n=3188). A complete occupational history of work in the textile industry was obtained for each woman, and was linked to a job exposure matrix developed for the textile industry to estimate exposures to specific dusts and chemicals. Cumulative exposures to cotton dust and endotoxin were reconstructed from historical and contemporaneous measurements.

Results: After adjusting for smoking status, a trend of decreasing risk of pancreatic cancer was observed for increasing cumulative exposures to cotton dust and endotoxin with a lag of 20 years. The hazard ratios for women cumulatively exposed to $>143.4 \text{ mg/m}^3 \times \text{years}$ of cotton dust and $>3530.6 \text{ EU/m}^3 \times \text{years}$ of endotoxin were 0.6 (95% CI 0.3 to 0.9) and 0.5 (95% CI 0.3 to 0.9), respectively, compared to unexposed women. There was little evidence that exposures to other textile dusts and chemicals were associated with risk of pancreatic cancer.

Conclusions: Occupational exposure to cotton dust and endotoxin in the textile industry may have reduced risks of pancreatic cancer in this cohort. These associations should be replicated by others before making a firm conclusion of their possible effects on pancreatic cancer.

Pancreatic cancer is a rapid fatal malignancy. It is the fourth leading cause of cancer death in the United States.¹ Cigarette smoking and diabetes are the well established risk factors for pancreatic cancer, although these two factors are thought to account for only small fraction of cases.² The aetiology of pancreatic cancer remains largely unknown. Results of a meta-analysis of data from six case control and eight cohort studies indicated a weak association between obesity and the risk of pancreatic cancer.³ Increased risks of pancreatic cancer have been linked to various industries and occupations, including the chemical industry,^{4–5} printing,^{6–8} the metal industry,^{9–10} leather tanning,^{11–13} mechanics,^{14–16} and agricultural workers applying pesticides.^{14–20} A recent meta-analysis of 92 studies suggested increased risks of pancreatic cancer associated with occupational exposures to chlorinated hydrocarbon solvents and nickel compounds.²¹

Employment in the textile industry can entail exposures to various dusts (for example, cotton, wool, silk, and synthetic fibres) and chemicals (for example, dyes, inks, formaldehyde, and benzene). Several studies have linked employment in the textile industry to risk of pancreatic cancer.^{12–15, 22–23} Ji *et al* reported a non-significant increased risk of pancreatic cancer (OR=1.4) among women who have worked as a textile worker in a population based case control study conducted in Shanghai, China. Most of these studies are case control studies that were not conducted in industrial settings, and none considered specific exposures within the textile industry. We conducted a case cohort study nested in a cohort of 267 400 female textile workers in Shanghai, China to investigate possible occupational risk factors for pancreatic cancer.

METHODS

Cohort population and case definition

The study population included 267 400 female employees in 526 factories in the Shanghai Textile Industry Bureau (STIB) who had been enrolled from October 1989 to October 1991 in a randomised trial of breast self-examination (BSE).^{24–25} All currently working and retired female employees, at the time of enrollment, who were born between 1 January 1925 and 31 December 1958 were eligible to participate in the trial. Thirty four former medical workers, who were trained to be BSE trial field workers, trained factory medical workers to administer a baseline questionnaire that elicited data on smoking, alcohol use, and reproductive history.

Both current and retired employees received routine health care through health clinics in their factories. A detailed description of incident cancer case finding and diagnostic confirmation has been presented previously.²⁶ Briefly, all cancers diagnosed during 1989 and 1998 were reported by clinic workers to a cancer and death registry operated by the STIB Station for the Prevention and Treatment of Cancer. Cancer diagnoses were confirmed by computer matching with records from the Shanghai Cancer Registry and medical record review when no computer match was found. For this study, 186 women with primary pancreatic cancer (International Classification of Diseases 9th Revision (ICD-9) codes 157.0, 157.1, 157.2, 157.9) were identified from the STIB cancer registry, and their diagnoses were subsequently confirmed by medical record review. Of the 186 pancreatic cases, 46 (25%) were histologically confirmed; 3 (1.6%) were

Abbreviations: BSE, breast self-examination; JEM, job exposure matrix; STIB, Shanghai Textile Industry Bureau

Table 1 Characteristics of cancer cases and non-cases at baseline

	Cases (n = 180), n (%)	Non-cases (n = 3183), n (%)
Year of birth		
1925–29	73 (40.6)	935 (29.4)
1930–34	65 (36.1)	916 (28.8)
1935–39	19 (10.6)	366 (11.5)
1940–44	10 (5.6)	163 (5.1)
1945–49	6 (3.3)	281 (8.8)
1950–54	6 (3.3)	322 (10.1)
1955–58	1 (0.6)	200 (6.3)
Marital status		
Never married	1 (0.6)	29 (0.9)
Married	162 (90.0)	2894 (90.9)
Divorced	2 (1.1)	22 (0.7)
Widowed	15 (8.3)	238 (7.5)
Alcohol consumption		
Never	150 (83.3)	2608 (81.9)
<1/month	18 (10.0)	432 (13.6)
1–3/month	1 (0.6)	49 (1.5)
1/week	6 (3.3)	25 (0.8)
2+/week	5 (2.9)	69 (2.2)
Smoking status		
Never	159 (88.3)	3039 (95.5)
Former smoker	5 (2.8)	26 (0.8)
Current smoker	16 (8.9)	118 (3.7)
Number of live birth		
1	18 (10.3)	750 (24.5)
2	30 (17.1)	573 (18.7)
≥3	127 (72.6)	1736 (56.8)
Age at first live birth		
19 or less	23 (13.1)	266 (8.7)
20–24	83 (47.4)	1302 (42.6)
25–29	49 (28.0)	1154 (37.7)
30 or older	20 (11.4)	337 (11.0)
Daily oral contraceptive use		
Never	161 (89.4)	2764 (86.8)
Ever	19 (10.6)	419 (13.2)

cytologically confirmed; 84 (45%) were diagnosed by x ray, CAT scan, or ultrasound.

Case cohort design

A case cohort study design was applied to explore associations between occupational exposures and risks of various cancers, including pancreatic cancer.²⁷ A subcohort of 3199 women was randomly selected from the cohort for comparison with pancreatic and 14 other cancer case groups. The subcohort was frequency matched by five year age group to correspond to the age distribution of all cancers in the study. Five women with pancreatic cancer were also included in the subcohort. Follow up began at the time of enrollment in the BSE trial, and ended at the earliest of subjects' dates of cancer diagnosis, death, or transfer out of the STIB, or at the termination date of follow up on 31 December 1998.

Exposure assessment

The Shanghai textile industry is an integrated system and had, at one time, well over 500 factories and more than 550 000 workers. Its production includes not only the manufacture of fibres, cloth, garment, but also the manufacture of textile production equipment and other support products for the industry.²⁸ A complete occupational history, including employment dates, workshop, and task description in the textile industry, was collected for each of the study participants by 30 trained interviewers by abstracting the relevant information from employment records (80.0%), or interviewing the woman's supervisor or co-workers (11.0%). If the work history information was incomplete or unavailable from these sources, the woman was interviewed by telephone or in-person (8.3%) following the same study

protocol. The distribution of the methods used to collect work history among cases is similar to that among women in the subcohort. All of the contacted women agreed to be interviewed. We were able to obtain information of factory employment for 180 pancreatic cancer cases and 3188 subcohort women. These women were included in the analysis.

A team of six industrial hygienists used a standardised factory profile form to record for each factory the production processes, type of workshops, and historical measurements of hazardous exposures since the establishment of the factory. This information was obtained from the factory or from the district branch of the Shanghai Centers for Disease Control and Prevention.

A job exposure matrix (JEM) was developed specifically for the Shanghai textile industry, as described previously.²⁹ The JEM was based on a composite of two sources: (1) an a priori assessment of exposures by process developed by US industrial hygienists to classify fibre/process combinations according to the likely presence of various categories of dusts, chemicals, and physical agents, and (2) the prevalence of exposures reported by Chinese industrial hygienists in specific textile processes within the factory. A process was considered a source of the exposure if exposure to a particular chemical or dust was reported with more than 30% frequency. The industrial hygienists judged whether each specific process resulted in exposure to textile dusts (cotton, wool, silk, total natural fibres, synthetic fibre, and mixed fibre) and chemicals (solvents, bleaching agents, acids and bases, sulphuric acid, dyes, inks, resin monomers, formaldehyde, pesticides, and metals).

In addition, we obtained quantitative information on cotton dust and endotoxin exposures. Details of this assessment have been published.³⁰ Briefly, quantitative assessment of the cotton dust exposure was estimated for each specific textile process using historical measurements collected by industrial hygienists from 56 factories between 1975 and 1999. Endotoxin concentrations were estimated using the predicted cotton dust estimates and average concentrations of endotoxin per unit dust mass (EU/mg dust) in each major process from the respiratory disease studies conducted by Christiani *et al*.^{31–33} and from additional dust and endotoxin measurements made for this study.³⁴ These quantitative estimates were combined with each subject's work history and information from the JEM to estimate cumulative historical exposures of cotton dust and endotoxin. The exposure assessment for all agents was made without knowledge of study subjects' disease status.

The study was approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center and the Station for Prevention and Treatment of Cancer of the Shanghai Textile Industry Bureau, in accordance with an assurance filed with the Office for Human Research Protections (OHRP) of the US Department of Health and Human Services.

Analysis

We applied Cox proportional hazards modeling, adapted for the case-cohort design, for risk analyses (Stata version 8 SE, Stata Corporation, College Station, TX, USA). A weight of one was applied to all cases, and weights equal to the reciprocal of the sampling fractions were applied to all of the non-cases in the subcohort. The weighting was accounted for in the Cox regression by including the natural logarithm of the weight as an offset term in the model statement. In this way, an offset value of zero was assigned to all cancer cases since all cases have been sampled with the probability of one.³⁵ The estimated association was the hazard ratio (HR) and its corresponding 95% confidence interval (CI). The likelihood

Table 2 Hazard ratio estimates of pancreatic cancer in relation to duration of work in job categories grouped by process

Duration of working in each process	Cases (n = 180)	Non-cases (n = 3183)	HR*	95% CI	p for trend
Warehouse, packing, quality control					
Never	150	2663	1.0	Ref	
<10 years	6	183	0.7	(0.3 to 1.5)	
10–20 years	9	147	1.2	(0.6 to 2.5)	
>20 years	15	190	1.4	(0.8 to 2.4)	0.28
Cotton handling, processing, spinning					
Never	143	2587	1.0	Ref	
<10 years	13	123	1.5	(0.8 to 2.8)	
10–20 years	4	154	0.5	(0.2 to 1.3)	
>20 years	20	319	0.9	(0.5 to 1.5)	0.43
Mixed fibre handling, processing, spinning					
Never	152	2741	1.0	Ref	
<10 years	9	126	1.1	(0.5 to 2.2)	
10–20 years	8	115	1.4	(0.7 to 2.9)	
>20 years	11	201	0.8	(0.5 to 1.6)	0.92
Weaving					
Never	118	2063	1.0	Ref	
<10 years	9	230	0.7	(0.3 to 1.4)	
10–20 years	17	296	1.0	(0.6 to 1.8)	
>20 years	36	594	0.9	(0.6 to 1.4)	0.70
Cutting/sewing					
Never	164	2889	1.0	Ref	
<10 years	9	85	2.3	(1.1 to 4.6)	
10–20 years	3	96	0.6	(0.2 to 2.0)	
>20 years	4	113	0.7	(0.3 to 2.1)	0.71
Maintenance					
Never	174	3077	1.0	Ref	
<10 years	2	48	1.0	(0.2 to 4.1)	
10–20 years	2	27	1.5	(0.3 to 6.4)	
>20 years	2	31	1.4	(0.3 to 6.1)	0.54
Administration (non-production)					
Never	130	2274	1.0	Ref	
<10 years	21	339	1.4	(0.9 to 2.3)	
10–20 years	17	268	1.5	(0.9 to 2.5)	
>20 years	12	302	0.8	(0.4 to 1.5)	0.78

*Age (continuous) and smoking status (categories) adjusted hazard ratio.

ratio test was used to test for exposure-response associations. Associations with smoking, alcohol use, and reproductive factors recorded on the baseline questionnaire were also estimated. Risks associated with various textile manufacturing processes were estimated for “ever” (≥ 1 year) versus “never” (< 1 year) employed, and by duration of employment (0, > 0 –10 years, > 10 –20 years, > 20 years). Risks associated with exposures to various dusts and chemical agents, ascertained by linking the women’s work history to the JEM, were investigated in the same manner. Cumulative exposures to cotton dust and endotoxin were categorised into quartiles according to the distributions among the subcohort members, with no lag, to estimate exposure-response gradients. The median values of the quartiles were used as weights in the trend tests. We also evaluated risks in relation to cotton dust and endotoxin exposures with lag intervals of 10 years and 20 years to take into account possible disease latency.

RESULTS

The cancer cases were older than the non-cases (table 1). More cases were former and current smokers compared to non-cases. The HR estimates for current and ex-smokers were 1.9 (95% CI 1.1 to 5.5) and 2.7 (95% CI 1.0 to 7.2), respectively. Therefore, all HR estimates for risk of pancreatic cancer presented were adjusted for age as a continuous variable and smoking status as a categorical variable, as shown in table 1. Alcohol consumption was similar in the two groups, and was not considered further as a possible

confounder. More cases had multiple births and earlier age at first live birth than non-cases. This is consistent with the reproductive pattern we observed in this cohort that the older women tend to have more children, and earlier age at first live birth than younger women. After taking age into consideration, cases and non-cases were similar regarding their reproductive factors recorded at baseline. Therefore, none of the reproductive factors was considered as a confounder.

There were no prominent or consistent associations of pancreatic risk with employment in jobs categorised by process type (table 2). We observed a 2.3-fold increased risk of pancreatic cancer among women who worked in cutting and sewing job categories for less than 10 years, but not among women who had worked in these jobs for longer durations.

No associations were found for duration of exposure to dusts, chemicals, or physical agents examined (table 3).

In the analysis of quantitative exposures to cotton dust and endotoxin, we observed no associations with cotton and endotoxin exposures when estimating HRs with no lag (table 4). When cumulative exposures were lagged by 10 years, we observed no association with cotton exposure, but a significant decreased trend with endotoxin exposure. Furthermore, when cumulative exposures were lagged by 20 years, we observed a significantly reduced risk of pancreatic cancer for women exposed to more than $143.4 \text{ mg/m}^3 \times \text{years}$ of cotton dust and for women exposed to more than $3530.6 \text{ EU/m}^3 \times \text{years}$ of endotoxin.

Table 3 Hazard ratio estimates of pancreatic cancer in relation to duration of occupational exposures

Exposure	Cases (n = 180)	Non-cases (n = 3183)	HR*	95% CI	p for trend
Wool					
Never	151	2733	1.0	Ref	
<10 years	2	94	0.3	(0.1 to 1.4)	
10–20 years	6	111	0.9	(0.4 to 2.2)	
>20 years	21	245	1.4	(0.9 to 2.3)	0.31
Silk					
Never	172	3019	1.0	Ref	
<10 years	2	37	1.0	(0.2 to 4.3)	
10–20 years	1	49	0.4	(0.1 to 3.1)	
>20 years	5	78	1.1	(0.4 to 2.8)	0.99
Synthetic fibre dust					
Never	100	1920	1.0	Ref	
<10 years	15	237	1.3	(0.7 to 2.3)	
10–20 years	19	362	1.1	(0.7 to 1.8)	
>20 years	46	664	1.3	(0.9 to 1.8)	0.21
Non-textile dust					
Never	147	2658	1.0	Ref	
<10 years	7	201	0.6	(0.3 to 1.4)	
10–20 years	15	163	1.5	(0.9 to 2.6)	
>20 years	11	161	1.2	(0.6 to 2.3)	0.33
Solvents					
Never	165	2724	1.0	Ref	
<10 years	4	170	0.5	(0.2 to 1.4)	
10–20 years	8	139	1.1	(0.5 to 2.2)	
>20 years	3	150	0.4	(0.1 to 1.3)	0.12
Lubricants					
Never	62	1210	1.0	Ref	
<10 years	20	330	1.2	(0.7 to 2.0)	
10–20 years	27	496	1.0	(0.7 to 1.7)	
>20 years	71	1147	1.0	(0.7 to 1.4)	0.72
Metals					
Never	171	2956	1.0	Ref	
<10 years	2	87	0.5	(0.1 to 2.1)	
10–20 years	5	58	1.5	(0.6 to 3.9)	
>20 years	2	82	0.6	(0.1 to 2.4)	0.73
EMF or non-ionising radiation					
Never	52	1016	1.0	Ref	
<10 years	24	343	1.4	(0.8 to 2.3)	
10–20 years	29	576	1.0	(0.6 to 1.6)	
>20 years	75	1248	1.0	(0.7 to 1.4)	0.63

*Age (continuous) and smoking status (categories) adjusted hazard ratio.

Additionally, there were statistically significant decreasing trends of risk with estimated cumulative exposures to these two agents when a 20 year lag was imposed. Collinearity between cotton dust and endotoxin cumulative exposures precluded mutual adjustment of risk trends. The correlation coefficient between cotton dust and endotoxin exposures was 0.57.

DISCUSSION

The most prominent findings of this study of female workers in the Shanghai textile industry were inverse gradients of pancreatic cancer associated with cumulative exposures to cotton dust and endotoxin when exposures were lagged 20 years. There were no other noteworthy findings for employment in broad job categories or for exposures to other textile industry dusts, chemicals, or physical agents.

There are several strengths to this study. It is the largest cohort study of confirmed incident pancreatic cancer conducted to date that has focused on textile exposures among female workers. Trained field staff collected detailed information on lifetime jobs in the textile industry for each woman. The comprehensive information on production processes, workshops, and measurement of hazardous exposures since the establishment of each factory collected by local industrial hygienists provided more extensive, detailed, and specific exposure data than those in previous studies on occupational risk for pancreatic cancer. Information on smoking status, alcohol consumption, and

reproductive risk factors was available to be investigated as potential confounding factors.

The study also has several limitations. Quantitative historical measurements of exposures for most agents of interest were not available. Relying on duration of exposure to estimate dose-response relations limited our ability to detect possible differences in risk related to exposure intensities. Although there was the potential for confounding between job categories if women held several different textile industry jobs, there was relatively little mobility between sectors or factories before 1994. Moreover, women usually held the same job in the same factory for their entire working career in this cohort. Women on average held two jobs in this study. We also restricted our analyses to women who only worked in one job. The results were not materially different. The study subjects are women who enrolled in the BSE trial. Therefore, cases that occurred before the BSE trial were not included. It is possible that we may have underestimated some associations because cases in this study may represent people who are resistant to pancreatic cancer. The magnitude of such bias is unclear.

Smoking is a well established risk factor for pancreatic cancer. We observed increased risks among smokers, which was consistent with previous findings.²⁹ However, the low smoking prevalence in this cohort of women provided us an opportunity to investigate possible effects on risk of occupational exposures largely in the absence of smoking, which minimised confounding. An excess risk of pancreatic cancer

Table 4 Hazard ratio estimates of pancreatic cancer in relation to cumulative quantitative cotton dust and endotoxin exposures

Exposure	Cases (n = 180)	Non-cases (n = 3183)	HR*	95% CI	p for trend†
<i>Cotton dust (mg/m³ × years)</i>					
No lag					
None	54	1016	1.0	Ref	
>0 to 55.9	30	542	1.1	(0.7 to 1.7)	
>55.9 to 97.0	27	542	0.9	(0.6 to 1.4)	
>97.0 to 143.4	36	540	1.0	(0.6 to 1.6)	
>143.4	33	543	0.9	(0.6 to 1.4)	0.60
10 year lag					
None	55	1026	1.0	Ref	
>0 to 55.9	33	611	1.1	(0.7 to 1.7)	
>55.9 to 97.0	30	520	1.0	(0.6 to 1.6)	
>97.0 to 143.4	30	509	0.8	(0.5 to 1.3)	
>143.4	32	517	0.9	(0.6 to 1.4)	0.34
20 year lag					
None	61	1198	1.0	Ref	
>0 to 55.9	41	637	1.2	(0.8 to 1.8)	
>55.9 to 97.0	31	455	1.0	(0.6 to 1.5)	
>97.0 to 143.4	27	457	0.7	(0.5 to 1.2)	
>143.4	20	436	0.6	(0.3 to 0.9)	0.006
<i>Endotoxin (EU/m³ × years)</i>					
No lag					
None	54	916	1.0	Ref	
>0 to 1517.4	32	530	1.0	(0.7 to 1.6)	
>1517.4 to 2430.0	36	529	1.1	(0.7 to 1.6)	
>2430.0 to 3530.6	24	530	0.6	(0.4 to 1.1)	
>3530.6	30	529	0.8	(0.5 to 1.2)	0.12
10 year lag					
None	55	926	1.0	Ref	
>0 to 1517.4	36	627	1.1	(0.7 to 1.7)	
>1517.4 to 2430.0	35	501	1.0	(0.7 to 1.6)	
>2430.0 to 3530.6	23	479	0.6	(0.4 to 1.1)	
>3530.6	27	501	0.7	(0.4 to 1.1)	0.04
20 year lag					
None	61	1093	1.0	Ref	
>0 to 1517.4	46	663	1.2	(0.8 to 1.8)	
>1517.4 to 2430.0	35	462	1.0	(0.6 to 1.5)	
>2430.0 to 3530.6	15	402	0.4	(0.2 to 0.8)	
>3530.6	19	414	0.5	(0.3 to 0.9)	<0.001

*Age (continuous) and smoking status (categories) adjusted hazard ratio.

†Trend test for exposed women only.

in textile workers has been reported in several studies.^{12 15 22 36} Zhang *et al* observed an increased risk of pancreatic cancer for textile sewing machine operators, with the greatest risk among workers with more than 10 years of employment in this occupation.³⁷ We observed an excess risk of pancreatic cancer for women who worked in cutting and sewing job categories for less than 10 years, but not for more than 10 years. This could be a chance finding because the number of women who have worked in cutting/sewing was small. An association with cutting and sewing jobs needs to be investigated further before any firm conclusion can be drawn.

An increased risk of pancreatic cancer in men exposed to cotton dust has been reported previously in a hospital based case control study in Louisiana. The association was based on only 14 exposed cases and four exposed controls.³⁶ In contrast, we observed an inverse association between risk of pancreatic cancer and cotton dust and endotoxin exposure. We repeated the analyses restricting to women who have never smoked, and the results did not change. Cotton dust is frequently contaminated with Gram negative bacteria that produce endotoxin. Collinearity between cotton dust and endotoxin exposure precluded mutually adjusted analyses that might reveal whether endotoxin or some other component of cotton dust was the more relevant factor. Insofar as endotoxin is probably the most biologically active agent in cotton dust, it would appear to be the most plausible factor. Enhanced immune surveillance due to endotoxin exposure has been hypothesised as the mechanism by which cotton dust might reduce risk of lung cancer.³⁸ It is possible that

exposure to endotoxin may reduce the risk of development of pancreatic cancer through the same mechanism. Alternatively, the decreased risk of pancreatic cancer with endotoxin was only observed when exposure was lagged by 20 years, which may indicate an early stage anticarcinogenic action.

Increased risk of pancreatic cancer has been associated with occupations in the chemical industry,^{4 5} printing,⁶⁻⁸ and metal industry.^{9 10} Chemicals involved in these industries may also be present in textile industry. However, we did not observe any associations between risk of pancreatic cancer and a variety of these chemicals.

In summary, we observed that exposures to cotton dust and endotoxin 20 years in the past were associated with a decreased risk of pancreatic cancer. To our knowledge, these associations have not been observed previously. With the large number of textile exposures considered, we believe that these results should be replicated by others before making a firm conclusion of their possible effects on pancreatic cancer.

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Main messages

- Pancreatic cancer risk in female textile workers in Shanghai, China was inversely associated with exposures to cotton dusts and endotoxin when exposures were lagged 20 years.
- Employment in the textile industry or exposure to other textile industry dusts, chemicals, or physical agents were not associated with risk of pancreatic cancer.

Policy implications

- Occupational exposures do not appear to contribute to the risk of pancreatic cancer.
- The associations of exposure to cotton dust and endotoxin with risk of pancreatic cancer should be replicated by others before making any firm conclusions.

exposure data that improved the cotton dust and endotoxin exposure assessments.

Authors' affiliations

W Li, R M Ray, K J Wernli, Z Feng, D B Thomas, H Checkoway, Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

D L Gao, Department of Epidemiology, Zhong Shan Hospital Cancer Center, Shanghai, China

W Li, N S Seixas, J E Camp, K J Wernli, Z Feng, D B Thomas, H Checkoway, School of Public Health and Community Medicine, University of Washington, Seattle, WA, USA

G Astrakianakis, Occupational Health and Safety Agency for Healthcare, Vancouver, BC, Canada

E D Fitzgibbons, Group Health Center for Health Studies, Seattle, WA, USA

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