

# Risk of Pancreatic Cancer in Female Textile Workers in Shanghai, China, Exposed to Metals, Solvents, Chemicals, and Endotoxin

## Follow-Up to a Nested Case-Cohort Study

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**Objective:** We studied associations between pancreatic cancer and occupational exposures to metals, solvents, chemicals, and endotoxin in a cohort of female textile workers in Shanghai, China. To assess the longer-term influences of these agents on pancreatic cancer we extended follow-up of this previously studied cohort. **Methods:** We utilized a job exposure matrix to assess occupational exposures for 481 pancreatic cancer cases and a randomly selected sub-cohort of 3191 non-cases. We calculated hazard ratios and 95% confidence intervals using Cox proportional hazards modeling adapted for the case-cohort design. **Results:** We observed a statistically significant trend of increasing hazard ratios associated with solvent exposure, but no associations with any of the remaining occupational exposures, including endotoxin and metals. **Conclusions:** Our findings of increasing risk of pancreatic cancer with solvent exposures are consistent with published literature.

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Potential conflicts of interest/sources of funding/all sources of support, including pharmaceutical and industry support, that require acknowledgment:

Grant sponsor (and statement): This publication was supported by the National Cancer Institute; Grant number: R01CA80180. The National Cancer Institute is one of the National Institutes of Health (NIH), Grant or Cooperative Agreement Number, T42OH008433, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Dr Reul received funding from the University of Washington, Centers for Disease Control and Prevention, National Cancer Institute, and Washington State Department of Labor and Industries. Dr Li received funding from the National Cancer Institute and Fred Hutchinson Cancer Research Center. Dr Gallagher received funding from the National Institutes of Health/National Cancer Institute. Ms Ray received funding from the University of Washington, Brown University, National Institute of Environmental Health, National Institute of Child Health and Human Development, and the National Cancer Institute. Dr Romano received funding from the University of Washington, Brown University, and the National Institute of Environmental Health. Dr Gao received funding from the National Cancer Institute, Zhongshan Hospital, and Fudan University. Dr Thomas received funding from Fred Hutchinson Cancer Research Center. Dr Vedral received funding from the National Cancer Institute, Centers for Disease Control and Prevention, University of Washington, Chinese Research Academy of Environmental Sciences, National Institutes of Health, US EPA, University of Utah, University of New Mexico, and AXA Research Fund. Dr Checkoway received funding from the University of Washington, the University of California at San Diego, Alcoa, Inc, Electric Power Research Institute, ENVIRON Corp, National Institutes of Health, and Oxford University Press.

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DOI: 10.1097/JOM.0000000000000596

**P**ancreatic cancer is the fourth most common cause of cancer-related death in the United States for both men and women.<sup>1</sup> Among less-developed regions of the world, pancreatic cancer mortality ranks 12th for men and 10th for women.<sup>2</sup>

Increasing age, smoking, chronic pancreatitis, and genetic disorders are considered among the most important risk factors for pancreatic cancer.<sup>3,4</sup> Other risk factors for which evidence of association exists include alcohol consumption, obesity, glucose metabolism abnormalities, and *Helicobacter pylori* infection.<sup>5</sup>

Recent literature suggests that polycyclic aromatic hydrocarbons and chlorinated hydrocarbons are the occupational exposures that have been linked most consistently to pancreatic cancer.<sup>6,7</sup> Cadmium, nickel, and chromium have also been implicated as risk factors for pancreatic cancer.<sup>6,7</sup> There is some evidence that endotoxin (lipopolysaccharide)—a component of gram-negative bacterial cell walls that is a widespread contaminant of cotton and other organic materials—might increase risk for pancreatic cancer.<sup>8,9</sup>

In a prior case-cohort study of occupational risk factors for pancreatic cancer nested within a cohort study of female textile workers in Shanghai, China, Li et al<sup>10</sup> found no consistent associations of pancreatic cancer risk with exposures to metals, solvents, lubricants, inks, resins, or pesticides. An unexpected initial finding, however, was an inverse exposure-response trend for endotoxin exposure.

Since publication of those results in 2006, follow-up for cancer incidence and work history data collection were extended by 8 years. The analysis of added exposure from further time at risk, as well as the additional capacity to identify associations gained through inclusion of hundreds of additional cases of pancreatic cancer permit a second, more powerful examination of the previously observed protective relationship between endotoxin exposure and pancreatic cancer, as well as of the relationship between pancreatic cancer and exposure to metals, solvents, and chemicals. Findings from the extended follow-up and exposure assessment are presented here.

## MATERIALS AND METHODS

The study population was initially selected for a randomized trial of the effect of breast self-examination in women employed by the Shanghai Textile Industrial Bureau (STIB). The cohort included 267,400 women from 502 factories.

Women were eligible for inclusion if they were permanent residents of Shanghai, at the time of enrollment were active or retired employees of the STIB, and were born between 1925 and 1958. From October 1989 through October 1991 factory medical workers administered a baseline questionnaire to all eligible women that included questions about working status and reproductive history, as well as smoking and tobacco use.<sup>11</sup>

Procedures to identify pancreatic cancer among enrolled women differed during the two follow-up periods. For the first follow-up period (1989 to 1998), women from the cohort with pancreatic cancer were identified through a Cancer and Death Registry maintained by the Station for the Prevention and Treatment of Cancer of the STIB. Pancreatic cancer diagnoses were verified by

electronically matching cases to the Shanghai Cancer Registry, and by manual review of medical records.

Beginning about 1999 the STIB was gradually disbanded as part of economic reforms initiated in China, and the STIB Tumor and Death Registry became inoperative. To identify pancreatic cancer cases for the additional follow-up period (1999 to 2006), the cohort was computer matched to the records of the Shanghai Cancer Registry on name, date of birth and factory of employment, and potential matches or their relatives were then interviewed to identify true matches. Verification of the diagnosis was conducted by manual medical record review.

A total of 498 women in the cohort were identified from the two registries as having had pancreatic cancer. Following identification, diagnosis of pancreatic cancer was confirmed in 474 (95%) of the cases from several sources: medical imaging in 52% of cases (x-ray, ultrasound, magnetic resonance imaging, or computed tomography); histology (24%); surgical reports (12%); cytology (3%); clinical history and physical examination (2%); or from death certificates (2%).

A birth-year-stratified, randomly selected sub-cohort of 3199 women was selected from the cohort for comparison.<sup>10,12</sup> By chance, eight of the women in the sub-cohort were diagnosed with pancreatic cancer; they were still included in the analysis as non-cases up to the dates of diagnosis; thereafter, they were treated as cases, with person-time of follow-up and exposure data allocated accordingly.

Work history in the STIB for pancreatic cancer cases and the sub-cohort was collected by experienced field workers who reviewed factory records on all jobs each woman held from the beginning of her employment in the textile industry. When records were not available, information was obtained by interview of the participant, her relatives, or supervisors or coworkers. All individuals approached agreed to be interviewed. Informed consent was obtained from all study participants. Consent was verbal for the original breast self-examination study.<sup>11</sup> Women who were interviewed about their work history provided verbal consent. Women who were interviewed as part of the case verification process provided written consent. In accordance with an assurance filed with the Office for Human Research Protections of the US Department of Health and Human Services, this study was approved by the institutional review boards of the Zhongshan Hospital, Fudan University; the University of Washington; and the Fred Hutchinson Cancer Research Center.

## ASSESSING EXPOSURES

The exposure assessment and generation of the job exposure matrix (JEM) have been previously described in detail.<sup>13</sup> Briefly, we collected occupational histories of all cases and all women in the sub-cohort. For each job held, information was collected on job tasks and associated dates; factory; and workshop within the factory. Factory records supplied this information for 85% of the 833 jobs held by women with pancreatic cancer. For 9% of jobs, we obtained this information by interviewing a relative. We obtained the remaining occupational histories from other interviews: 42 with a supervisor, nine by telephoning study subjects, and six with coworkers.

Among non-cases, factory records supplied this information for 81% of 5976 jobs. For 10% of these jobs, we obtained this information by interviewing a supervisor. We used telephone interviews with study subjects for 8% of jobs. To obtain the remaining occupational histories, we interviewed 36 coworkers and 22 relatives.

STIB industrial hygienists culled historical records for contemporaneous data about factory processes, fibers, jobs, and hazardous agents. But as records were incomplete, expert opinion was also used to complete the JEM, in what was designated the *a priori*

assessment. The final matrix included three axes of data: industry sector and fiber types; job-specific textile processes; and agents considered hazardous.<sup>13</sup>

Endotoxin exposures, however, were estimated using available historical data, as has been previously described.<sup>14</sup> Cotton dust concentration measurements gathered by local industrial hygienists from 1975 to 1999 in 56 factories were assembled.<sup>14</sup> Endotoxin data generated by investigators from the University of Washington<sup>15</sup> and Harvard University<sup>16–19</sup> were used to correlate cotton dust concentration to endotoxin concentration.

We excluded 17 cases due to missing work history, leaving 481 cases for all but the endotoxin analysis. We excluded an additional 13 cases from the endotoxin analysis who held jobs with exposure to endotoxin that was not quantified in the JEM. Specifically, women who worked in wool production, sanitation, or machinist positions likely had endotoxin exposure that was not quantified. Of the 3191 non-cases in the sub-cohort, we excluded an additional 12 women due to missing work history, leaving 3179 non-cases available for all but the endotoxin analysis. We excluded an additional 145 non-cases for unknown endotoxin exposure in the endotoxin analysis.

## Statistical Analysis

We evaluated the associations between the eight exposure categories and pancreatic cancer risk using Cox proportional hazard modeling adapted for stratified case-cohort designs.<sup>20,21</sup> For endotoxin exposures, we included 468 cases and 3034 non-cases in the final analysis. For all remaining exposure categories, we included 481 cases and 3179 non-cases in the final analysis.

We generated hazard ratio (HR) estimates and 95% confidence intervals (CIs) based on robust variance estimates using the methodology described by Langholz and Jiao.<sup>21</sup> We accounted for the sampling scheme by using birth year stratum-specific sampling weights in the variance estimation. The period of risk was from entry into the base cohort until diagnosis of pancreatic cancer, death, date of last known follow-up, or end of follow-up on December 31, 2006. We controlled for age and smoking status by incorporating these variables into the regression model. We did not control for alcohol consumption because of low levels of self-reported exposure.

For endotoxin, we analyzed the data including all cases identified during the entire 1989 to 2006 follow-up period. We sought to increase precision by creating exposure categories for endotoxin using cut points derived from the distribution of all exposed cases, a method that kept the number of cases in each exposure stratum of the analysis approximately the same.<sup>22</sup> We generated HRs and 95% CIs for each exposed group compared with the unexposed reference group. For exposures other than endotoxin, we estimated HRs for unexposed, 0 to 10, 10 to 20, and more than 20 years of exposure. We evaluated trend among the exposed by assigning the median value of exposure within each exposure category as the score variable, and performing a Wald test on that variable. We considered  $P < 0.05$  to be statistically significant. We completed all analyses with SAS software version 9.3 (SAS Institute Inc, Cary, NC), including macros developed by Langholz and Jiao.<sup>21</sup> We compiled certain demographic information using Stata 12 (StataCorp, College Station, TX).

## RESULTS

Women with pancreatic cancer (median birth year 1931) tended to be older than non-cases (median birth year 1933). Over 90% of both cases and non-cases had never smoked. Slightly more cases than non-cases were current or former smokers. Cases were less likely than non-cases to be working at the time of questionnaire administration. Over 80% of both cases and non-cases did not report drinking alcohol. The proportion of cases who consumed

alcohol more than weekly was slightly higher in cases than non-cases (Table 1).

We observed an association between pancreatic cancer and ever smoking (HR 1.61, 95% CI 1.11–2.33), and between pancreatic cancer and ever consuming alcohol (HR 1.08, 95% CI 0.84–1.40), but the number of exposed women in each case was small.

As shown in Table 2, there was a statistically significant trend of increasing risk with increasing duration of exposure to solvents. Risk was highest for the group exposed greater than 20 years: HR 1.51, 95% CI 0.99 to 2.30.

For dyes and inks, we observed increased HRs, but CIs were very wide and included the null value. For resins, lubricants, and pesticides, HR estimates did not reliably increase with increasing exposure and we did not observe any statistically significant associations (Table 2). The CIs for these exposures were very wide and covered the null value.

For endotoxin exposures from 1989 to 2006, HR estimates did not reliably increase with increasing endotoxin exposure and we did not observe any statistically significant tests for trend (Table 3). Results were similar with lagged analysis (data not shown.) All CIs for these estimates included 1.0.

## DISCUSSION

We report two principal findings. First, our results no longer suggest a protective relation between endotoxin and pancreatic cancer. Second, we found limited evidence that increasing duration of exposure to solvents was associated with increasing risk of having pancreatic cancer.

## ENDOTOXIN

Cotton dust—which contains endotoxin—has been associated with increased risk of pancreatic cancer.<sup>9</sup> In addition, a biomolecular signaling pathway mediated by NF-κB that links endotoxin to pancreatic cancer progression has been described.<sup>23</sup>

But when all exposures—even with the additional follow-up through 2006—were analyzed together, contrary to the findings from the initial follow-up,<sup>10</sup> we did not find strong evidence of a relationship between endotoxin exposure and pancreatic cancer. We found this to be the case irrespective of the degree to which we

discounted recent endotoxin exposure through lagged analysis. The relationships between endotoxin exposure, inflammatory cytokines, such as tumor necrosis factor, and cancer are complex, with both seemingly anti- and pro-carcinogenic effects.<sup>24</sup>

## Solvents, Metals, and Chemicals

The statistically significant trend of increasing HRs that we observed for solvents combined with the nearly significant 95% CI with greater than 20 years of solvents exposures provides some evidence of excess risk of pancreatic cancer associated with those substances. These results are concordant with studies by others.<sup>6,7</sup> These findings did not emerge from the analysis for the follow-up period that ended in 1998.<sup>10</sup> A more detailed interpretation of these results is limited by the lack of solvent-specific exposure data.

Although our HR estimates for metal exposures increased with duration of exposure, this trend was not statistically significant and the 95% confidence limits of all HR estimates included one. Unfortunately, we did not have data to quantify the degree of exposure to specific metals that have been previously implicated as risk factors for pancreatic cancer, such as cadmium, nickel, and chromium.<sup>6,7</sup> For example, chromium exposures vary according to welding process and shield gas used.<sup>25</sup> Thus, our study's ability to identify an association between exposure and risk of pancreatic cancer was limited for the metals analysis. Our results suggest that additional studies of risk of pancreatic cancer and exposures to specific metals are warranted.

We did not observe any statistically significant associations with exposure to dyes, inks, resins, lubricants, or pesticides.

## Strengths and Limitations

With 481 cases of pancreatic cancer available for analysis—about 300 more than were included in the earlier follow-up period<sup>10</sup>—this follow-up case-cohort analysis builds on the strengths of this study design and data set, with detailed work-history incorporating the best-available information from several sources. It also includes additional exposure data and follow-up time for an already large and well-characterized cohort of female textile workers. It, therefore, has increased statistical power to detect

**TABLE 1.** Baseline Characteristics of Pancreatic Cancer Cases and Non-Cases

Baseline Characteristics of Pancreatic Cancer Cases and Non-Cases	Cases (n = 481)	Non-Cases (n = 3,179)
	n (%)	n (%)
Year of birth		
1925–1929	172 (35.8)	933 (29.3)
1930–1934	169 (35.1)	915 (28.8)
1935–1939	60 (12.5)	366 (11.5)
1940–1944	22 (4.6)	163 (5.1)
1945–1949	22 (4.6)	281 (8.8)
1950–1954	26 (5.4)	321 (10.1)
1955–1958	10 (2.1)	200 (6.3)
Smoking status		
Never smoked	440 (91.5)	3,035 (95.5)
Former smoker	8 (1.7)	26 (0.8)
Current smoker	33 (6.9)	118 (3.7)
Alcohol consumption		
Never	396 (82.3)	2,605 (81.9)
Less than weekly	63 (13.1)	480 (15.1)
Greater than weekly	22 (4.6)	94 (3.0)
Working status at interview		
Employed	95 (19.8)	1,071 (33.7)
Retired	386 (80.2)	2,108 (66.3)

**TABLE 2.** Hazard Ratio Estimates of Pancreatic Cancer by Exposure and Duration of Employment: 1989–2006\*

Exposure Duration	Pancreatic Cancer Cases (n = 481)	Pancreatic Cancer Non-Cases (n = 3,179)	HR	95% CI
Metals				
Unexposed	457	2,972	1.00	Referent
0–10 yrs	6	77	0.59	0.25–1.37
10–20 yrs	8	52	0.94	0.43–2.02
>20 yrs	10	78	1.02	0.51–2.01
P trend			0.32	
Solvents				
Unexposed	418	2,718	1.00	Referent
0–10 yrs	14	171	0.61	0.35–1.07
10–20 yrs	19	139	0.99	0.60–1.63
>20 yrs	30	151	1.51	0.99–2.30
P trend			0.004	
Dyes				
Unexposed	467	3,084	1.00	Referent
0–10 yrs	3	29	0.88	0.26–3.01
>10–20 yrs	6	36	1.12	0.46–2.71
>20 yrs	5	30	1.40	0.53–3.75
P trend			0.75	
Inks				
Unexposed	476	3,149	1.00	Referent
0–10 yrs	1	8	1.19	0.15–9.80
>10–20 yrs	2	10	1.88	0.38–9.22
>20 yrs	2	12	1.55	0.33–7.31
P trend			0.66	
Resins				
Unexposed	472	3,092	1.00	Referent
0–10 yrs	3	29	0.80	0.24–2.69
>10–20 yrs	4	31	0.90	0.31–2.65
>20 yrs	2	27	0.51	0.12–2.18
P trend			0.49	
Lubricants				
Unexposed	169	1,208	1.00	Referent
0–10 yrs	40	325	0.85	0.59–1.23
>10–20 yrs	62	494	0.88	0.64–1.21
>20 yrs	210	1,152	1.11	0.89–1.39
P trend			0.08	
Pesticides				
Unexposed	476	3,131	1.00	Referent
0–10 yrs	2	18	0.83	0.19–3.66
>10–20 yrs	1	11	0.58	0.07–4.70
>20 yrs	2	19	0.58	0.13–2.51
P trend			0.92	

CI, confidence interval; HR, hazard ratio.

\*All hazard ratio estimates include adjustment for age and smoking status through inclusion in the regression model. Trend performed among exposed individuals using median exposure in each category.

associations between pancreatic cancer and the eight occupational risk factors considered for this follow-up.

The findings were controlled for two important known risk factors for pancreatic cancer: age and smoking status. Smoking was unlikely to be a confounder due to low prevalence and our ability to

control for smoking in the analysis. We did not control for alcohol consumption as the prevalence of consuming alcohol at least weekly was small among both cases and non-cases.

The accuracy of the exposure assessment for endotoxin relies upon cotton dust data gathered from 56 factories, which were

**TABLE 3.** Hazard Ratio Estimates of Pancreatic Cancer by Cumulative Quantity of Endotoxin Exposure: 1989–2006

Endotoxin Exposure (EU/m <sup>3</sup> × yrs)	Cases (n = 468)	Non-Cases (n = 3,034)	HR	95% CI
Never	138	915	1.00	Referent
0–1758.0	82	658	0.84	0.63–1.13
1758.0–2599.3	83	496	1.04	0.77–1.40
2599.3–4011.6	83	528	0.91	0.67–1.23
>4011.6	82	437	1.08	0.80–1.45
P trend			0.17	

CI, confidence interval; HR, hazard ratio.

correlated to quantitative endotoxin exposures using five data sets.<sup>15–19</sup> Given the number of factories, the potential for variable sources of cotton, and different environmental conditions, there was likely nontrivial variability in endotoxin exposures during the decades of work considered in this analysis. Although the methodology we relied on for endotoxin exposure assessment represents the best available reconstruction, there is probably some inaccuracy in these modeled estimates.

Nonetheless, estimation of endotoxin exposure was done without regard for pancreatic cancer status. Any misclassification of endotoxin exposure would be expected to be non-differential, diminishing chances of detecting true associations.<sup>12</sup>

Our assessment of associations for metals, solvents, dyes, inks, resins, lubricants, and pesticides was limited for several reasons. We used length of employment as a proxy for quantitative exposure estimates for these agents; our data contained relatively few women with these exposures; and the nature of the job tasks within these classifications varied.

## CONCLUSIONS

Despite adding a substantial number of cases to a prior analysis of occupational risk factors for pancreatic cancer, we did not find strong evidence of a relationship between endotoxin exposure and pancreatic cancer. We did, however, observe a statistically significant trend of increasing HRs associated with solvent exposure, which is consistent with published literature suggestive of an etiologic relation.<sup>6,7</sup>

We did not have adequate information to quantify the exposure to specific metals known to be associated with excess risk of pancreatic cancer, and did not observe any statistically significant associations between metals exposure and pancreatic cancer.

We did not observe any associations with exposure to dyes, inks, resins, lubricants, or pesticides.

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