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Occupational Risk Factors for Pancreatic Cancer Among Female Shanghai, China Textile Workers: An Updated Nested Case-cohort Study

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Abstract

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Pancreatic cancer is of particular public health importance given its disproportionate contribution to cancer death. In the United States pancreatic cancer is the fourth most common cause of cancer-related death. Yet occupational risk factors for pancreatic cancer have been inadequately studied in large populations, particularly among textile workers. These occupational exposures represent a potential target for reduction in pancreatic cancer death.

A prior nested case-cohort study of 180 incident cases and 3188 non-cases investigated occupational risk factors for pancreatic cancer in a Shanghai, China cohort of 267,400 female textile workers followed from 1989-1998. The findings indicated dose-related reduced risks associated with endotoxin, a contaminant of cotton dust. We have since updated that Shanghai cohort with an additional eight years of data (now including 1989-2006), and repeated the case-cohort analysis to look for associations between pancreatic cancer and three groups of exposures: metals, solvents, and endotoxin.

We did not find much evidence of an association between estimated endotoxin exposures and the risk of developing pancreatic cancer. We did not find strong evidence of association between metals and solvents exposures and the risk of developing pancreatic cancer.

INTRODUCTION:

Pancreatic cancer is the fourth most common cause of cancer-related death in the United States for both men and women. (U.S. Cancer Statistics Working Group 2008). In the developed world, it is fifth for men, and fourth for women. (Jemal et al. 2011) Considering disease incidence in both settings, pancreatic cancer disproportionately contributes to cancer-related death. This is likely a consequence of the poor prognosis for afflicted patients. (Castillo and Jimenez 2012)

Known and possible risk factors for pancreatic cancer include smoking (established in multiple studies); abnormalities of glucose metabolism; alcohol consumption; obesity; nonhereditary pancreatitis; certain hereditary conditions and germline mutations; surgical history of partial gastrectomy or cholecystectomy; and infection with Helicobacter pylori. (Castillo and Jimenez 2012)

Though their estimate was unstable and may suffer from "misclassification of exposures and end points," Ojajarvi et al calculated that occupational exposures are responsible for 12% of pancreatic cancer cases. (2000 p. 322) Given the lethality of the disease, we agree with other authors (Andreotti and Silverman 2012) who state that occupational exposures represent important targets of disease reduction, as exposure is avoidable. Recent literature suggests that "the strongest and most consistent findings linking occupational exposures with pancreatic risk to date are for chlorinated hydrocarbons and [polycyclic aromatic hydrocarbons]." (Andreotti and Silverman 2012) Some metals (such as cadmium, nickel, and chromium) have also been implicated as risk factors for pancreatic cancer. (Ibid)

Metal and solvent exposures were two of many analyzed by Li et al in their 2006 case-cohort study of occupational risk factors for pancreatic cancer. That publication was one of several such studies examining occupational risk factors for cancer. (Camp et al 2003) An unexpected finding in their study was an apparently protective association between increasing doses of endotoxin and the risk of developing pancreatic cancer. (Li et al 2006) Though attenuated, this finding remained in a reanalysis of those data. (Romano 2012)

Endotoxin is a component of gram-negative bacterial cell walls. Bacterial contamination of cotton dust exposes textile workers, as they inhale the contaminated fibers. (Castellan et al. 1984) Endotoxin has been implicated as a mediator of both organ-specific (particularly the lung) and systemic disease in humans. (Castellan et al. 1984; Heine, Rietschel and Ulmer 2001) Although other studies have shown that endotoxin may exert a protective effect on the risk of developing lung cancer (Astrakianakis et al 2010, 2006; Agalliu et al 2011; Enterline et al 1985), this apparently protective effect contradicted literature suggesting a harmful association. (Falk et al 1990)

Follow-up of cohort members has continued, and more than twice as many cases of pancreatic cancer have been identified as were available for consideration in the Li et al 2006 analysis. With the benefit of these additional cases, we sought to update this nested case-cohort study, and analyzed not only the metal and solvent exposures that continue to be implicated in the risk of developing pancreatic cancer (*vide supra*), but also to see if our estimates of the association between endotoxin exposure and pancreatic cancer continue to appear dose-related, and protective.

MATERIALS AND METHODS:

The foundation cohort from which all individuals were selected was identified for a randomized control trial of breast cancer and comprised about 290,000 women from Shanghai, China (prior to consideration of elimination criteria.) Women were eligible if they were permanent residents of Shanghai, were currently or previously employed by the Shanghai Textile Industry Bureau, and were born between 1925 and 1958. Baseline questionnaires were administered from October 1989 through October 1991. (Thomas et al. 2002) Women were excluded if they transferred employment away from the Shanghai Textile Industry Bureau, left Shanghai, died, could not be located, had an out-of-bounds birthdate, or did not complete the baseline questionnaire either because they refused, changed factories before completing the form, or were considered mentally or physically unable to do so by a factory medical worker. (Ibid)

The 267,400 women who remained following exclusion are the population from which all cases of pancreatic cancer were identified for this study. Follow-up monitoring for each individual commenced with gathering of baseline questionnaire information (time zero), and ended with diagnosis of pancreatic cancer, death from other causes, or moving away from Shanghai. Follow-up began at the earliest in 1989, and for the purposes of this update was considered until 31 December 2006. For this update 471 individuals with pancreatic cancer were identified, more than twice the number available for consideration by Li et al in 2006.

For the follow-up period that ended 31 December 1998, cases of pancreatic cancer were identified following reporting by factory health clinic workers to the

Shanghai Textile Industry Bureau Station for the Prevention and Treatment of Cancer. Diagnosis was confirmed by querying the Shanghai Cancer Registry, and also through medical record review. The latter was attempted for all individuals, and successful for most, either by histology (25%), cytology (1.6%), or medical imaging (45%). (Li et al. 2006)

For follow-up from 1999 through 31 December 2006 pancreatic cancer cases were identified by directly crossmatching subcohort members with the Shanghai Cancer Registry. Women with pancreatic cancer as identified through the Registry had their diagnosis confirmed by medical record review if a histologic diagnosis was not provided by the Registry. The information came from multiple potential sources: hospital- and factory-based medical records; pathology reports; and interviews of family members to determine if other records were available. (Family members were only interviewed to locate records, not to gather medical information.)

A case-cohort design was chosen for the prior analysis, and was used again for this update. All non-cases selected for inclusion in the analysis were drawn from the foundation cohort by one of two different mechanisms. A stratified, randomly-selected subcohort of 3199 women was identified from the foundation cohort for occupational exposure assessment and inclusion in the analysis. These 3199 women were selected from five year birth-year strata to mirror the distribution of all women identified as having cancer at the time of the earlier Shanghai textile industry occupational risk factors studies performed by this group. (Li et al 2006) For our updated analysis, we were unable to consider 11 of those individuals due to missing work history; we analyzed the 3188 who remained, which included eight individuals who were also cases diagnosed with pancreatic cancer. An additional 1631 controls—drawn from a pool of 1814 who were originally selected for two nested case-control studies of breast disease (Wong et al 2009)—were also included in the analyzed subcohort for our updated analysis. This pool comprised only controls, and did not contribute any cases of pancreatic cancer to the analysis. Additionally, these auxiliary controls had been matched by five year age group to the cases in the breast disease studies, not those with pancreatic cancer.

After dropping one individual who was missing job duration, there were a total of 471 cases and 4810 non-cases included in our updated analysis (see figure 1).

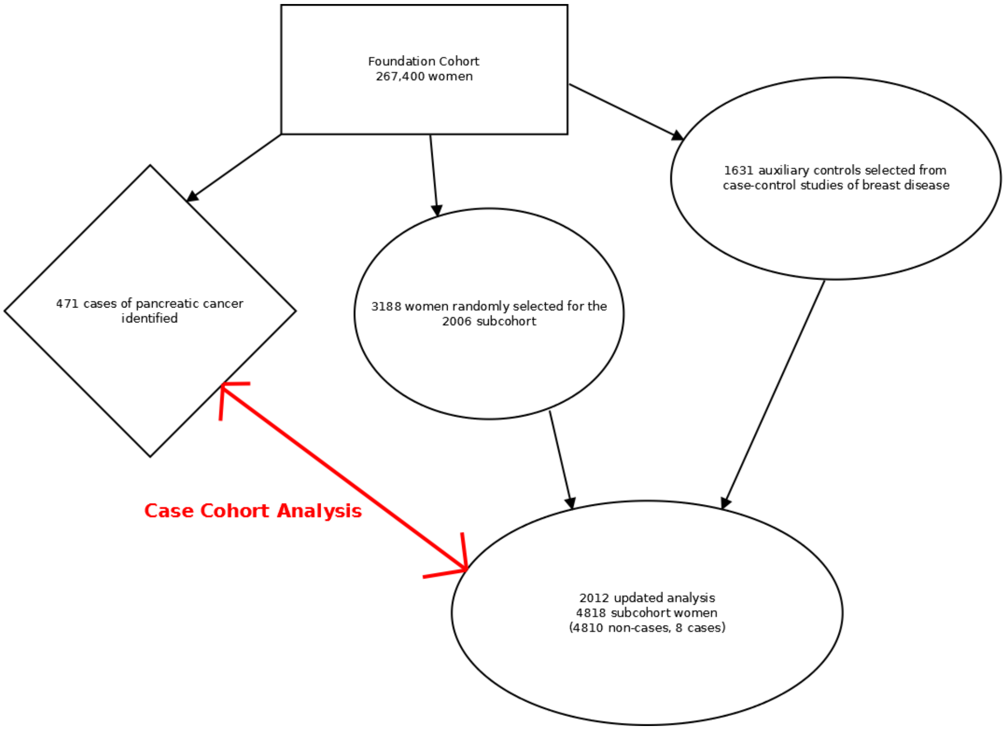

Figure 1

ASSESSING EXPOSURES:

Exposure assessment and the generation of a job exposure matrix were extensively described by Wernli et al. (2006) To briefly summarize their work, in the mid-twentieth century the textile industry in Shanghai was organized under the Shanghai Textile Industry Bureau. A variety of factories fell under the Shanghai Textile Industry Bureau's authority; the industry was vertically integrated. 526 factories contributed data and participated in the generation of the job exposure matrix, which included three axes of information: industry sector and fiber types; job-specific textile processes; and agents considered hazardous.

Exposure was assessed for all identified cases and non-cases included in the nested analysis. All jobs held in textile factories were assessed. Dates, site, and type of employment (including job tasks) were identified via historical records from the factory, or interviewing supervisors, coworkers, family members, or the individual herself.

After receiving training from the study researchers, local industrial hygienists gathered data about factory processes, fibers, jobs, and hazardous agents. These data were gathered from historical records. Some hazardous agents were required to be quantitatively measured and monitored starting in the late 1970s, but not earlier.

If a job process was recorded associated with exposure in at least 30% of the 239 individually reported exposures, then for the purposes of this study the exposure was considered to have taken place for all employment where that job process existed.

As records were incomplete, expert opinion was also required to complete the job exposure matrix, in what has previously been referred to as the *a priori* assessment. (Wernli et al 2006) A group of Seattle-based experts comprising three occupational epidemiologists, three industrial hygienists, and a textile engineer developed consensus opinions about the exposures they believed a worker in a given job process would and also would not likely sustain. They reached consensus for all considered processes and exposures. (Ibid)

These were the methods used to characterize metal and solvent exposures for the analysis. We did not have adequate metal- and solvent-specific data to justify breaking out these categories in favor of specific metals (such as nickel and lead) or specific solvents (such as trichloroethane or tetrachloroethylene) for this updated analysis.

Because no historical data containing actual endotoxin measurements were available, specific procedures were used to estimate endotoxin exposures. Astrakianakis et al. assembled cotton dust concentration measurements gathered by local industrial hygienists from 1975-1999 in 56 factories. (*Modeling*, 2006) They then used five datasets generated both by the University of Washington (Astrakianakis et al., *Exposure levels*, 2006) and elsewhere (Olenchock et al 1983; Kennedy et al 1987; Christiani et al 1993, 1999) correlating cotton dust concentration to endotoxin concentration. Finally, they estimated endotoxin exposures for all the analyzed members of the subcohort by merging these predicted endotoxin concentrations with the process and job information assembled as described for inclusion in the job exposure matrix. (Astrakianakis et al. *Modeling*, 2006)

ANALYSIS:

We evaluated the associations between the three exposures analyzed in this update (metals, solvents, and endotoxin) and pancreatic cancer using cox-proportional hazard modeling for stratified case-cohort studies as described by Langholz and Jiao. (2007) Included in the analysis were 471 cases and 4811 non-cases. Fewer individuals (458 cases and 4569 non-cases) were included in the endotoxin analysis due to missing endotoxin exposure history, or if there was uncharacterized exposure to endotoxin not quantified in the job exposure matrix, as might have happened for women who worked in wool production, sanitation, or machinist positions outside the Shanghai Textile Industry Bureau.

The individuals were organized into risk sets, one for each case included in the analysis. (Small modifications were made to the failure times to break ties.) Citing Cox (1972), Langholz and Jiao describe the structure of the risk sets to be that of "individually matched case-control data with a risk set formed at each failure time with the failure the 'case' and all those at risk at the failure time as 'controls.'" (2007 p. 3739) Thus, each risk set is defined by follow-up time for the reference case from administration of the baseline questionnaire (time zero) until diagnosis. For comparison individuals in the subcohort with follow-up time in excess of that of the case used to define the risk set, the included exposure is truncated at that accumulated as of the follow-up time equal to that of the reference case. This describes the unlagged analysis.

For endotoxin we also conducted lagged analysis that discounts the most recent ten and twenty years of exposure accumulated by each individual by deliberately ignoring exposures accumulated during that period.

For all analyses—lagged and unlagged—we generated exact hazard ratio estimates and robust 95% confidence intervals using the methodology described by Langholz and Jiao. (2007) We accounted for the fraction of each age-adjusted stratum sampled by incorporating stratum-specific sampling weights into our variance estimates. We controlled for age and smoking status by incorporating these variables into our regression model. For endotoxin, we analyzed the data in two ways. First we used the cutpoints selected by Li et al in 2006 to enable direct comparison with those results as updated by Romano. (2012) To increase precision we also analyzed the data using new endotoxin cutpoints, selected to keep the number of cases in each exposure stratum of the unlagged analysis approximately the same. For metals and solvents, we generated hazard ratios for unexposed, 0-10, 10-20, and > 20 years of exposure.

The cox proportional hazard analysis and variance estimates were created using SAS software version 9.3. Demographic information was compiled using Stata 11.

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

RESULTS:

Baseline characteristics of pancreatic cancer cases and non-cases	Cases (n=471) (%)	Non-cases (n=4810) (%)
Year of birth		
1925-1929	170 (36.1)	1091 (22.7)
1930-1934	164 (34.8)	1152 (24.0)
1935-1939	58 (12.3)	515 (10.7)
1940-1944	21 (4.5)	251 (5.2)
1945-1949	22 (4.7)	450 (9.4)
1950-1954	26 (5.5)	627 (13.0)
1955-1958	10 (2.1)	724 (15.1)
Working status		
Employed	93 (19.7)	2226 (46.3)
Retired	378 (80.3)	2584 (53.7)
Unknown	0 (0)	0 (0)
Smoking status		
Never smoked	431 (91.5)	4636 (96.4)
Former smoker	8 (1.7)	29 (0.6)
Current smoker	32 (6.8)	145 (3.0)
Unknown	0 (0)	0 (0)
Alcohol consumption		
Never	386 (82.0)	3870 (80.5)
Less than weekly	63 (13.4)	812 (16.9)
Greater than weekly	22 (4.7)	128 (2.7)
Unknown	0 (0)	0 (0)

Table 1

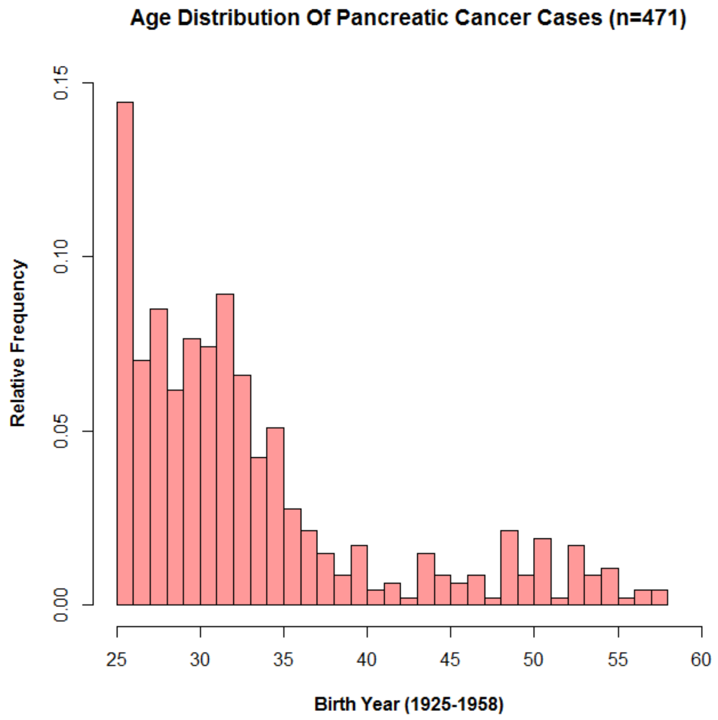

Figure 2

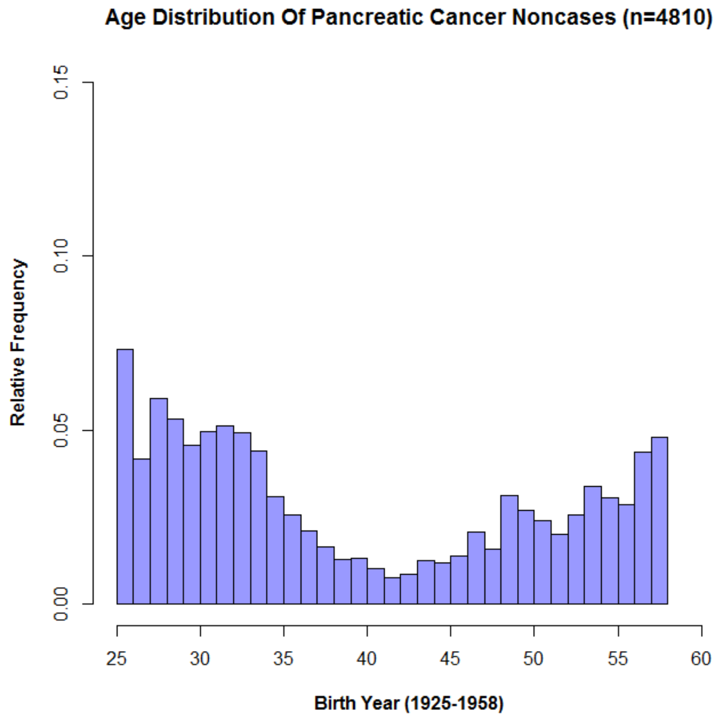

Figure 3

Exposure	# Cases Exposed (% of cases)	# Non-cases exposed (% of non-cases)
metals	22 (4.7)	354 (7.4)
solvents	59 (12.5)	754 (15.7)
endotoxin	319 (69.7)	3108 (68.0)

Table 2

2012 Metals Results[1]	Cases	Non-cases	HR	Lower bound	Upper bound
Unexposed	449	4456	1.0	Referent	Referent
0-10 years	6	104	0.642	0.277	1.484
10-20 years	8	111	0.855	0.404	1.807
> 20 years	8	139	0.736	0.354	1.531
Totals	471	4810			

Table 3

2012 Solvents results	Cases	Non-cases	HR	Lower bound	Upper bound
Unexposed	412	4056	1.0	Referent	Referent
0-10 years	14	251	0.655	0.376	1.143
10-20 years	18	243	0.914	0.552	1.515
> 20 years	27	260	1.256	0.823	1.916
Totals	471	4810			

Table 4

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[1] HR is hazard ratio adjusted for age and smoking. Upper bounds and lower bounds were calculated at the 95% confidence interval

2012 ENDOTOXIN RESULTS—2006 CUTPOINTS

EU/m^3 × years Unlagged	Pancreatic cancer cases (n=458)	Pancreatic cancer non-cases (n=4613)	Hazard ratio (adjusted for age and smoking)	95% Confidence interval
None	139	1479	1.00	Referent
0-1517.4	62	895	0.80	0.58-1.1
1517.4-2430.0	85	770	1.04	0.77-1.4
2430.0-3530.6	81	712	0.96	0.71-1.2
> 3530.6	91	757	0.99	0.74-1.32
10-year lag				
None	140	1481	1.0	Referent
0-1517.4	67	933	0.82	0.6-1.12
1517.4-2430.0	85	761	1.04	0.78-1.40
2430.0-3530.6	79	688	0.95	0.70-1.28
> 3530.6	87	750	0.97	0.72-1.29
20-year lag				
None	151	1541	1.0	Referent
0-1517.4	89	1152	0.88	0.66-1.16
1517.4-2430.0	80	678	0.94	0.70-1.26
2430.0-3530.6	61	582	0.83	0.60-1.14
> 3530.6	77	660	0.95	0.70-1.29

Table 5

2006 REANALYZED RESULTS (ROMANO 2012)

Unlagged 2006 analysis with corrections				
EU/m^3 × years	**Cases**	**Noncases**	**HR**	**95% CI**
None	54	914	1.0	Referent
0-1517.4	32	534	1.1	0.7-1.7
1517.4-2430.0	37	528	1.1	0.7-1.8
2430.0-3530.6	23	527	0.6	0.4-1.1
> 3530.6	30	529	0.8	0.5-1.3
10-year lag from 2006 analysis with corrections				
None	55	924	1.0	Referent
0-1517.4	36	627	1.1	0.7-1.7
1517.4-2430.0	35	505	1.0	0.7-1.6
2430.0-3530.6	23	476	0.7	0.4-1.1
> 3530.6	27	500	0.7	0.5-1.2
20-year lag from 2006 analysis with corrections				
None	61	1091	1.0	Referent
0-1517.4	46	663	1.0	0.7-1.5
1517.4-2430.0	36	462	1.0	0.6-1.5
2430.0-3530.6	14	402	0.5	0.3-0.9
> 3530.6	19	414	0.6	0.4-1.1

Table 6

2012 ENDOTOXIN RESULTS—2012 CUTPOINTS

EU/m^3 × years Unlagged	Pancreatic cancer cases (n=458)	Pancreatic cancer non-cases (n=4569)	Hazard ratio	LL	UL
unexposed	139	1461	1.000	referent	
0-1698.3	79	1043	0.866	0.646	1.163
1698.3-2569.0	81	718	1.011	0.749	1.366
2569.0-3873.1	80	690	0.947	0.704	1.274
> 3873.1	79	657	0.981	0.727	1.322
10-year-lag					
unexposed	140	1463	1.000	referent	
0-1698.3	82	1077	0.860	0.644	1.149
1698.3-2569.0	85	706	1.072	0.798	1.442
2569.0-3873.1	74	674	0.889	0.656	1.205
> 3873.1	77	649	0.977	0.723	1.321
20-year-lag					
unexposed	151	1522	1.000	referent	
0-1698.3	108	1287	0.918	0.704	1.195
1698.3-2569.0	69	611	0.848	0.623	1.155
2569.0-3873.1	61	575	0.840	0.610	1.157
> 3873.1	69	574	0.973	0.712	1.329

Table 7

The age distribution tended to be older among individuals with cancer compared to the non-cases (see figures 2 and 3). Those with cancer were also more likely to be retired from work at the time the baseline questionnaire was administered. A supermajority of both cases and noncases abstained from alcohol, and did not use tobacco. Nearly the same proportion of cases and non-cases abstained from alcohol. Although there were more never-smokers in the non-cases group, we adjusted for smoking status in our analysis.

Almost 70% percent of cases were exposed to endotoxin, about the same as the 68% of non-cases who were exposed. A relatively low proportion of cases and non-cases alike were exposed to either metals or solvents (see table 2). The 95% confidence intervals for metals and solvents hazard ratio estimates were relatively wide, and included one in all estimates. The confidence intervals for all 2012 endotoxin results included one.

Considering both lagged and unlagged results, the hazard ratio estimates for the 2012 endotoxin analysis did not dramatically change when using new cutpoints.

DISCUSSION AND CONCLUSIONS:

With 471 cases of pancreatic cancer available for analysis—more than twice as many as Li et al had available for their 2006 publication—this updated case-cohort analysis enjoys greater discriminatory power to detect associations between pancreatic cancer and the three occupational risk factors (metals, solvents, and endotoxin) considered for this update. The interval publication by Langholz and Jiao (2007) of methods that enable the practical analysis of confounder-stratified case-cohort studies such as ours also encourages an updated analysis.

ENDOTOXIN:

The most surprising result from Li et al's 2006 analysis was the apparent protective effect seen with increasing estimated concentrations of endotoxin exposure, particularly when viewed with 20-years of lag. The authors of the 2006 analysis had no *a priori* hypothesis regarding endotoxin and pancreatic cancer. To take advantage of the aforementioned confounder-stratified methods published by Langholz and Jiao, and to correct an error in estimating the hazard ratios for lagged exposure estimates (see Astrakianakis et al 2010) Romano (2012) reanalyzed the 2006 data, with results as reported above. Though weaker following reanalysis, the effect appeared to remain.

The 2012 endotoxin results, however, did not replicate the pattern observed in the reanalyzed 2006 hazard ratio estimates of endotoxin exposure; we did not find much evidence of an association between endotoxin exposure and the risk of developing pancreatic cancer. We did not replicate the earlier finding despite the precision gained from the additional cases with the update. The earlier finding may merely have been due to chance.

Cohort members accumulated additional follow-up time since the 2006 data were collected. If the hypothesis that endotoxin exerts a protective effect on the risk of developing pancreatic cancer is true, the effect may appear more or less pronounced at varying times, or "windows" following exposure. As described earlier, the etiology of pancreatic cancer is multifactorial. The additional follow-up time incorporated into this updated study may have permitted other influences on the risk of developing pancreatic cancer to effectively mask any effects secondary to endotoxin exposure. Given the existence of uncontrolled competing risks for pancreatic cancer, the results we observe may possibly reflect the consequences of these other factors that make it difficult to detect an association with endotoxin.

By discounting recent exposures, the lagged analysis we performed for this update only accounts for potential latency for disease to manifest. A method of unmasking any competing risk effects would be to perform a time-window analysis such as that conducted by Agalliu et al. in 2011. We intend to reanalyze the updated endotoxin data using time-windows.

METALS AND SOLVENTS:

With the metals and solvents analysis we conducted we did not find strong evidence of association between these exposures and the risk of developing pancreatic cancer. This finding is unsurprising given the non-specificity of the exposure assessment—limited to binary classification and broad groupings—for these classes of chemicals. As Li et al point out (2006), this may be a consequence of the fact that our study contains no men, who were probably more likely to work in jobs with metal and solvent exposures than the women under study. The lack of precision we observe limits the inferences we can make about metal and solvent exposures on the risk of developing pancreatic cancer.

STUDY LIMITATIONS:

The accuracy of the exposure assessment for endotoxin relies upon cotton dust data gathered from 56 factories, which were correlated to quantitative endotoxin exposures using five datasets. (Astrakianakis et al., *Exposure levels*, 2006; Olenchock et al. 1983; Kennedy et al. 1987; Christiani et al. 1993, 1999) Given the number of factories, the potential for variable sources of cotton, and different environmental conditions, there was likely nontrivial variability in endotoxin exposures over the decades of work considered in this analysis. While the methodology we relied on for endotoxin exposure assessment represents best available reconstruction, absent the existence of historical measurements, there is probably some inaccuracy in these estimates, which could potentially either overestimate or underestimate exposure in a given individual.

Bias introduced through selective migration of sick workers out of illness-causing jobs was likely constrained in this cohort by the organization of work in a planned economy. “From the time the socialist system in China was established after 1949 until economic reforms began in about 1994, women entering the work force were assigned to a factory where they typically remained until they retired.” (Thomas et al. 2002, p. 1446)

The auxiliary controls we included in the analysis were matched by age to cases of breast disease, not to the cases of pancreatic cancer under study. As a consequence, the distribution of ages in the non-cases did not match that of the cases of pancreatic cancer (see figures 2 and 3). By controlling for age in our regression model, however, we controlled the potentially confounding influence of age on our results.

REFERENCES

Agalliu, Ilir, Sadie Costello, Katie M. Applebaum, Roberta M. Ray, George Astrakianakis, Dao Li Gao, David B. Thomas, Harvey Checkoway, and Ellen A. Eisen. 2011. "Risk of Lung Cancer in Relation to Contiguous Windows of Endotoxin Exposure among Female Textile Workers in Shanghai." *Cancer Causes & Control* 22 (10): 1397-1404. doi:10.1007/s10552-011-9812-x.

Andreotti, Gabriella and Debra T. Silverman. 2012. "Occupational Risk Factors and Pancreatic Cancer: A Review of Recent Findings." *Molecular Carcinogenesis* 51 (1): 98-108. doi:10.1002/mc.20779.

Astrakianakis, G., N. S. Seixas, R. Ray, J. E. Camp, D. L. Gao, Z. Feng, W. Li, et al. 2010. "Re: Lung Cancer Risk among Female Textile Workers Exposed to Endotoxin." *Journal of the National Cancer Institute* 102 (12): 913-914. doi:10.1093/jnci/djq155.

Astrakianakis, George, Noah S. Seixas, Janice E. Camp, David C. Christiani, Ziding Feng, David B. Thomas, and Harvey Checkoway. 2006. "Modeling, Estimation and Validation of Cotton Dust and Endotoxin Exposures in Chinese Textile Operations." *Annals of Occupational Hygiene* 50 (6): 573-582. doi:10.1093/annhyg/mel018.

Astrakianakis, George, Noah Seixas, Janice Camp, Thomas J. Smith, Karen Bartlett, and Harvey Checkoway. 2006. "Cotton Dust and Endotoxin Exposure Levels in Three Shanghai Textile Factories: A Comparison of Samplers." *Journal of Occupational and Environmental Hygiene* 3 (8): 418-427. doi:10.1080/15459620600793672.

Camp, JE, NS Seixas, K. Wernli, D. Fitzgibbons, G. Astrakianakis, DB Thomas, DL Gao, and H. Checkoway. 2003. "Development of a Cancer Research Study in the Shanghai Textile Industry." *International Journal of Occupational and Environmental Health* 9 (4): 347-356.

Castellan, RM, SA Olenchock, JL Hankinson, PD Millner, JB Cocke, CK Bragg, HH Perkins, and RR Jacobs. 1984. "Acute Bronchoconstriction Induced by Cotton Dust - Dose-Related Responses to Endotoxin and Other Dust Factors." *Annals of Internal Medicine* 101 (2): 157-163.

Christiani, DC, DH Wegman, EA Eisen, TT Ye, PL Lu, and SA Olenchock. 1993. "Cotton Dust and Gram-Negative Bacterial-Endotoxin Correlations in 2 Cotton Textile Mills." *American Journal of Industrial Medicine* 23 (2): 333-342. doi:10.1002/ajim.4700230210.

Christiani, DC, T. Ye, S. Zhang, DH Wegman, EA Eisen, LA Ryan, SA Olenchock, L. Pothier, and H. Dai. 1999. "Cotton Dust and Endotoxin Exposure and Long-Term Decline in Lung Function: Results of a Longitudinal Study." *American Journal of Industrial Medicine* 35 (4): 321-331. doi:10.1002/(SICI)1097-0274(199904)35:4<321::AID-AJIM1>3.0.CO;2-L.

Cox, DR. 1972. "Regression Models and Life-Tables." *Journal of the Royal Statistical Society Series B-Statistical Methodology* 34 (2): 187-&.

Enterline, P. E., G. Keleti, J. L. Sykora, and J. H. Lange. 1985. "Endotoxins, Cotton Dust, and Cancer." *Lancet* 2 (8461): 934-935.

Falk, R. T., L. W. Pickle, E. T. Fontham, P. Correa, A. Morse, V. Chen, and J. J. Fraumeni. 1990. "Occupation and Pancreatic-Cancer Risk in Louisiana." *American Journal of Industrial Medicine* 18 (5): 565-576. doi:10.1002/ajim.4700180507.

Fauci, AS, DL Kasper, DL Longo, E. Braunwald, SL Hauser, JL Jameson, and J. Loscalzo, eds. 2008. *Harrison's Principles of Internal Medicine*. 17th ed.: McGaw-Hill.

Fernandez-del Castillo, Carlos and Ramon E. Jimenez. 2012. "Epidemiology and Risk Factors for Exocrine Pancreatic Cancer." In *UpToDate*, edited by Diane MF Savarese and Kenneth K. Tanabe. Waltham, MA: UpToDate.

Hariharan, D., A. Saied, and H. M. Kocher. 2008. "Analysis of Mortality Rates for Pancreatic Cancer Across the World." *HPB : The Official Journal of the International Hepato Pancreato Biliary Association* 10 (1): 58-62. doi:10.1080/13651820701883148.

Heine, H., ET Rietschel, and AJ Ulmer. 2001. "The Biology of Endotoxin." *Molecular Biotechnology* 19 (3): 279-296. doi:10.1385/MB:19:3:279.

Jemal, A., F. Bray, M. M. Center, J. Ferlay, E. Ward, and D. Forman. 2011. "Global Cancer Statistics." *CA: A Cancer Journal for Clinicians* 61 (2): 69-90. doi:10.3322/caac.20107.

Jemal, Ahmedin, Freddie Bray, Melissa M. Center, Jacques Ferlay, Elizabeth Ward, and David Forman. 2011. "Global Cancer Statistics." *Ca-a Cancer Journal for Clinicians* 61 (2): 69-90. doi:10.3322/caac.20107.

Kennedy, SM, DC Christiani, EA Eisen, DH Wegman, IA Greaves, SA Olenchock, TT Ye, and PL Lu. 1987. "Cotton Dust and Endotoxin Exposure-Response Relationships in Cotton Textile Workers." *American Review of Respiratory Disease* 135 (1): 194-200.

Langholz, Bryan and Jenny Jiao. 2007. "Computational Methods for Case-Cohort Studies." *Computational Statistics & Data Analysis* 51 (8): 3737-3748. doi:10.1016/j.csda.2006.12.028.

Li, W., R. M. Ray, D. L. Gao, E. D. Fitzgibbons, N. S. Seixas, J. E. Camp, K. J. Wernli, et al. 2006. "Occupational Risk Factors for Pancreatic Cancer among Female Textile Workers in Shanghai, China." *Occupational and Environmental Medicine* 63 (12): 788-793. doi:10.1136/oem.2005.026229.

Ojajarvi, I. A., T. J. Partanen, A. Ahlbom, P. Boffetta, T. Hakulinen, N. Jourenkova, T. P. Kauppinen, et al. 2000. "Occupational Exposures and Pancreatic Cancer: A Meta-Analysis." *Occupational and Environmental Medicine* 57 (5): 316-324. doi:10.1136/oem.57.5.316.

Olenchock, SA, DC Christiani, JC Mull, TT Ye, and PL Lu. 1983. "Endotoxins in Baled Cottons and Airborne Dusts in Textile Mills in the Peoples-Republic-of-China." *Applied and Environmental Microbiology* 46 (4): 817-820.

Romano, Megan. 2012 "Hazard Ratios for Pancreatic Cancer by Cumulative Exposure to Endotoxin: Re-Analysis."University of Washington. Unpublished data.

SAS Institute Inc. 2011. *SAS Software, Version 9.3*. Cary, NC.

StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.

Thomas, DB, DL Gao, RM Ray, WW Wang, CJ Allison, FL Chen, P. Porter, et al. 2002. "Randomized Trial of Breast Self-Examination in Shanghai: Final Results." *Journal of the National Cancer Institute* 94 (19): 1445-1457.

U.S. Cancer Statistics Working Group. 2012. *United States Cancer Statistics: 1999-2008 Incidence and Mortality Web-Based Report*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute.

Wernli, Karen J., George Astrakianakis, Janice E. Camp, Roberta M. Ray, Chin-Kuo Chang, Gao Dao Li, David B. Thomas, Harvey Checkoway, and Noah S. Seixas. 2006. "Development of a Job Exposure Matrix (JEM) for the Textile Industry in Shanghai, China." *Journal of Occupational and Environmental Hygiene* 3 (10): 521-529. doi:10.1080/15459620600902166.

Wong, E. Y., R. M. Ray, D. -L Gao, K. J. Wernli, W. Li, E. D. Fitzgibbons, J. E. Camp, et al. 2009. "Dust and Chemical Exposures, and Miscarriage Risk among Women Textile Workers in Shanghai, China." *Occupational and Environmental Medicine* 66 (3): 161-168. doi:10.1136/oem.2008.039065.

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