Published in final edited form as:

Am J Ind Med. 2008 September ; 51(9): 673–679. doi:10.1002/ajim.20614.

Occupational Risk Factors for Endometrial Cancer among Textile Workers in Shanghai, China

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Abstract

Objective—A case-cohort study was conducted to investigate associations between occupational exposures and endometrial cancer nested within a large cohort of textile workers in Shanghai, China.

Methods—The study included 176 incident endometrial cancer cases diagnosed from 1989-1998 and a randomly-selected age-stratified reference subcohort (n=3061). Study subjects' complete work histories were linked to a job-exposure matrix developed specifically for the textile industry to assess occupational exposures. Hazard ratios (HR) and 95 percent confidence intervals were calculated using Cox proportional hazards modeling adapted for the case-cohort design, adjusting for age at menarche and a composite variable of gravidity and parity.

Results—An increased risk of endometrial cancer was detected among women who had worked for ≥10 years or more in silk production (HR=3.8, 95% CI 1.2-11.8) and had exposure to silk dust (HR=1.7, 95% CI 0.9-3.4). Albeit with few exposed women (2 cases and 8 subcohort women), there was a 7.4-fold increased risk associated with ≥10 years of silica dust exposure (95% CI 1.4-39.7).

Conclusions—The findings suggest that some textile industry exposures might play a role in endometrial carcinoma and should be further replicated in other occupational settings.

Keywords

endometrial cancer; occupation; silica; silk; textile

Introduction

Worldwide, there were approximately 199,000 women diagnosed with corpus uteri cancer, and there were approximately 50,000 deaths due to the disease in 2002 [1]. It is the seventh most common tumor in women globally, and it was estimated to be 10th most common

tumor among women in China in 2005 [1,2]. Approximately 95% of corpus uteri tumors are in the endometrium, and identified as endometrial carcinoma [3].

Various reproductive and menstrual risk factors for endometrial cancer have been identified, whereas few occupational or environmental risk factors have been explored. Several studies have investigated exposure to insecticides, specifically organochlorine compounds, but no consistent associations have been reported [4-6]. Although solvents are considered endocrine disruptors [7], the only study to date to specifically address solvent exposure and endometrial cancer detected no association [8]. In our previous analysis of cancer incidence in the cohort on which this study is based, we detected no significant differences in the rate of endometrial cancer in textile workers in Shanghai compared to the rate in the general population of Shanghai women (standardized incidence ratio (SIR)=1.0, 95 percent CI: 0.9-1.2) [9].

We extend this work with an investigation of potential associations of endometrial cancer risk with occupational exposures to chemicals, specifically solvents, and dusts in a large, well-defined cohort of women workers in the Shanghai textile industry.

Materials and Methods

Study subjects

Details of the enumeration and follow-up of the study cohort have been published elsewhere [10,11]. Briefly, 267,400 active and retired women workers from 526 textile factories in the Shanghai Textile Industry Bureau (STIB) were enrolled from 1989-1991 in a randomized trial of breast self-examination (BSE). The cohort was restricted to residents of Shanghai, who were born between January 1, 1925 and December 31, 1958.

A baseline questionnaire was administered in-person to all women by factory medical personnel to elicit information on smoking history, alcohol consumption, reproductive history, and medical history (including previous hysterectomy and oophorectomy). Ninety-eight percent of eligible women completed the baseline questionnaire [10].

There were 206 incident corpus uteri cancer cases [International Classification of Disease, Ninth Revision (ICD-9) = 182] diagnosed from enrollment into the trial through December 31, 1998. In the planned economy in China, all active and retired workers received initial medical care through health clinics in their factory. Factories reported all incident cancer diagnoses to a Tumor and Death Registry operated by the STIB. For verification of cancer diagnosis, all cancer cases were matched to the Shanghai Cancer Registry or trained field workers reviewed medical records to confirm the diagnosis for cancer cases that did not match to the registry [9]. We confirmed an endometrial cancer diagnoses through a cancer registry match or medical record review for 81.5% (n=168) of the cases.

A subcohort (n=3199) was selected from the entire cohort for comparison to the cancer cases. The subcohort was selected as a stratified random sample of the entire cohort to match the combined birth-year distribution (in five-year age strata) of all cancer cases included in a nested case-cohort study of multiple cancer sites [12-14]. Six endometrial cancer cases were also included in the subcohort by chance.

To assess work history in the textile industry, experienced field workers visited all of the factories where study subjects had worked, and collected information regarding all textile industry jobs that the women had held. The information collected included the textile process, task description, and dates of employment for each job. Work history information was obtained from factory personnel records (79.6% subcohort, 75.8% cases), or interviews

with supervisors (10.5% subcohort, 8.3% cases), the subject themselves (8.7% subcohort, 13.9% cases), co-workers (<1% subcohort, <1% cases), or a family member (<1% subcohort, 1.6% cases). If subjects were contacted for in-person interviews, they provided oral consent to the field workers.

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 STIB, in accordance with an assurance filed with the Office for Human Research Protections (OHRP) of the U. S. Department of Health and Human Services.

Exposure assessment

Textile job-exposure matrix—A job-exposure matrix (JEM) was developed for the Shanghai textile industry by our team of industrial hygienists [15]. Each woman's job in the textile industry was linked to the job-exposure matrix and assigned exposure as yes/no. We classified jobs according to exposures to 23 different chemical or dust types and 12 specific hazardous agents. We present only a few of these findings.

We also constructed quantitative exposures to cotton dust and endotoxin. Endotoxin is a component of gram-negative bacteria that contaminates cotton dust. Details of this assessment are provided elsewhere [16]. Briefly, quantitative assessment of cotton dust was estimated for each specific textile process based on historical measurements collect by industrial hygienists from 56 factories between 1975 and 1999. Endotoxin concentrations were estimated using the predicted cotton dust estimates (mg/m³) and average concentrations of endotoxin, in endotoxin units (EU), per unit dust mass (EU/mg dust) in each major textile process [17-19] [16,20].

Statistical analysis—Complete textile industry work history information was obtained for 188 endometrial cancer cases and 3188 subcohort women. We excluded from the sample cases confirmed as leiomyosarcoma (n=10) and endometrial hyperplasia (n=2). We excluded 127 subcohort women who reported a hysterectomy on the baseline questionnaire. The final sample included 176 endometrial cancer cases and 3061 subcohort women.

We calculated hazard ratios (HR) and their 95 percent confidence intervals (CI) using Cox proportional hazards modeling, adapted for the case-cohort design (Stata version 9, Stata Corporation, College Station, Texas). A weight of one was applied for each case, and weights equal to the reciprocal of the sampling fractions in each five-year age stratum were applied for all of the non-cases in the subcohort [21]. Robust variance methods were used to estimate the standard error of the hazard ratio [22].

Person-time was contributed from time of enrollment into the cohort until cancer diagnosis for the cases. For non-case subcohort members, person-time was accumulated from the date of enrollment into the original study until date of death, date left the STIB, or December 31, 1998 (end of follow-up), whichever came first.

Risks associated with various textile manufacturing processes and exposures were estimated according to duration of employment (0, <10 years, and ≥ 10 years). Each exposure variable was added individually to the model.

Cumulative exposures to endotoxin and cotton dust were categorized into quartiles according to the distribution of the subcohort members among those with exposure. For endotoxin analysis, we excluded case women (n=9) and subcohort women (n=144) who had ever held jobs as machinists, sanitation workers, or those who worked in wool production;

these jobs entail exposure to endotoxin from sources other than cotton dust, and there were no measurement data available for these jobs.

Hazard ratio trends were tested with the Wald statistic by entering the median values of duration within each category for the subcohort and entered into the models as continuous parameters. All estimates were adjusted for age (continuous), age at menarche (indicator), and reproductive category (indicator variable of nulligravid, nulliparous, one live birth, two, three, four, and five or more live births) as ascertained at baseline.

Results

Endometrial cancer cases tended to be of similar age and marital status as subcohort women, but less likely to smoke or drink alcoholic beverages occasionally (Table I). As reported previously [23], endometrial cancer cases initiated menarche at earlier ages and were more likely to be nulligravid or nulliparous compared to subcohort women (Table I). Both cases and subcohort women began working in the textile industry, on average, in 1958.

There were textile processes which conferred either an increase or a decrease in risk of endometrial cancer. There was an increasing trend in risk with increasing years of work within the silk industry (Table II); only five cases had ever worked in silk manufacturing.

In our assessment of specific occupational exposures, we observed a 70-90% increase in risk of endometrial cancer associated with exposure to silk dust, regardless of duration of exposure (Table III), a finding of borderline statistical significance. There were two cases exposed to silica dust for more than 10 years, resulting in a 7.4-fold increased risk of endometrial cancer. Only weak elevated associations were observed for exposures to solvents, dyes and dye intermediates, and inks. We detected no associations with wool, synthetic fiber, and non-textile dusts, electromagnetic fields or lubricants.

There were no associations between endometrial cancer and exposure to cotton dust or endotoxin. Compared to women in the lowest quartile, women in the highest quartile had no increased risk of endometrial cancer associated with cotton dust (HR=1.3, 95% CI 0.7-2.2) or endotoxin (HR=1.1, 95% CI 0.6-1.9) (data not shown).

Discussion

To our knowledge, this is the first comprehensive investigation of endometrial cancer in relation to workplace hazards in the textile industry. We detected few positive associations, including increased risks of endometrial cancer with silk production and exposure to silica dust. These findings are based on a relatively small number of women and may be due to chance.

No prior studies have reported silk dust exposure as a risk factor for endometrial cancer. Potential exposures to silk dust or the chemicals used in the process might be important etiologic agents, but no information is currently available with these exposures.

We also observed an association of increased risk, albeit based on small numbers, with exposure to silica. It was not possible to reconstruct quantitative exposure levels to silica dust due to the absence of historical exposure measurement data. Silica dust exposure in this study most likely occurred with exposures to welding and foundry work, which were classified into "other manufacturing" processes. Crystalline silica dust exposure has been classified as carcinogenic to humans (Group 1) by IARC, based on associations with lung cancer [24]. It is possible that silica dust is a surrogate exposure for other agents in foundries, such as polycyclic aromatic hydrocarbons. A previous census linkage study from

Finland did not indicate an association between endometrial cancer and silica dust [8]. We have detected similarly elevated risks of ovarian cancer [25] associated with silica dust but not with breast cancer [14]. Our observation of an association with silica will therefore require confirmation in other studies with more detailed exposure assessments before causal interpretations can be inferred.

Solvent exposures were of prior interest due to their potential influence on reproductive hormones. In a study of women employees of the U.S. Air Force, Reutman et al. determined that aliphatic hydrocarbons were associated with significantly lower pre-ovulatory luteinizing hormone (LH) levels, suggesting that fuels and solvents could be endocrine disruptors [7]. Although we detected an increased risk with exposure to solvents, we did not find a consistent dose-response relation between solvent exposures and endometrial cancer. Our analyses were limited to a category combining all solvents due to sparse data on specific chemicals. Common solvents used with the textile industry include benzene, toluene, and xylene. Thus, possible associations with specific solvents may have been missed.

There are some considerable strengths to this study. This is a well-defined cohort with reproductive data collected at baseline that, unlike most occupational studies, allowed for adjustment of potential confounding factors [23]. We followed the cohort for cancer incidence even after retirement from the STIB. By linkage to cancer incidence data, we estimated associations with disease incidence rather than with mortality, which is influenced by survival as well as incidence. We collected complete occupational work histories for the majority of the women in the study, which we could link to a job-exposure matrix that was developed specifically for this textile industry. The availability of quantitative exposure data for cotton dust and endotoxin was also advantageous.

Our study has some limitations that should be acknowledged. One is the potential for exposure misclassification. The job-exposure matrix most likely underestimated exposures in the women [15]. Women with a greater probability of exposure are most likely to be classified as exposed, whereas women with intermittent or low exposures are more likely to be classified as unexposed. Our exposure assessment was performed blinded as to case status. Therefore, misclassification of exposure is most likely to be non-differential, which generally results in under-estimated associations. With a lower exposure prevalence, the power of the study would be reduced and we would be less likely to detect an effect if one exists.

Although we were able to adjust the hazard ratios for several reproductive risk factors that might have been confounding variables, we could not adjust for hormone therapy or body mass index (BMI) because data on these factors were not available from the baseline questionnaire. The prevalence of hormone therapy use is about 4% in this population of women, so it is not likely to be a strong confounder [26,27]. Conversely, BMI has been associated with endometrial cancer risk among Chinese women. It is unclear whether BMI would be considered a potential confounder with the occupational exposures of interest. Solvents can be fat-soluble, so the risk estimates presented would be attenuated after adjustment for BMI. Given that the majority of women began their working careers at age 16 to 18 years, BMI as a factor as women age is less likely to be a problem as the mandatory retirement age was 45 years. Further, we were also unable to censor women who might have had a hysterectomy during the follow-up period. However, the prevalence of hysterectomy is low in this population (approximately 3%) compared to the US population which ranges from 30-50% [28].

Notwithstanding these limitations, our study is the largest, most comprehensive investigation of textile industry exposures and endometrial cancer undertaken to date. This

study suggests that some occupational exposures might play a role in endometrial carcinoma and warrants further corroboration. We will further explore the role of night shift work and electromagnetic fields in relation to endometrial cancer.

Acknowledgments

This research was supported by the grant R01 CA80180 from the US National Cancer Institute and by the training grant ES07262 (KJW) from the US National Institute of Environmental Health Sciences.

The authors would like to thank Drs. Fan Liang Chen, Yong Wei Hu, Guan Lin Zhao, and Lei Da Pan for their ongoing support. The authors thank Wang Wen Wan for project management; Drs. Dai He Lian, Wang Zhu Ming, Qi A Zhen, Wang Zia Ming, Ziang Wei Ping, and Li Yu Fang for their diligence in collection of factory information; the 30 field workers for the collection of women's personnel records and confirmation of cancer diagnoses; and Dr. David Christiani for providing data that contributed to the cotton dust and endotoxin exposure assessment. The authors are also grateful to Georgia Green, Shirley Zhang, Richard Gandolfo, and Ted Grichuhin for technical and administrative support.

Financial Support: This research was supported by US National Cancer Institute (R01 CA80180) and US National Institute of Environmental Health Sciences (ES07262 to KJW).

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Glossary

STIB	Shanghai Textile Industry Bureau
JEM	Job exposure matrix
BSE	Breast self-exam
CI	Confidence Intervals
EU	Endotoxin Units
HR	Hazard Ratio

Table 1
Distribution of demographic characteristics of subcohort members and endometrial cancer cases among textile workers, Shanghai, China, 1989-1998

Characteristic	Subcohort (n=3061)		Endometrial cancer (n=176)		Age-adjusted	
	N	%	N	%	HR	95% CI
Year of birth						
1925-1929	884	28.9	43	24.4	1.0	Referent
1930-1934	875	28.6	57	32.4	1.3	0.9-2.0
1935-1939	348	11.4	24	13.6	1.4	0.8-2.3
1940-1944	157	5.1	16	9.1	2.0	1.1-3.6
1945-1949	277	9.0	19	10.8	1.4	0.8-2.3
1950-1954	320	10.5	11	6.3	0.7	0.4-1.4
1955-1958	200	6.5	6	3.4	0.7	0.3-1.6
Marital Status						
Married	2784	91.0	159	90.3	1.0	Referent
Widowed	228	7.4	14	8.0	1.0	0.6-1.8
Divorced	20	0.7	1	0.6	0.9	0.1-6.4
Never married	29	0.9	2	1.1	1.2	0.3-4.9
Smoking (regular) ^a						
Never	2923	95.5	171	97.2	1.0	Referent
Ever	138	4.5	5	2.8	0.6	0.2-1.5
Alcohol consumption						
Never	2501	81.7	162	92.0	1.0	Referent
< 1 per month	422	13.8	10	5.7	0.4	0.2-0.7
≥ 1 per month	138	4.5	4	2.3	0.4	0.2-1.2
Age at menarche (years)						
≤13	259	8.5	26	14.8	1.0	Referent
14	488	15.9	22	12.5	0.5	0.3-0.8
15	610	19.9	42	23.9	0.7	0.4-1.1
16	664	21.7	49	27.8	0.7	0.4-1.1
≥17	1039	34.0	37	21.0	0.3	0.2-0.6

Characteristic	Subcohort (n=3061)		Endometrial cancer (n=176)		Age-adjusted	
	N	%	N	%	HR	95% CI
Reproductive Category						
Nulligravid	102	3.3	10	5.7	1.5	0.7-3.4
Nulliparous	14	0.5	5	2.8	5.3	1.8-15.5
1 live birth	734	24.0	39	22.2	1.0	Referent
2 live births	551	18.0	24	13.6	0.7	0.4-1.3
3 live births	612	20.0	42	23.9	1.0	0.5-1.8
4 live births	488	15.9	32	18.2	0.9	0.5-1.8
≥5 live births	560	18.3	24	13.6	0.6	0.3-1.2

^aEver smoking regularly for ≥ 6 months

Table II
Risks associated with endometrial cancer by duration of work in textile processes in Shanghai, China, 1989-1998

Subcohort Endometrial Cancer						
Textile process	No.	%	No.	%	HR ^a	95% CI ^{a,b}
Warehouse						
Never	2562	83.7	144	81.8	1.0	Referent
<10 years	179	5.8	9	5.1	0.9	0.5-1.9
≥10 years	320	10.5	23	13.1	1.2	0.8-2.0
Cotton						
Never	2489	81.3	142	80.7	1.0	Referent
<10 years	118	3.9	9	5.1	1.4	0.7-2.9
≥10 years	454	14.8	25	14.2	0.9	0.6-1.4
Silk						
Never	3030	98.9	171	97.2	1.0	Referent
<10 years	8	0.3	1	0.5	3.1	0.4-26.1
≥10 years	23	0.8	4	2.3	3.8	1.2-11.8 ^c
Mixed fiber						
Never	2629	85.9	158	89.8	1.0	Referent
<10 years	119	3.9	8	4.5	1.1	0.5-2.3
≥10 years	313	10.2	10	5.7	0.5	0.3-1.0 ^c
Weaving						
Never	1991	65.0	115	65.3	1.0	Referent
<10 years	220	7.2	11	6.3	0.8	0.4-1.6
≥10 years	850	27.8	50	28.4	1.0	0.7-1.5
Cutting and sewing						
Never	2775	90.7	161	91.5	1.0	Referent
<10 years	86	2.8	4	2.3	0.8	0.3-2.4
≥10 years	200	6.5	11	6.3	0.9	0.5-1.7
Administration and non-production						
Never	2187	71.4	118	67.0	1.0	Referent
<10 years	329	10.7	21	11.9	1.2	0.7-2.0

Textile process	Subcohort		Endometrial Cancer		HR ^a	95% CI ^{a,b}
	No.	%	No.	%		
≥10 years	545	17.8	37	21.0	1.2	0.8-1.8
Other manufacturing ^d						
Never	2897	94.6	174	92.6	1.0	Referent
<10 years	59	1.9	8	4.3	2.7	1.2-5.9
≥10 years	105	3.4	6	3.2	1.2	0.5-2.8

^aHR, hazard ratio; CI, confidence interval.

^bAdjusted for current age, reproductive category, and age at menarche as measured at baseline.

^cp-trend<0.05.

^dOther manufacturing includes metal machining, welding, foundry work, forging, metal finishing, gluing and cement production.

Table III
Risks associated with endometrial cancer by duration of exposure to hazardous agents, Shanghai, China, 1989-1998

Subcohort Endometrial Cancer							
Agent	No.	%	No.	%	HR ^a	95% CI ^b	
Wool dust							
Never	2626	85.8	151	85.8	1.0	Referent	
<10 years	92	3.0	5	2.8	0.9	0.3-2.2	
≥10 years	343	11.2	20	11.4	1.0	0.6-1.6	
Silk dust							
Never	2905	94.9	161	91.5	1.0	Referent	
<10 years	37	1.2	4	2.3	1.9	0.6-5.5	
≥10 years	119	3.9	11	6.3	1.7	0.9-3.4	
Synthetic fiber dust							
Never	1840	60.1	116	65.9	1.0	Referent	
<10 years	231	7.5	9	5.1	0.6	0.3-1.2	
≥10 years	990	32.3	51	29.0	0.8	0.6-1.1	
Mixed fiber dust (synthetic/natural)							
Never	2926	95.6	164	93.2	1.0	Referent	
<10 years	41	1.3	5	2.8	2.2	0.8-5.9	
≥10 years	94	3.1	7	4.0	1.4	0.6-3.1	
Non-textile dust							
Never	2555	83.5	152	86.4	1.0	Referent	
<10 years	197	6.4	10	5.7	0.9	0.4-1.7	
≥10 years	309	10.1	14	8.0	0.8	0.4-1.4	
Silica dust							
Never	3053	99.7	174	98.9	1.0	Referent	
<10 years	2	0.1	0	-	-		
≥10 years	6	0.2	2	1.1	7.4	1.4-39.7 ^c	
Solvents							
Never	2615	85.4	142	80.7	1.0	Referent	
<10 years	167	5.5	16	9.1	1.8	1.0-3.2	

Subcohort		Endometrial Cancer				
Agent	No.	%	No.	%	HR ^a	95% CI ^b
≥10 years	279	9.1	18	10.2	1.2	0.7-2.0
Acids, bases, and caustics						
Never	2802	91.5	155	88.1	1.0	Referent
<10 years	89	2.9	10	5.7	2.0	1.0-4.1
≥10 years	170	5.6	11	6.3	1.3	0.7-2.4
Dyes						
Never	2967	96.9	168	95.5	1.0	Referent
<10 years	29	0.9	4	2.3	2.1	0.7-6.4
≥10 years	65	2.1	4	2.3	1.1	0.4-3.0
Dye and dye intermediates						
Never	3014	98.5	169	96.0	1.0	
<10 years	17	0.6	4	2.3	3.3	1.0-10.6
≥10 years	30	1.0	3	1.7	1.8	0.5-6.0
Inks						
Never	3033	99.1	172	97.7	1.0	Referent
<10 years	7	0.2	2	1.1	4.6	0.9-25.0
≥10 years	21	0.7	2	1.1	1.9	0.4-8.4
Metals						
Never	2839	92.7	160	90.9	1.0	Referent
<10 years	87	2.8	7	4.0	1.5	0.6-3.3
≥10 years	135	4.5	9	5.1	1.3	0.6-2.6

^aHR, hazard ratio; CI, confidence interval.

^bAdjusted for current age, reproductive category, and age at menarche as measured at baseline.

^cp-trend<0.05.