ORIGINAL ARTICLE

Unexpected excessive chronic obstructive pulmonary disease mortality among female silk textile workers in Shanghai, China

Ling Cui,[1] Lisa G Gallagher,[1] Roberta M Ray,[2] Wenjin Li,[2,3] Daoli Gao,[4] Yingzhe Zhang,[5] Sverre Vedal,[1] David B Thomas,[2,3] Harvey Checkoway[1,3]

[1]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA
[2]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
[3]Department of Epidemiology, University of Washington, Seattle, Washington, USA
[4]Department of Epidemiology, Zhong Shan Hospital, Fudan University, Shanghai, PR China
[5]Research Management Division, China Academy of Safety Science and Technology, Beijing, PR China

Correspondence to
Ling Cui, Department of Environmental and Occupational Health Sciences, University of Washington, 4225 Roosevelt Way NE, Seattle, WA 98105, USA;
cuiling@u.washington.edu

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ABSTRACT
Objective To investigate chronic obstructive pulmonary disease (COPD) mortality among textile workers.
Methods A total of 267 400 Chinese female textile employees were monitored for COPD mortality from 1989 to 2000. Textile factories in the cohort were classified into 10 industrial sectors. Age-adjusted mortality, standardized mortality ratios (SMRs) and 95% CIs were calculated by sector. In addition, RRs (HRs) adjusted for smoking and age were calculated for exposure to cotton and silk textile work compared with the other sectors in the cohort.
Results A majority of textile sectors had lower or similar COPD mortality (age-adjusted SMRs=0.58—1.15) compared with the general female population in the city of Nanjing, China. SMRs for cotton and silk workers were, respectively, 1.02 (95% CI: 0.81 to 1.28) and 2.03 (95% CI: 1.13 to 3.34). Compared with all other textile sectors in the cohort, there was greater COPD mortality among cotton workers (HR=1.40, 95% CI: 1.03 to 1.89) and silk workers (HR=2.54, 95% CI: 1.47 to 4.39).
Conclusion Elevated COPD mortality among cotton workers is consistent with previous reports of adverse respiratory effects of cotton dust. The higher rate of COPD deaths among silk workers was unexpected.

What this paper adds

- ► Respiratory symptoms and accelerated lung function decline among cotton textile workers are well-recognised outcomes; however, there remains an uncertainty about subsequent risks for COPD.
- ► This study demonstrates excessive COPD mortality among mostly non-smoking women cotton textile workers in Shanghai, China. Unexpectedly, an even larger COPD mortality RR was observed among silk factory workers from the same cohort.
- ► Cotton dust and endotoxin exposures may be risk factors for COPD, and exposures to silk manufacturing may also pose respiratory hazards.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a diverse group of lung disorders whose hallmark is airflow obstruction that impedes normal respiration. According to the latest available WHO estimates (2008), 210 million people worldwide have COPD and 3 million people died from COPD in 2005. WHO predicts that COPD will become the third leading cause of death worldwide by 2030.[1] COPD remains a leading cause of death, illness and disability in the USA and the prevalence of COPD is 8.2% in people 40 years of age or older in China.[2]

The primary known cause of COPD is exposure to tobacco smoke[3]; however, air pollutants in the working environment may also increase the risk.[4] Numerous previous studies indicate that cotton textile workers have a higher prevalence of respiratory symptoms and greater decline in lung function compared with the general population and compared with other textile workers, specifically, man-made fibre and silk workers.[5 6] Historically, it was believed that byssinosis, whether acute or chronic, could be associated with some impairment of ventilatory

capacity, but the overall decline in lung function was small.[7] However, emerging evidence indicates that cumulative exposure to cotton dust may cause a chronic decline in lung function, potentially resulting in COPD.[8 9] The main occupational exposures of concern are cotton dust and endotoxin in the dust and both were found to be related to the decrease in FEV_1.[10 11] Other potential respiratory hazards in the textile industry include wool dust, silk dust, synthetic fibres, finishing agents, bleaches and highly acidic or basic chemicals.[12]

To characterise the remaining uncertainty of risks for COPD among textile workers, we conducted a mortality study among a large cohort of female textile workers in Shanghai, China. The study was approved by the Institutional Review Boards of the University of Washington, the Fred Hutchinson Cancer Research Center in Seattle, WA and Zhong Shan Hospital in Shanghai.

METHODS
Study population
The cohort was composed of 267 400 female textile employees recruited from over 500 factories in the Shanghai Textile Industry Bureau (STIB). These women were born between 1st January 1925 and 31st December 1958 and had been previously enrolled in a randomised trial of breast self-examination. Although the participation in the study was not mandatory, almost all the women meeting the

eligibility criteria in the STIB were enrolled in the study. Baseline questionnaires were administered to subjects during the period from 1989 to 1991, with a response rate of 98%.[13] Information regarding demographics, lifestyle, reproductive history, smoking and alcohol use were collected during enrolment through questionnaires.

Outcome and exposure definition
All deaths were registered at each factory, and reported annually to a tumour and death registry operated by the STIB. Mortality in the cohort was analyzed using data from 1989 to 2000 by matching the cohort with the STIB registry. In addition, death certificates were reviewed to determine the causes of death. Mortality from COPD and allied conditions was defined when one or more causes of death was indicated by ICD-9 codes 490–496, which encompass bronchitis (not specified as acute or chronic); chronic bronchitis; emphysema; asthma; bronchiectasis; extrinsic allergic alveolitis and chronic airway obstruction (not elsewhere classified).

Information on 503 factory profiles were collected, including date of commencement of operations, number of workers and primary and secondary fibres used in production. The primary fibre was defined as the material that was used most often or in the greatest quantity in the factory; the secondary fibre was the next most used material. Ten industry sectors of interest were identified according to the type of fibres used: cotton spinning, weaving and knitting (SWK); silk SWK; wool SWK; synthetic fibre SWK; mixed fibre SWK; assembly and sewing; bleaching, dyeing, printing; machine and manufacturing; combined and other services. Each factory was classified into one sector accordingly, and factories that had multiple production lines were designated to a combined sector. Every subject was assigned to only one of these sectors on the basis of employment status at baseline. Each cohort member contributed in person-years from their enrolment until death, or until severance of ties with STIB, or until the end of follow-up (31 December 2000), whichever occurred first.

Data analysis
The number of deaths and person-years were calculated for each 5-year age category from 1989 to 2000. Age-adjusted mortality was computed using the 2000 World Standard Population as the standard population.[14] The female general population in the city of Nanjing in China was used as an external reference group. This population was chosen because it is, to our knowledge, the only female Chinese population with age-specific COPD mortality data available for 1997–2005.[15] Standardized mortality ratios (SMRs) for 1989–2000 comparing the observed and expected numbers of COPD deaths were calculated for the entire cohort and for different sectors, and 95% CIs were calculated using the Byar method.[16] HRs and associated 95% CIs were calculated using the Cox proportional hazard model, adjusting for age and smoking (ever/never) using PROC PHREG in SAS 9.2 (SAS Institute, Cary, North Carolina, USA).

Table 1 Characteristics of the cohort for specific sectors and age

	Cotton SWK		Silk SWK		Other sectors		Total	
	No.	Percent (%)	No.	Percent	No.	Percent	No.	Percent
Total number	86265		11121		170014		267400	
All COPD and allied conditions	77		15		92		184	
Bronchitis, NOS	0	0.0	1	6.7	0	0.0	1	0.5
Chronic bronchitis	25	32.5	4	26.7	27	29.3	56	30.4
Emphysema	26	33.8	5	33.3	27	29.3	58	31.5
Asthma	23	29.9	5	33.3	37	40.2	65	35.3
Bronchiectasis	3	3.9	0	0.0	1	1.1	4	2.2
Extrinsic allergic alveolitis	0	0.0	0	0.0	0	0.0	0	0.0
Chronic airway obstruction NOS	0	0.0	0	0.0	0	0.0	0	0.0
Age at baseline (years)								
30–34	17051	19.8	2333	21.0	32769	19.3	52153	19.5
35–39	15613	18.1	2386	21.5	36703	21.6	54702	20.5
40–44	10805	12.5	1675	15.1	24917	14.7	37397	14.0
45–49	4084	4.7	438	3.9	9608	5.7	14130	5.3
50–54	5735	6.6	705	6.3	14136	8.3	20576	7.7
55–59	16090	18.7	1587	14.3	27132	16.0	44809	16.8
60–64	15574	18.1	1694	15.2	22055	13.0	39323	14.7
65+	1313	1.5	303	2.7	2694	1.6	4310	1.6
Age at death or end of follow-up								
30–34	1530	1.8	220	2.0	2131	1.3	3881	1.5
35–39	3655	4.2	572	5.1	6651	3.9	10878	4.1
40–44	13747	15.9	2152	19.4	31273	18.4	47172	17.6
45–49	14031	16.3	2069	18.6	32370	19.0	48470	18.1
50–54	10645	12.3	1513	13.6	23020	13.5	35178	13.2
55–59	4288	5.0	403	3.6	9977	5.9	14668	5.5
60–64	6592	7.6	858	7.7	15872	9.3	23322	8.7
65–69	16509	19.1	1662	14.9	27601	16.2	45772	17.1
70–74	14279	16.6	1597	14.4	19932	11.7	35808	13.4
75+	989	1.1	75	0.7	1187	0.7	2251	0.8
Retired	36656	42.5	3957	35.6	59622	35.1	100235	37.5
Ever smokers	3086	3.6	300	2.7	4482	2.6	7868	2.9

COPD, chronic obstructive pulmonary disease; NOS, not otherwise specified; SWK, spinning, weaving and knitting.

Table 2 Age-standardised mortality (per 100 000) for specific sectors, 1989—2000

Sectors	Employee no.	Deaths	Person-years	Adjusted mortality
Cotton SWK	86265	77	838191	3.19
Silk SWK	11121	15	102377	9.21
Wool SWK	29181	20	277579	1.85
Synthetic fibre SWK	11335	9	107394	2.13
Mixed fibre SWK	26262	12	248493	1.33
Assembly and sewing	18495	9	173202	4.57
Bleaching dyeing, printing	21424	14	209919	2.15
Machine and manufacturing	17275	7	166201	1.39
Combined	39408	18	379148	1.42
Other services	6634	3	62930	1.54

SWK, spinning, weaving and knitting.

Table 3 Standardised mortality ratio (SMR) for specific sectors using female general population of city of Nanjing as reference, 1989—2000

	Observed	Expected	SMR	95% CI
All sectors	184	200.7	0.92	(0.79 to 1.06)
Cotton SWK	77	75.3	1.02	(0.81 to 1.28)
Silk SWK	15	7.4	2.03	(1.13 to 3.34)
Wool SWK	20	22.5	0.89	(0.54 to 1.37)
Synthetic fibre SWK	9	7.9	1.15	(0.52 to 2.18)
Mixed fibre SWK	12	20.6	0.58	(0.30 to 1.02)
Assembly and sewing	9	9.2	0.98	(0.45 to 1.86)
Bleaching, dyeing, printing	14	13.8	1.01	(0.55 to 1.70)
Machine and manufacturing	7	10.3	0.68	(0.27 to 1.41)
Combined	18	30.1	0.60	(0.35 to 0.95)
Other services	3	3.8	0.79	(0.16 to 2.32)

SWK, spinning, weaving and knitting.

RESULTS

There were 184 COPD deaths identified in the cohort during 12 years of follow-up (2 565 433 person-years). The distributions of age at baseline, age at the end of follow-up (or death) and the causes for 184 COPD deaths are summarised in table 1. For the entire cohort, mean (SD) age at baseline was 45.9 (11.1) and mean age at end of follow-up was 55.0 (11.6). Mean (SD) age at death from COPD was 63.5 (7.7). Approximately 3% of the textile workers had ever smoked and 37% of the subjects had retired at baseline.

By sectors, the highest age-standardised COPD mortality rates per 100 000 were found in silk SWK (9.21), assembly and sewing (4.57) and cotton SWK (3.19) (table 2).

When stratifying by smoking habits, the mortality rate was 2.89 for cotton workers who never smoked and 8.11 for cotton workers who had smoked. No COPD deaths were observed among smokers in the silk SWK sector; the COPD mortality rate was 9.41 among non-smoker silk workers. Compared with the general female population of Nanjing (table 3), the entire cohort of textile workers had a reduced mortality rate (SMR=0.92, 95% CI=0.79 to 1.06). Most textile sectors had lower or similar mortality from COPD compared with the female population in Nanjing (age-adjusted SMRs=0.58—1.15). However, the SMR of the silk workers was significantly higher (SMR=2.03, 95% CI=1.13 to 3.34).

Due to this excess mortality in silk SWK workers and given our prior hypothesis that cotton dust would contribute to COPD mortality, we calculated expected deaths in cotton and silk sectors based on mortality rates in the remainder of the cohort, excluding the cotton and silk SWK sectors. Using this reference group, SMRs were 1.54 (95% CI=1.21 to 1.92) for cotton workers and 2.79 (95% CI=1.56 to 4.61) for silk workers. Among workers who never smoked, SMRs were 1.81 (95% CI=1.39 to 2.30) for cotton workers and 3.79 (95% CI=2.12 to 6.26) for silk workers (table 4). The HRs for death from COPD were elevated for both cotton workers (HR=1.40, 95% CI=1.03 to 1.89) and silk workers (HR=2.54, 95% CI=1.47 to 4.39), adjusted for smoking (ever/never) and age at death and duration of follow-up.

DISCUSSION

It has been widely recognised that exposure to cotton dust leads to byssinotic symptoms. The acute inflammatory response, manifested as Monday morning chest tightness (byssinosis), and chronic inflammation may be different pathogenic phenomena. Although there is evidence that repeated episodes of byssinosis are associated with accelerated loss of lung function,[10] [17] clear distinctions between the relative contributions of acute, reversible inflammation and chronic inflammation to COPD are not established. Unfortunately, we do not have data on byssinosis among cohort members to address this question. Several studies have demonstrated a reduced risk or, at least, no overall increase in mortality rates from chronic bronchitis, emphysema or lung cancer among cotton workers.[18–20] One study in USA reviewed 2895 consecutive autopsies during an 18-year period, and found no significant difference in the prevalence of emphysema or other chronic lung diseases among 282 employees of a cotton textile mill when compared with the non-textile worker population.[21] However, it is difficult for these studies to fully compensate for the 'healthy worker' effect, resulting in an underestimation of the true risk.

In our cohort, excess COPD mortality was observed among cotton workers when compared with the remainder of the cohort. This finding corresponds to recent reports of a higher risk of COPD and chronic respiratory symptoms among cotton workers.[22] [23] However, this increased mortality was not seen when the general Nanjing female population was used as a reference. This discrepancy might be due to the manifestation of a 'healthy worker effect' that would lead to underestimated effects in the workforce. In contrast, silk workers had significantly higher COPD mortality rates compared with both the remainder of the cohort and the Nanjing female population. An increase in COPD mortality among silk workers was unexpected. In the series of lung function and symptom studies conducted by Christiani et al, cotton textile workers had more chronic cough and chronic bronchitis and greater decline in FEV_1 than silk workers.[6] [8] Silk workers in these studies were regarded as the non-exposed reference group, largely because silk dust had only background levels of endotoxin, compared with the

Table 4 SMRs for cotton and silk SWK sectors compared with the remainder of the cohort by smoking history

Sectors	All				Never Smokers				Ever Smokers			
	Obs	Exp	SMR	95% CI	Observed	Exp	SMR	95% CI	Observed	Expected	SMR	95% CI
Cotton SWK	77	50.0	1.54	(1.21 to 1.92)	65	36.0	1.81	(1.39 to 2.30)	12	16.4	0.73	(0.38 to 1.28)
Silk SWK	15	5.4	2.79	(1.56 to 4.61)	15	4.0	3.79	(2.12 to 6.26)	0	1.4	0.00	(0.00 to 2.62)

SMR, standardised mortality ratio; SWK, spinning, weaving and knitting.

relatively high levels found in cotton dust.[24] A recently published report from this study found both cotton and silk workers have improved FEV_1 and reduced prevalence of chronic respiratory symptoms after work cessation, suggesting that there may be respiratory hazards in silk factories as well.[25]

The main components of silk dust are organic compounds, mostly protein, fats and carbohydrates. Contaminants of silk, such as silkworm larval proteins and constituents of fungal cell walls, could induce hypersensitivity pneumonitis and occupational asthma,[26] which in turn could lead to COPD if exposure occurred over a prolonged period of time. Significantly, spirometric abnormalities (FVC, FEV_1, MMF, V_{50} and V_{25}) were observed among 158 non-smoking female tussah ('wild') silk processing workers in Liaoning Province, China, compared with 20 non-smoking referent workers from an appliance assembling factory.[27] Other studies in the Chinese literature reported an association between mulberry dust and cough, expectoration, and shortness of breath.[28 29] Animal fibres, free silica, fungi and bacteria are all possible causes of these respiratory effects. Depending on the quality of the raw silk, pesticides and heavy metals such as lead may also be present in this dust. Other possible hazardous exposures include chemicals involved in processing, such as dyes and highly oxidative bleaching compounds. Previous studies have shown that humidifiers contaminated with microorganisms could cause byssinosis-like symptoms, and that this could be the mechanism by which the risk of COPD is increased among silk workers. A more extensive assessment of silk factory exposures is therefore suggested.

This study has several strengths. First, COPD is rarely seen in non-smokers. Patients diagnosed with COPD are expected to have smoked the equivalent of about 20 cigarettes per day for more than 20 years.[30] The prevalence of smoking is less than 3% in our cohort and none of the silk workers who developed COPD were smokers. Although the confounding effects of secondhand smoke outside the workplace cannot be completely discounted, it is unlikely that this exposure would differ among women working in other sectors of the textile industry or the general female population in Nanjing. The textile workers in this study were relatively homogeneous with regard to residence, religion, race, marital status and social-economic status. Also, the vast majority of the women in this study had held only one job and worked in the same factory for their entire career. During the follow-up period, only 1.14% (n=3056) of the entire cohort transferred to a different sector. Among textile workers, 0.03% (n=30) transferred from cotton to silk and 0.04% (n=5) transferred from silk to cotton. None of the women who died from COPD had a factory transfer. Therefore, it is unlikely that changes in exposures due to job transfers influenced our results.

One limitation of this study is the possible misclassification of COPD using death certificate data. We included asthma as one of the underlying or contributing causes of death from COPD for several reasons. COPD and asthma share many clinical characteristics. In order to distinguish severe asthma from COPD, we would require more detailed clinical data than was available. It has been noted that chronic illnesses, COPD in particular, are prone to misdiagnosis and misclassification on death certificates in China. In an independent review of death certificates in China, 178 (73.5%) of 242 actual deaths due to COPD were correctly coded as such and 50 (20.1%) of 228 deaths coded as COPD were actually due to other causes.[31] Under the reasonable assumption that misclassification of cause of death in our study was not associated with any of the possible risk factors considered, misclassification of this order of magnitude would have biased our OR estimates towards unity, but would not

have resulted in spurious associations. Indeed, both conditions might be present simultaneously in an individual patient to variable degrees. In our study, 33 of the 184 COPD deaths had COPD listed as a secondary cause of death. The first causes listed were primarily heart failure, chronic cor pulmonale (pulmonary heart disease) or other respiratory illnesses. Those deaths were kept in the final analysis as COPD deaths because we believe COPD was an important contributing cause. Similar results were found when those deaths were excluded. We did not have complete employment history record and exposure for each individual worker. Complete work history information was available only for a subset (n=3199) of the cohort who were recruited for a series of cancer case-cohort studies,[32 33] and there were six COPD deaths in the subcohort. Future work will assess complete work history and exposures of COPD cases compared with controls from this cohort.

Already a common cause of death in developed countries, COPD is an increasingly important cause of death and disability in the developing world.[34] Much of this increased prevalence is likely due to cigarette smoking, but occupational exposures, particularly among non-smokers, are also driving this increase. Recent studies from Nicaragua,[35] Turkey,[36] India,[37] Pakistan,[38] Nigeria[39] and Ethiopia all report on byssinosis in textile workers and several authors also describe chronic and irreversible changes in lung function in these workers.[40] These chronic changes may go by the term 'chronic bronchitis,' 'chronic declines in FEV_1' or 'chronic respiratory symptoms,' but all are likely equivalent terms for what we term COPD. Epidemiologic assessments of COPD in developing countries should therefore be a high priority to identify preventable causes of disease.

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