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Cotton dust, endotoxin and cancer mortality among the Shanghai textile workers cohort: a 30-year analysis

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Abstract

Background—Although occupational exposure to cotton dust and endotoxin is associated with adverse respiratory health, associations with cancer are unclear. We investigated cancer mortality in relation to cotton dust and endotoxin exposure in the Shanghai textile workers cohort.

Methods—We followed 444 cotton textile and a reference group of 467 unexposed silk workers for 30 years (26 777 person-years). HRs for all cancers combined (with and without lung cancer) and gastrointestinal cancer were estimated in Cox regression models as functions of cotton textile work and categories of cumulative exposure (low, medium, high), after adjustment for covariates including pack-years smoked. Different lag years accounted for disease latency.

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Results—Risks of mortality from gastrointestinal cancers and all cancers combined, with the exclusion of lung cancer, were increased in cotton workers relative to silk workers. When stratified by category of cumulative cotton exposure, in general, risks were greatest for 20-year lagged medium exposure (all cancers HR=2.7 (95% CI 1.4 to 5.2); cancer excluding lung cancer HR=3.4 (1.7–7.0); gastrointestinal cancer HR=4.1 (1.8–9.7)). With the exclusion of lung cancer, risks of cancer were more pronounced. When stratified by category of cumulative endotoxin exposure, consistent associations were not observed for all cancers combined. However, excluding lung cancer, medium endotoxin exposure was associated with all cancers and gastrointestinal cancer in almost all lag models.

Conclusions—Cotton dust may be associated with cancer mortality, especially gastrointestinal cancer, and endotoxin may play a causative role. Findings also indirectly support a protective effect of endotoxin on lung cancer.

INTRODUCTION

Cotton dust is a heterogeneous mixture containing plant matter, fibre, bacteria, fungi, soil, pesticides, and other non-cotton matter and contaminants. Occupational exposure occurs during the handling and processing of cotton in textile manufacturing, and is associated with acute respiratory responses such as coughing, wheezing, chest tightness and bronchoconstriction,[1] as well as diseases such as byssinosis.[2] Long-term exposure has also been associated with chronic airway disease[3–5] and excessive loss of lung function.[3, 6, 7] Gram-negative bacterial endotoxin present in cotton dust is likely a causative agent, able to produce airway inflammation and obstruction.[6, 8] At the same time, endotoxin also appears to possess antineoplastic properties,[9, 10] which may explain reduced rates of lung cancer observed in epidemiological studies of cotton dust exposed workers.[11–15] Not all organic dust exposed workers however appear to experience decreased risk of lung cancer.[16]

Links between cotton dust and related endotoxin exposure with other types of cancer have been more limited and less compelling. In general, mortality and cancer incidence studies in cotton textile workers, lacking quantitative data on exposures, have compared exposed workers to the general population. Findings from some studies suggest increased risks of cancers such as larynx,[17] non-Hodgkin's lymphoma,[18] sinonasal[19] and gastrointestinal cancers[20, 21] among cotton textile workers. More recently, studies from a large cohort of female textile workers in Shanghai, China, which used quantitative estimates of cotton dust and endotoxin exposure, found a positive association with nasopharyngeal cancer[22] and inverse associations with a number of site-specific cancers, including lung and those from the digestive and reproductive systems.[13, 23–28]

In our own study of male and female cotton textile workers in Shanghai, we previously observed increased risk of overall cancer mortality in comparison with silk textile workers.[29] Further, we found that the removal of lung cancer cases increased this risk, suggesting a protective effect of cotton dust exposure on lung cancer. We also previously observed an increased risk of gastrointestinal cancers in cotton workers. In the present study, we updated our investigation of cancer mortality patterns in this cohort of Chinese textile workers by using estimates of personal cumulative cotton dust and endotoxin exposures.

Consistent with our previous findings, we hypothesised that cumulative exposure to cotton dust would be associated with increased risk of cancer. Due to the small number of cases we could not directly assess the association with lung cancer and thus we hypothesised that risk of death from cancer would be elevated with the removal of lung cancers. We also expected to observe an exposure–response relationship between cotton dust and gastrointestinal cancers. Finally, we investigated associations with cumulative endotoxin exposures, expecting similar findings as with cotton dust exposure.

METHODS

Study population

The study population consisted of a closed cohort of 444 cotton textile workers exposed to airborne cotton dust and endotoxin, and a demographically similar reference group of 467 unexposed silk textile workers from the Shanghai textile workers cohort. Participants were enrolled in 1981 in a longitudinal study on the respiratory health effects of cotton dust and endotoxin exposures and included all workers actively employed in 1981 for at least 2 years in the yarn preparation areas of two cotton textile mills in Shanghai and in a nearby silk-thread processing mill. Activities in yarn preparation include opening, cleaning, carding, drawing, combing and spinning, and typically result in a wide range of cotton dust levels from low to very high.

Study procedures and data collection for the longitudinal study of respiratory symptoms are described elsewhere.[30] In brief, participants completed a modified American Thoracic Society questionnaire[31] and underwent pulmonary function testing at baseline in 1981, with subsequent follow-ups in 1986, 1992, 1996, 2001 and 2006. Data on years worked, smoking status and pack-years smoked were collected at each survey. The institutional review boards of the Harvard School of Public Health, the Putuo District People's Hospital and the Human Resources Administration of China approved the study protocols, and all participants gave written informed consent prior to data collection.

Outcome ascertainment

Vital status and cause of death were determined through records of the Shanghai Textile Industry Bureau, the death registry in Shanghai and family members. One individual with an unknown date of death was excluded from the analysis. All cancer cases were confirmed by pathological or other diagnostic exams. The cause of death was coded using the 9th edition of the International Classification of Diseases. Individuals alive at the end of follow-up were censored on 1 August 2011.

Exposure assessment

Details of methods for exposure assessment have been described elsewhere.[3, 6, 32] In brief, detailed work history was gathered at each survey through 2006, while full-shift measurements of airborne cotton dust were performed at each survey through 1996. Sampling did not occur during the 2001 and 2006 surveys because the cotton and silk textile mills closed major operations in 1997 and 1998, respectively. Stationary measurements of cotton dust were performed with a vertical elutriator (General Metalworks Corp., Mequon,

Wisconsin, USA) in accordance with NIOSH recommended guidelines[33] in six work areas where yarn was prepared in the two cotton textile mills (opening, cleaning, carding, drawing, roving, combing and spinning). Sampling at each occasion occurred in the same location of each work area. A total of 802 air samples (130 at the first survey, 192 at the second survey, 408 at the third survey and 72 at the fourth survey) were collected in the yarn preparation areas of the two mills. Endotoxin was measured from collected cotton dust sample filters using Limulus amoebocyte lysate assay, chromogenic method (Kinetic-QCL; BioWhittaker, Walkersville, Maryland, USA).[34] A limited number of full-shift samples were also taken in the silk mill, and measurements for endotoxin were non-detectable (below the limit of detection); thus, silk workers were considered unexposed to endotoxin and to cotton dust.

Cumulative exposures to cotton dust (mg/m^3-years) and endotoxin (endotoxin unit (EU)/m^3-years) in between each survey period were estimated for each participant using geometric mean levels of dust and endotoxin exposure from the samplings of the four time surveys multiplied by years of work in the various work areas. Pre-1981 cumulative exposure were calculated using work history data and estimated pre-1981 dust and endotoxin levels that were determined from measurements taken at the first survey. To obtain time-varying cumulative exposure through the end of follow-up for each individual, the average yearly exposure between each survey was calculated and a cumulative exposure variable was created by summing pre-1891 cumulative exposure with the product of the number of years exposed in each survey period multiplied by average yearly exposure for the survey period.

Statistical analysis

Person-years of observation were accrued from the date of entry into the study in 1981 until the date of death or end of follow-up in 2011. To compare the survival experience of cotton and silk textile workers, we plotted Kaplan–Meier (KM) survival estimates and tested the difference between the two groups with a log-rank test. To quantify the association between cotton textile work (yes/no) and cancer mortality outcomes, we fit Cox proportional hazards models, adjusting for time-varying pack-years smoked and work years, and estimated hazard rate ratios and 95% CIs. We fit separate models for all-cause mortality, all cancers combined (with and without lung cancer) and gastrointestinal cancer. To verify the proportional hazards assumption of the Cox models using dichotomous exposure, we compared survival curves in KM plots as well as log(-log(survival)) plots, and an interaction term between the indicator for exposure and age was included in the proportional hazards model.

We also investigated exposure–response relationships with the cancer outcomes. Cumulative exposure to cotton dust and endotoxin was categorised into low, medium or high exposure based on the distribution of exposure (tertiles) in cotton workers with cancer. This method was chosen to ensure an adequate number of cases in each category.[35] Unexposed silk workers served as a reference category and were assigned a value of 0 for both cotton dust and endotoxin exposure. We fit models using time-varying categories exposure to cotton dust and endotoxin separately, while adjusting for time-varying pack-years smoked. In all models, age in years was used as the time scale to most finely adjust for confounding by age. Pack-years and age were moderately correlated (r=0.27). Virtually all smokers were men

(eg, 95% of ever smokers were men) and thus gender was not included in models which controlled for pack-years smoked. We did not construct models with both cotton dust and endotoxin because the two were highly correlated (r=0.76). Trends were assessed by assigning the mean value within each exposure category (cotton dust or endotoxin) and entering a continuous term for trend in the models. We constructed lagged models to account for latency period using 0-, 5-, 10-, 15- and 20-year lags. For ease of comparison, cut-points for exposure categories were based on the average of the tertiles for each lag. Person-years of observation which would have been excluded because of discounting exposures in years prior to end of follow-up (ie, 'lagged out') were retained in the models by setting the exposure to 0, the lowest category of exposure. The number of observations set to 0 for each model was: lag 5, n=294; lag 10, n=1646; lag 15, n=3523; and lag 20, n=6025. This method has been shown to produce unbiased estimates in analogous case-control studies[36] and has been used in other settings.[37] Statistical significance for all testing was considered at the α=0.05 level. Analyses were performed with SAS V.9.2 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

In this study, 444 cotton workers and 467 silk textile workers were followed for 30 years beginning in 1981 for a total of 26 777 person-years of observation (table 1). The characteristics of the two groups were comparable; approximately half were women and the average age at end of follow-up was 65 years. Smoking rates were also similar; however, a slightly greater proportion of cotton workers were ever smokers (39% vs 34%). Virtually all smokers were men. By the end of follow-up, all workers were retired. The median years of exposure cessation were 17 and 18 years among cotton and silk workers, respectively. Cumulative cotton dust and endotoxin exposures were skewed; median cumulative cotton dust exposure was 15.9 mg/m^3-years (range 0.74–85.9) and median cumulative endotoxin exposure was 39 565 EU/m^3-years (range 163–232 452).

Follow-up for mortality was excellent, with only two individuals with unknown vital status who were censored on the date of last follow-up. In total, 73 cotton workers (16%) and 58 silk textile workers (12%) were deceased at the end of follow-up. Cancer was the leading cause of death (49% cotton and 41% silk). Gastrointestinal cancers accounted for the majority of cancer deaths in cotton workers (67%) and less than half of cancer deaths in silk workers (46%).

Based on KM plots of survival estimates for cotton and silk workers, overall risk of mortality was similar (data not presented). There was also no difference in cancer risk when looked at as a whole (figure 1). However, with the exclusion of lung cancer cases, there was a marginally increased risk of cancer mortality among cotton workers (log rank p=0.06). Plots also indicated an increased risk of mortality from gastrointestinal cancers among cotton workers (p=0.03). Cox proportional hazards models comparing cotton with silk workers while adjusting for age, pack-years smoked and years worked provided similar findings (table 2). Plots comparing log(-log(survival)) among cotton and silk workers over age on the log scale suggested reasonable assumptions of proportional hazards. Further, for

each model, interaction terms for age and exposure status were not significant, further suggesting the proportional hazards assumption of the Cox models was adequate.

We subsequently fit models using categories of cumulative cotton dust exposure while adjusting for time-varying pack-years smoked, work years and age (table 3). There were 26 591 person-years of observation with information on pack-years. When exposures were lagged <20 years, risk of death increased with increasing exposure for all three of the outcome groups. Tests for trend were statistically significant. When exposures were lagged by 20 years, however, medium cumulative cotton dust exposure (15.2–30.2 mg/m^3-year) was associated with the greatest risk of death for all three outcome categories (HR=2.7 for all cancers combined (95% CI 1.4 to 5.2); HR=3.4 for cancer excluding lung cancer (95% CI 1.7 to 7.0); HR=4.1 for gastrointestinal cancers (95% CI 1.8 to 9.7)) and was in general stronger than effects for high exposure lagged by <20 years.

When we investigated the role of cumulative endotoxin exposure in mortality outcomes, exposure–response patterns were varied (table 4). For all cancers combined, consistent patterns of association were not observed. After excluding lung cancer cases, effect estimates generally increased. Effects for cumulative endotoxin were, in general, most pronounced and statistically significant with the medium exposure category across lags. The magnitudes of the effect estimates for medium exposure category were also similar across lags (eg, 20-year lag model HR=2.0; 95% CI 1.0 to 4.0). For gastrointestinal cancers, medium endotoxin exposure was consistently associated with risk and was strongest when exposure was lagged by 15 years (HR=3.4; 95% CI 1.5 to 7.6).

DISCUSSION

In this updated 30-year mortality study of Chinese cotton and silk textile workers, we investigated the risk of cancer, and specifically gastrointestinal cancers in relation to cumulative cotton dust and endotoxin exposures. We also indirectly assessed associations with lung cancer by investigating all cancers combined and subsequently excluding lung cancers. Consistent with our preliminary findings,[29] we observed an increased risk of cancer with the exclusion of lung cancer, and specifically an increased risk of gastrointestinal cancers, among cotton workers as compared with silk textile workers. When we used quantitative estimates of exposure, cumulative cotton dust was associated with an increased risk of all cancers combined in all lag models, and risks were more pronounced with the exclusion of lung cancer. Increased risk of gastrointestinal cancers was also observed in all models using cumulative cotton dust. Significant trends in the exposure–response relationship were observed in models lagged up to 15 years. By the 20-year lag, however, medium category of exposure was associated with the greatest risk as compared with the unexposed. Across all models, the greatest risks for all cancers combined and gastrointestinal cancers were observed with medium cumulative cotton dust exposure when exposure were discounted in the 20 years prior to end of follow-up.

Models that included cumulative endotoxin in place of cotton dust showed that, in general, medium endotoxin exposure was associated with cancers once lung cancer cases were removed, suggesting that endotoxin exposure may play a causative role in cancer among

cotton textile workers. Because effect estimates increased when lung cancer was removed, these findings also indirectly support that endotoxin is associated with a decreased risk of lung cancer. Observations of reduced risks of lung cancer in cotton exposed cohorts have been reported in a number of studies[11–13] including a recent update of lung cancer in cotton workers in the UK[15] and meta-analysis of cotton-textile workers and agricultural workers,[14] supporting the hypothesis that bacterial endotoxin present in organic dusts is anticarcinogenic.[9] In the UK study, a strong linear trend for decreased risk of lung cancer was observed with increasing endotoxin exposure while controlling for smoking. Other groups exposed to airborne organic substances contaminated with endotoxin, such as dairy farmers[38] and auto manufacturing workers,[39] have also been identified to have reduced rates of lung cancer. A recent population-based study using a job exposure matrix to estimate organic dust exposure, however, observed increased risk of lung cancer in organic dust exposed workers.[16] There was no association with endotoxin, however, after controlling for organic dusts. Notably, while this study included cotton exposed workers, these could not be separated in their analyses. Endotoxin elicits a strong systemic inflammatory response upon inhalation[40] but the exact mechanisms by which endotoxin exposure results in anticarcinogenic effects are still unclear. It is likely however that the mechanisms involve the activation of macrophages and the release of TNF-α which stimulates a response to tumours.[9, 10]

While there is a large amount of evidence from previous studies, and indirect support from this current study, that endotoxin may be protective against lung cancer, findings from this study also suggest that conversely, endotoxin may be carcinogenic at other sites in the body. In this cohort, cumulative endotoxin exposure was associated with increased risk of gastrointestinal cancers. In all lag models, medium endotoxin exposure was associated with gastrointestinal cancer mortality, with the greatest effect observed when exposures were lagged by 15 years. As observations with gastrointestinal cancer were also observed with cotton dust, these findings suggest that the endotoxin component may be at least partially responsible for associations with cotton dust. How endotoxin exposure acts on the gastrointestinal tract is unclear. While acute gastrointestinal responses to endotoxin exposure have been reported, these have not been associated with development of cancer. It is plausible though that upon a potent inflammatory response in the lungs, subsequent triggering of systemic inflammation plays a role in initiating or progressing tumour activity at downstream sites. It is also possible that airborne endotoxin is introduced into the gastrointestinal tract through ingestion of airborne dust and fibres. A recent study of patients with and without colorectal adenomas demonstrated a greater risk of adenomas among those with high endotoxin levels and greater levels of inflammatory cytokines among those with higher plasma endotoxin levels.[41] Experimental data also suggest that endotoxin may be carcinogenic in the gastrointestinal tract. Using human colorectal tumour cell lines, lipopolysaccharide promoted tumour cell extracellular matrix adhesion and invasion through activation of the urokinase plasminogen activator system and was dependent on TLR-4 and NF-κB.[42] Further work is needed to determine the role of endotoxin in tumour suppression and promotion.

In this study, stomach cancer was the predominant form of gastrointestinal cancer in both cotton and silk workers. *Helicobacter pylori* infection is a well-established major risk factor for stomach cancer.[43] While it is possible that differences in *H pylori* infection between the two groups accounted for increased risk of gastrointestinal cancer in cotton workers, the observed exposure–response relationships with cotton dust and endotoxin and gastrointestinal cancer make it unlikely that *H pylori* accounted for all the increased risk of gastrointestinal cancer in cotton-exposed workers. Colorectal and liver cancers were also predominant forms of gastrointestinal cancer in this study population. Diet, physical activity, smoking and alcohol are to varying degrees risk factors for colorectal and liver cancers.[44, 45] The proportion of ever smokers in cotton textile workers was only slightly greater than in silk textile workers, and it is unlikely that in models accounting for pack-years that the increased risk of gastrointestinal cancer was entirely due to smoking. It is also unlikely that alcohol consumption, eating habits or other risk factors for gastrointestinal cancer differed in these two demographically similar groups and were related to exposure level.

Some studies have found increased risks of gastrointestinal cancers in relation to airborne occupational exposures such as cement dust, quartz dust, diesel exhaust[46] silica dust[25, 47, 48] and polycyclic aromatic hydrocarbons,[49] but to our knowledge studies of organic dust exposed workers have not noted increases risks of gastrointestinal cancer. Few studies have investigated gastrointestinal cancers among workers exposed to cotton dust and this is the first study to show a positive association between cotton dust and endotoxin exposures and gastrointestinal cancers using quantitative estimates. Older standardised mortality ratio studies in Finland and Poland reported elevated, but not statistically significant, risks of gastrointestinal cancers in cotton textile workers.[17, 20] In both these studies, cancers of the stomach were the most common gastrointestinal cancer, as in our study. Comparable in design to our study are more recent large case-cohort studies conducted among female employees from the Shanghai Textile Industry Bureau. These studies investigated occupational risk factors for various site-specific cancers of the gastrointestinal system, including oesophageal and stomach,[25] colorectal,[24] liver,[23] biliary tract,[50] and pancreatic cancers.[26] Work histories linked to a job exposure matrix developed for exposures in the textile industry were used to assign exposure to various chemicals and physical agents including cotton dust and endotoxin.[51] Contrary to our findings, the authors consistently found significant inverse associations with these site-specific gastrointestinal cancers and cotton dust and endotoxin exposures lagged by 20 years. While we found an overall positive association with gastrointestinal cancers, it is possible that had we been able to look at site-specific gastrointestinal cancers, some findings may have been more consistent with these inverse findings from the case-cohort studies. Differences in the reference group for the two study cohorts however may explain why we found a positive association and the site-specific studies found inverse associations. That is, in our study, we used a reference group of silk workers whose exposures would have been homogenous, whereas in the case-cohort studies, the reference group was comprised of workers unexposed to the substance of interest, but with heterogeneous exposures from across the textile industry. It is possible in our study that the relative excess of cancer mortality among the cotton workers may be due to an unmeasured confounder that is protective against cancer among silk workers. However, we know of no such substances. Notably, in a meta-analysis by Mastrangelo *et al*,

digestive cancers were found in excess among textiles workers using synthetic fibres or silk.[19] Further studies are needed to clarify these associations.

This study is strengthened by a well-characterised cohort, which allowed us to control for important potential confounders, and the availability of quantitative exposure estimates. We were also able to use a demographically similar group of silk textile workers as the unexposed reference group, which minimised confounding by demographic and lifestyle factors. We sampled from silk yarn processing areas, rather than weaving shops, the latter in which exposure to polycyclic aromatic hydrocarbons may be present. Thus, in this group of silk workers unexposed to endotoxin, exposure was mainly to silk which is an animal protein not known to be carcinogenic. Further, while our sample size was small, workers were followed for a relatively long period of 30 years, contributing a substantial number of person-years of observations (26 591).

We acknowledge however that there are also a number of limitations in this study. An important limitation is the relatively small sample size of the cohort, which precluded our ability to investigate site-specific cancer outcomes. It is possible that not all gastrointestinal cancers are equally impacted by cotton dust or endotoxin exposure; however, we found strong evidence of an increased risk of gastrointestinal cancers related to cotton dust and endotoxin exposure in this group which warrants further investigation. Also important is that we did not have the date of diagnosis but only the date of death. Ideally, cumulative exposure and the calculation of lags would be based on the date of development or diagnosis of tumour to best characterise the exposure–response relationship. Therefore, our effect estimates are likely influenced by prognosis and other factors that may impact cancer survival.

It should also be noted that the relatively small sample size may influence the exposure–response relationships because effect estimates can be sensitive to the choice of cut-points when categories are small. In sensitivity analyses however, use of cut-points based on the actual tertile distribution specific to the lags did not alter findings for cotton dust. Findings with endotoxin exposure were less robust to the choice of cut-points, though overall conclusions were not substantially altered. For example, use of the exposure distribution for the 20-year lag revealed significant associations with high endotoxin category rather than medium.

Another concern is potential exposure misclassification from the use of area measurements to predict personal exposure. In a validation study comparing work area samples and personal cotton dust and endotoxin measurements obtained from three cotton textile mills in Shanghai, work area measurements for endotoxin in particular were a good proxy of personal exposure.[52] The lack of exposure data in the interim years between surveys, before 1981 and after the 1996 sampling period would have also contributed to exposure misclassification. However, because workers tended to remain in the same job our assumption of constant exposure in the years between study periods was reasonable. Another limitation was the lack of data on potential coexposures. Even though all workers were recruited from yarn preparation areas, workers may have been exposed to substances such as aerosolised oils from machinery used in yarn preparation. Thus, we cannot rule out

confounding by potential coexposures. However, it is unlikely that some of the observed risks in cotton workers were due to exposures from other work since job mobility was restricted for this cohort and workers stayed in the same sector for their entire working lives. In addition, the mean age starting work in the mills was 19 and 20 for silk and cotton workers, respectively, and the mean number of years worked was 27 for both groups which further suggests that observations were unlikely due to other work or previous exposures. We also cannot rule out confounding by dietary factors, though it is unlikely that diet was correlated with level of exposure.

Further, we did not have exposure and covariate data for individuals censored after the last survey in 2006. We assumed constant exposure after 2006. Because all participants had retired from the mills by the last survey it was reasonable to assume that exposure had ceased in subsequent years and did not alter cumulative exposures estimates from 2006 onwards. This would however ignore exposures among individuals who may have sought textile work or other work with relevant exposures elsewhere. We did observe significant associations with unlagged exposures (at the end of follow-up), which may have been biased by any recent exposures; however, we observed the strongest effects with exposures lagged by 20 years. Similarly, we made assumptions about smoking patterns and number of pack-years, carrying forward the number of time-varying pack-years in 2006 through the end of follow-up in 2011. Confounding by smoking is not a major concern however given the small number of lung cancer cases. Finally, we were unable to estimate the independent effects of endotoxin exposure while controlling for cotton dust because of high correlation with one another (r=0.76), leading to inestimable effect estimates for high exposure in the categorical exposure models. Thus, while endotoxin is the most likely causative agent, cotton dust is a mixture of different substances and it is possible that constituents other than endotoxin play a role in the observed associations.

CONCLUSIONS

Despite the limitations of this study, we were able to use quantitative estimates of cumulative exposure to cotton dust and endotoxin to investigate the risk of cancer mortality in a well-characterised cohort of cotton textile workers. The findings suggest that cotton dust may be associated with cancer mortality, especially gastrointestinal cancer. Further, our findings also indirectly support the hypothesis that endotoxin exposure is protective against lung cancer.

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What this paper adds

▶ Occupational exposure to cotton dust and endotoxin is associated with adverse respiratory health; however, associations with cancer are unclear.

▶ The findings from this study suggest that cotton dust may be associated with cancer mortality, especially gastrointestinal cancer, and that endotoxin may play a causative role.

▶ In addition, our findings indirectly support the hypothesis that endotoxin is protective against lung cancer.

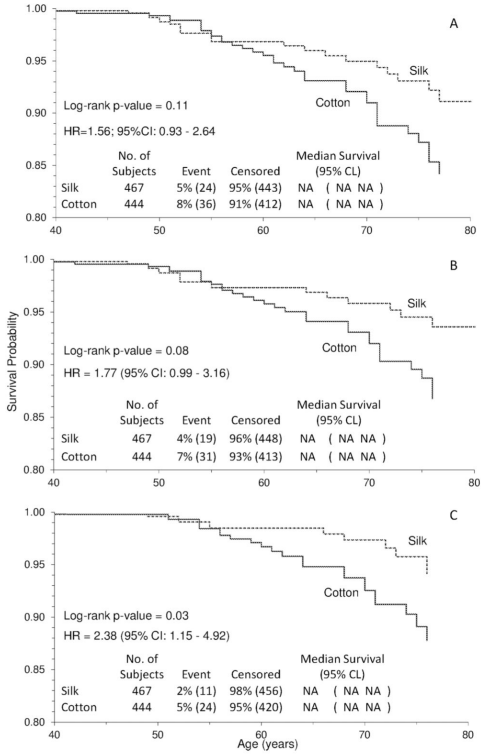

Figure 1.

Kaplan–Meier curves for mortality from (A) all cancers combined; (B) cancers excluding lung cancer; and (C) gastrointestinal cancers among cotton and silk textile workers.

Table 1

Characteristics of cotton and silk textile workers in study cohort

	Silk (n=467)	Cotton (n=444)
Female, no. (%)	271 (50.0)	233 (52.5)
Ever smoker, no. (%)	158 (33.8)	175 (39.4)
Pack-years among ever smokers, mean (range)	24.4 (<0.1–90.4)	28.4 (0.2–179.3)
Age started work, mean (range)	19 (6–36)	20 (12–40)
Age at entry into cohort, mean (range)	36 (21–61)	37 (22–60)
Age at end of follow-up, mean (range)*	64.5 (29.0–88.0)	65.1 (37.0–89.0)
Age died among deceased, mean (range)*	65.1 (29.0–85.0)	65.8 (37.0–84.0)
Years of follow-up since 1981, mean (range)*	29.2 (6.0–31.0)	26.9 (1.0–31.0)
Years worked, mean (range)†*	27.0 (3.0–50.2)	26.9 (2.0–49.6)
Years of cessation from exposure, median (range)‡*	17.8 (1.0–32.0)	17.1 (3.0–30.0)
Person-years	13 855	12 922
Cotton dust (mg/m^3-year), median (range)	0	15.8 (0.74–58.9)
Endotoxin (EU/m^3-year/10 K), median (range)	0	4.0 (0.02–232.5)
Died, no. (%)	58 (12.4)	73 (16.4)
Cause of deaths (ICD9), no.:		
All cancers combined (140–239)	24	36
Cancers, excluding lung cancer (excluding 162.9)	19	31
Gastrointestinal cancers (150–159)	11	24
Oesophageal (150)	0	1
Stomach (151)	3	7
Colorectal (153–154)	2	5
Liver (155)	4	5
Small intestine and ill-defined sites (152, 159)	2	4
Pancreas (157)	0	2
All other causes	34	37
Diseases of the circulatory system (390–459)	24	28
Cerebrovascular disease (430–438)	17	18
Other	8	7

*Measured at end of follow-up.

†Excludes one participant whose work years greater than age at end of follow-up.

‡n=380 for silk and 390 for cotton.

EU, endotoxin unit; ICD9, International Classification of Diseases, 9th edition.

Table 2

Multivariable association between mortality and exposure (cotton vs silk textile worker)*

	HR	95% CI
All deaths	1.31	0.92 to 1.86
All cancers	1.56	0.93 to 2.64
Cancers excluding lung cancer	1.77	0.99 to 3.16
GI cancers	2.38	1.15 to 4.92

* From Cox proportional hazards models adjusted for time-varying age, pack-years smoked and work years, person-years=26 591.

Table 3

Association between cumulative cotton dust exposure (mg/m^3-year) and risk of death from cancer*

		All cancers combined‡				Cancers excluding lung cancer§				Gastrointestinal cancers¶			
Lag	**Cotton dust level†**	**Cases**	**HR**	**95% CI**	**p Trend**	**Cases**	**HR**	**95% CI**	**p Trend**	**Cases**	**HR**	**95% CI**	**p Trend**
0 years	Low	9	1.0	0.5 to 2.1	0.01	6	0.8	0.3 to 1.9	<0.001	5	1.2	0.4 to 3.4	<0.01
	Medium	12	1.5	0.7 to 2.9		11	1.8	0.8 to 3.7		10	2.7	1.1 to 6.3	
	High	15	2.3	1.2 to 4.5		14	3.2	1.6 to 6.6		9	3.2	1.3 to 8.0	
5 years	Low	9	0.9	0.4 to 1.9	<0.01	6	0.7	0.3 to 1.8	<0.001	5	1.1	0.4 to 3.1	<0.01
	Medium	12	1.5	0.8 to 3.1		11	1.9	0.9 to 3.9		10	2.8	1.2 to 6.7	
	High	15	2.5	1.3 to 4.9		14	3.6	1.7 to 7.4		9	3.5	1.4 to 8.7	
10 years	Low	12	1.1	0.5 to 2.2	0.01	9	0.9	0.4 to 2.1	<0.01	8	1.6	0.6 to 4.0	<0.01
	Medium	11	1.4	0.7 to 3.0		10	1.8	0.8 to 3.8		7	2.0	0.8 to 5.3	
	High	13	2.5	1.2 to 5.1		12	3.6	1.6 to 7.8		9	3.9	1.5 to 9.9	
15 years	Low	14	1.1	0.6 to 2.2	0.04	11	1.0	0.5 to 2.2	<0.01	10	1.8	0.7 to 4.2	0.02
	Medium	13	1.8	0.9 to 3.6		12	2.3	1.1 to 4.8		8	2.5	1.0 to 6.2	
	High	9	2.1	0.9 to 4.8		8	3	1.2 to 7.3		6	3.0	1.1 to 8.8	
20 years	Low	15	1.0	0.5 to 1.9	0.02	12	1.0	0.5 to 2.0	<0.01	10	1.5	0.6 to 3.5	0.01
	Medium	16	2.7	1.4 to 5.2		14	3.4	1.7 to 7.0		11	4.1	1.8 to 9.7	
	High	5	1.6	0.6 to 4.4		5	2.6	0.9 to 7.6		3	2.1	0.5 to 8.0	

*From Cox proportional hazards models adjusted for time-varying age and pack-years smoked; person-years=26 591.

†Cumulative cotton dust categories: Low: <15.2; Medium: 15.2–30.2; High: >30.2 mg/m^3-years (cut-points based on the average of distributions from all lags).

‡Unexposed cases=24.

§Unexposed cases=19.

¶Unexposed cases=11.

Table 4

Association between cumulative endotoxin exposure (EU/m^3-year/10 K) and risk of death from cancer*

		All cancers combined‡				Cancers excluding lung cancer§				Gastrointestinal cancers¶			
Lag	**Endotoxin level†**	**Cases**	**HR**	**95% CI**	**p Trend**	**Cases**	**HR**	**95% CI**	**p Trend**	**Cases**	**HR**	**95% CI**	**p Trend**
0 years	Low	9	1.6	0.8 to 3.5	0.82	5	1.2	0.4 to 3.2	0.20	5	2	0.7 to 5.8	0.43
	Medium	14	1.9	1.0 to 3.6		13	2.1	1.0 to 4.2		11	3.2	1.4 to 7.4	
	High	13	1.2	0.6 to 2.3		13	1.6	0.8 to 3.2		8	1.6	0.6 to 4.0	
5 years	Low	9	1.5	0.7 to 3.3	0.58	5	1.1	0.4 to 3.0	0.11	5	1.9	0.6 to 5.4	0.27
	Medium	14	1.8	0.9 to 3.4		13	2	1.0 to 4.0		11	3.1	1.3 to 7.2	
	High	13	1.2	0.6 to 2.5		13	1.7	0.8 to 3.5		8	1.7	0.7 to 4.3	
10 years	Low	11	1.8	0.9 to 3.6	0.43	7	1.4	0.6 to 3.4	0.06	6	2.1	0.8 to 5.7	0.17
	Medium	12	1.4	0.7 to 2.8		11	1.5	0.7 to 3.2		10	2.6	1.1 to 6.1	
	High	13	1.4	0.7 to 2.8		13	2	1.0 to 4.1		8	1.9	0.8 to 4.9	
15 years	Low	13	1.8	0.9 to 3.6	0.83	9	1.5	0.7 to 3.5	0.25	7	2.2	0.8 to 5.7	0.63
	Medium	15	1.6	0.8 to 3.1		14	1.9	0.9 to 3.8		14	3.4	1.5 to 7.6	
	High	8	1	0.5 to 2.3		8	1.5	0.6 to 3.4		3	0.8	0.2 to 3.0	
20 years	Low	16	1.8	0.9 to 3.4	0.91	11	1.5	0.7 to 3.2	0.26	9	2.3	1.0 to 5.7	0.73
	Medium	15	1.6	0.8 to 3.0		15	2	1.0 to 4.0		14	3.2	1.4 to 7.1	
	High	5	0.9	0.3 to 3.0		5	1.3	0.5 to 3.6		1	0.4	0.05 to 2.9	

*From Cox proportional hazards models adjusted for time-varying age and pack-years smoked; person-years=26 591.

†Cumulative endotoxin categories: Low: <12 310; Medium: 12 310–49 424; High: >49 424 EU/m3-years (cut-points based on the average of distributions from all lags).

‡Unexposed cases=24.

§Unexposed cases=19.

¶Unexposed cases=11.