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Evidence of a paradoxical relationship between endotoxin and lung cancer after accounting for left truncation in a study of Chinese female textile workers

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Abstract

Introduction—Occupational exposure to endotoxin, found in Gram-negative bacteria in organic material, has been associated predominantly with a reduced risk of lung cancer among workers. An inverse exposure–response gradient among women textile workers in Shanghai, China, has

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been reported previously. In this case–cohort study, we investigated the influence of left truncation, which can itself induce a downward trend, on the observed association.

Methods—Subjects were enrolled between 1989 and 1991 and followed until 1998. The data were left-truncated as all subjects were hired before baseline. An analysis was performed with 3038 subcohort members and 602 cases of incident lung cancer. To evaluate left truncation, we compared lung cancer rates in those hired longer ago with those hired more recently among unexposed subjects. Cox proportional hazards modelling was used to estimate incident rate ratios (IRRs) and 95% CIs.

Results—Among those who were never exposed to workplace endotoxin, we compared lung cancer rates in those hired >35 years before enrolment with workers hired ≤35 years before enrolment and observed a reduced risk in the former group, IRR=0.74, 95% CI (0.51 to 1.07). After accounting for this downward bias from left truncation, the reduced risk associated with endotoxin remained among those hired ≤50 years before enrolment. In contrast, there was suggestion of an increased risk of lung cancer among those hired >50 years ago.

Conclusions—After examination of left truncation bias, an inverse dose–response between endotoxin and lung cancer remained for all subjects except those hired longest ago.

INTRODUCTION

Endotoxin, also referred to as lipopolysaccharide (LPS), is found in organic material, including cotton dust, and has been associated with a reduced risk of lung cancer.[12] Located on the outer membrane of Gram-negative bacteria, endotoxin is released during lysis and cellular replication. It enters the body through inhalation and is detected by airway macrophages, triggering responses involving both the innate and acquired immune systems.[34] It is hypothesised that this immunomodulation may be anticarcinogenic because the heightened presence of cells from the immune system may restrict tumour growth, leading to a lower occurrence of cancer in exposed populations.[5]

Reduced lung cancer risks have been observed in various occupational groups with exposure to organic substances, most notably in cotton textile workers.[267] There are methodological challenges that hinder interpretation of these findings, notably uncontrolled confounding (eg, by smoking) and the absence of quantitative exposure estimates of endotoxin in some studies.[2] In a recent analysis of a large case–cohort study of female textile workers in which both quantitative exposure estimates and smoking histories were available, an inverse exposure–response gradient for cumulative endotoxin exposure and lung cancer risk was reported.[89] In the present study, we address another potential threat to validity of the results: the impact of left-truncated data on the observed downward trend.

The Shanghai female textile workers study does not include any workers hired during the follow-up period, that is, incident hires. Incident hires are distinct from prevalent hires who worked prior to follow-up starting.[10] In occupational cohorts, incident hires have been found to have lower cumulative exposure, shorter duration of work[1011] and higher mortality rates[1112] than prevalent hires, defined as workers hired prior to follow-up starting.[i]

Left truncation occurs when subjects who otherwise meet entry criteria do not remain observable for a later start of follow-up.[13] For an occupational cohort, the unobserved subjects typically are those who left the worker population before study baseline but would have been included in the study if they had remained in the population. Thus, a cohort comprised of prevalent hires is left-truncated and subjects at baseline have variable lengths of time since hire. Left-truncated data have been found to influence the exposure–response between occupational exposures and lung cancer. In previous studies, prevalent hires induced a downward bias on estimates[101114] (ie, the measures of association were spuriously underestimated). In a study of lung cancer and silica, the strongest exposure–response was observed among incident hires only.[10] A similarly steep exposure–response was observed when prevalent hires hired close to the start of follow-up were included in the analysis with incident hires. When those hired longer ago, relative to the start of follow-up, were included in the analysis, the exposure–response was biased downwards. These results indicated that left-truncated data can induce bias in the exposure–response, and that the bias is greatest for subjects hired much in advance of study baseline.

The operation of this bias was examined in a simulation study of occupational cohort data comprised of prevalent and incident hires.[15] When subjects were allowed to vary in their susceptibility to exposure-related health effects, left-truncated data produced a downward bias in the exposure–response estimates under either a true positive or true null association. The downward bias was stronger for prevalent hires who were hired farther in advance of study baseline (eg, hired ≥30 years prior to start of follow-up). The bias was stronger as the time between study baseline and the earlier date of hire increased because the proportion of workers susceptible to the effects of exposure decreased. In other words, among subjects hired longer ago, those who remain observable for later start of follow-up differed in susceptibility from the entire cohort of workers employed during that earlier time period.

Ideally, we would study the relationship between endotoxin and lung cancer in an inception cohort (incident hires only) over an extended period of follow-up. On the other hand, a cohort with a mix of incident and prevalent hires who represent a range of time since hire and cumulative exposure can be just as informative and sometimes more than studying incident hires only, provided that time since hire at baseline was at random given the other measured covariates.[16] The absence of incident hires in the Shanghai textile cohort thus warrants closer investigation of the exposure–response relationship presented here.

METHODS

The methods of the case–cohort study have been described in detail elsewhere.[1718]

Cohort enumeration and cancer incidence

The source cohort was comprised of 267 400 active and retired female employees of the Shanghai Textile Industry Bureau (STIB) born between 1925 and 1958 who were enrolled during 1989–1991 in an intervention trial of the efficacy of breast self-examination. At

[i]The use of the terms ‘incident hire’ and ‘prevalent hire’ refers specifically to whether subjects were hired during the dates of study follow-up or before the study follow-up, respectively, and these terms do not refer in any way to disease status or exposure status.[10]

enrolment, subjects completed a baseline questionnaire in which they reported on demographic, reproductive and lifestyle factors, including smoking. Cancer incidence was ascertained for the years 1989–1998 by linkage of the cohort with the STIB's Station for Prevention and Treatment of Cancer, an industry-wide cancer registry, and the Shanghai Cancer Registry.[19] As previously reported, loss to follow-up was less than 10% and unrelated to case status.[18,19]

Case–cohort design

A case–cohort design was implemented to allow for more detailed examination of occupational exposures and how they may contribute to cancer risk.[20,21] A subcohort of workers from the full cohort study was selected by frequency-matching to year of birth distribution of all cancers (including lung and 14 other tumour sites) and randomly sampled within year of birth strata (each stratum represented a 5-year window). The size of the subcohort (n=3188) was chosen to be two times the size of the most common cancer, breast cancer. Three subjects randomly selected to be in the subcohort later developed lung cancer but still contributed disease-free person-time prior to diagnosis.

Exposure assessment

Details of the quantitative estimation of cotton dust and endotoxin for individual workers have been described previously.[22,23] Briefly, over 2400 cotton dust measurements were taken by Chinese government and factory occupational hygienists in 56 cotton factories between 1975 and 1999. A predictive model, containing factory, major process, specific process and year, was used to estimate annual cotton dust exposures for each job. Jobs in administration or non-cotton factories were classified as not having cotton dust exposure. Information on endotoxin content in cotton dust (as endotoxin level per milligram of cotton dust) came from 765 samples collected over a 15-year period[24–27] and from endotoxin measurements taken at 1625 jobs from three Shanghai factories in 2002.[22] When job-specific endotoxin exposures were not collected directly, the average levels associated with their major processes were used. Endotoxin measurements were linked to each subject's complete work history[23] and cumulative exposure to endotoxin was estimated by summing across the product of job duration and the endotoxin concentration within each year for all jobs held.

Analysis

Of the 641 lung cancer cases and 3188 subcohort members identified, 1 subcohort member and 13 cases were excluded because complete work histories were not available. Another 149 subjects in the subcohort and 26 cases were excluded because potentially they had occupational exposure to endotoxin from holding jobs in non-cotton factories (eg, sanitation, wool processing), leaving 602 cases and 3038 subcohort members for analysis.

We first used time since enrolment (specifically, completion of the baseline questionnaire) in person-months as our primary analytic timeline. In Cox proportional hazards regression, we accounted for the sampling of the subcohort[28,29] in the estimates of the hazard ratios and 95% CIs for cumulative endotoxin exposures and incident lung cancer. We assumed constant hazards and rare events in order to use the hazard ratio as our estimate of the

incident rate ratio (IRR). Models controlled for smoking at baseline (never, former, current) and age at baseline (with a linear term). Cumulative endotoxin was classified into four categories, with the reference category representing person-months in which subjects had never previously held a job with endotoxin exposure, and the remaining ever exposed person-months were classified into tertiles of cumulative endotoxin (≤1747, >1747–3022, >3022 endotoxin units (EU)/m^3-year) based on the distribution of cases. We also controlled for time since hire (in quartiles based on cases: ≤28 years, 29–37 years, 38–46 years and ≥47 years since hire) so that we could compare these initial results with later models using time since hire as the timeline rather than time since enrolment.

To examine the influence of left truncation on the association between lung cancer and endotoxin, we stratified analyses by years hired prior to baseline. Years hired prior to baseline was dichotomised at the median based on cases, dividing into those hired within 35 years or hired more than 35 years before baseline. We generated a joint effects model, using those hired within 35 years of baseline and never exposed to endotoxin as the reference category. In addition, IRRs and 95% CIs for endotoxin and lung cancer were also estimated separately within both strata of years hired relative to baseline.

At baseline, some previously exposed subjects no longer held jobs that involved endotoxin exposure. This raised a question about the persistence of reduced lung cancer risk following cessation of exposure. Previously, a study of dairy farmers reported that a reduction in lung cancer was no longer apparent 15 years after leaving agricultural work.[30] Therefore, to examine the effects of exposure cessation, time since last endotoxin exposure was dichotomised into ≤15 years and >15 years. A joint effects model was created, using never exposed to endotoxin as the reference category. Additional analyses were restricted to never smokers to see if smoking influenced the observed relationships.

To further investigate the issue of left truncation, we changed our analytic timeline (from time in study) to time since hire. In other words, at enrolment, a subject's baseline time since hire is the number of years that passed since she was hired at STIB. Since all subjects were hired before the start of follow-up, we used delayed entry in order to exclude immortal person-time.[31] For example, if at enrolment a subject had been hired 30 years prior, she would first contribute at-risk person-time at 30 years since hire, whereas for someone hired more recently (eg, at enrolment she was hired 20 years previously), she would contribute person-time beginning at 20 years since hire on this analytic timeline. We estimated IRRs and 95% CIs with Cox proportional hazards regression as described earlier. We calculated an overall association between categorical cumulative endotoxin and lung cancer and then estimated these IRRs within three strata of time since hire (within 35 years, >35–50 years, and >50 years).

We also examined the association between cumulative endotoxin and lung cancer with an accelerated failure time model, which has been recommended to examine changes in an association over time.[32] We fit the model using a piecewise-exponential accelerated failure time model with Poisson regression based on the method of Clark and Ryan,[33] allowing estimation of the effects of both time since hire (eg, the analytical timeline) and endotoxin exposure. The piecewise-exponential model was selected as it can flexibly accommodate

both left truncation and right censoring,[34] allows time-varying exposures, provides rate ratio estimates and can be adjusted to accommodate case–cohort studies.[35] For the piecewise model, we generated IRRs and 95% CIs within the same categories of time since hire and cumulative endotoxin as were used in the Cox proportional hazards model while adjusting for smoking and age at baseline. The overall event rate was assumed to be constant within each interval, but was allowed to vary between intervals, and the effect of the level of endotoxin exposure was allowed to vary from interval to interval. The data analysis was conducted using the GENMOD procedure in SAS V.9.1.3 (SAS Institute Inc., Cary, North Carolina, USA). These accelerated failure time models provided virtually the same IRR estimates as the Cox proportional hazards models for cumulative endotoxin within strata of time since hire, and as a result, we only present the Cox proportional hazards model results here.

The data analysis was conducted using SAS V.9.1.3. The institutional review boards at Boston University Medical Center (Boston, Massachusetts, USA), The University of Washington (Seattle, Washington, USA), Fred Hutchinson Cancer Research Center (Seattle, Washington, USA) and Zhong Shan Hospital (Shanghai, China) approved the study procedures and subjects provided informed consent.

RESULTS

Characteristics of cases and subcohort members at baseline are presented in table 1, stratified by their baseline cumulative endotoxin estimates. Age was somewhat older, on average, for those in the highest cumulative endotoxin group compared with those with lower or no cumulative endotoxin exposure. The prevalence of having ever smoked was very low among all study subjects. Those with higher cumulative endotoxin at baseline were younger at hire, had longer time since hire, had worked longer and were less likely to be currently working at baseline compared with workers who had lower or no endotoxin exposure. The percentage of subjects in each exposure group who became cases during the follow-up period was the same.

Next, we examined the overall association between cumulative endotoxin and lung cancer (table 2). Using a model adjusting for age and smoking at baseline, there was a reduced risk of lung cancer with increasing endotoxin exposure, as published previously.[8] This pattern remained after further adjustment for time since hire.

Table 3 presents data regarding the influence of left truncation. Although all subjects worked prior to follow-up, subjects were categorised into those hired more recently (>0–35 years of baseline) and those hired longer ago relative to baseline (>35 years before baseline). Within these categories, we examined the association between cumulative endotoxin and lung cancer. Among those never exposed to endotoxin, the IRR comparing those who were hired more than 35 years before baseline with those hired more recently was 0.74 (95% CI 0.51 to 1.07), indicating a reduced risk among those hired longer ago even in the absence of exposure. In the stratum with more recent hires, the reduced risk of lung cancer with greater cumulative endotoxin was evident, but this was no longer observed in the stratum of those hired more than 35 years ago.

A question that follows is whether the disappearance of the inverse association between endotoxin and lung cancer in those hired longest ago may actually be explained by exposure cessation rather than left truncation. That is, the absence of a reduced risk in workers hired longer ago may have occurred because exposure had ceased many years previously. In the online supplementary appendix, we present results of exposure cessation in combination with cumulative endotoxin exposure. Those never exposed to endotoxin comprise the reference group and remaining subjects were classified as last endotoxin exposure either within the last 15 years or more than 15 years ago. For workers who were exposed to endotoxin within the preceding 15 years, there was still a reduced risk with increasing cumulative endotoxin exposure. Among those last exposed to endotoxin more than 15 years ago, there was also a pattern of a reduced risk of lung cancer with increasing cumulative endotoxin; however, the IRRs are closer to the null compared with the group exposed more recently. Data based on models restricted to never smokers are not presented here as the results did not change.

We examined years hired before baseline concurrently with time since last exposure and cumulative endotoxin (table 4). To preserve statistical power, we combined categories of cumulative endotoxin into ever or never exposed. Among those hired more recently (within 35 years), a reduced risk of lung cancer remained for those ever exposed regardless of whether last endotoxin exposure was within the last 15 years or more than 15 years ago (IRR for ever and exposed within the last 15 years=0.81, 95% CI (0.61 to 1.07); IRR for ever and last exposed >15 years ago=0.80, 95% CI (0.57 to 1.12)). Among the strata of workers hired more than 35 years ago, there was suggestion of a reduced risk of lung cancer among those exposed within the last 15 years, albeit with CIs that included the null (IRR=0.88, 95% CI (0.59 to 1.33)), but there was no longer an association with endotoxin in those last exposed more than 15 years ago (IRR=1.14 95%, CI (0.81 to 1.61)). We examined cumulative endotoxin exposures in these groups and found that those hired more than 35 years ago had nearly double the mean cumulative endotoxin compared with the more recent hires (hired >35 years before baseline, 8998.9 EU/m^3-year (SE=20848.7); hired ≤35 years before baseline, 4986.5 EU/m^3-year (SE=12634.9)).

We analysed the relationship between endotoxin and lung cancer using time since hire as the analytic timeline to evaluate more closely changes in the association as time since hire varied (table 5). All subjects had worked prior to the start of follow-up. The full range of time since hire at baseline for all subjects was 0.2–56.0 years (mean=31.8±11.6 years) and on this analytic timescale, the first case occurred at 3.3 years since hire. There was a change in the distribution of cases in exposure categories within time since hire categories. For person-time within 35 years of hire, the majority of cases (41%) had never been exposed to endotoxin, while for time since hire over 50 years ago, the majority of cases (46%) had endured the highest cumulative endotoxin exposure and there were only 10 cases that had never been exposed to endotoxin. For time since hire within 35 years or >35–50 years since hire, evidence of an inverse association between endotoxin and lung cancer persisted. However, in the >50 years since hire stratum, the IRRs for all categories of endotoxin exposure were elevated relative to the non-exposed. When data were collapsed into never/ever exposed to endotoxin, ever exposed was associated with decreased risks of lung cancer for person-time within 35 years since hire (IRR=0.81, 95% CI (0.57 to 1.14)) and >35–50

years since hire (IRR=0.87, 95% CI (0.65 to 1.15)) but was associated with an increased risk for person-time with >50 years since hire (IRR=1.77, 95% CI (0.84 to 3.73)), albeit with wide CIs due to the low number of cases never exposed to endotoxin.

DISCUSSION

The primary objective of this analysis was to examine whether the downward trend in lung cancer risk with increasing endotoxin exposure previously reported in this study population[89] was an artefact of the study design that entailed left-truncated data. Among those never exposed to endotoxin, lung cancer incidence decreased with greater years since hire. This is compatible with a downward bias from left truncation. After accounting for years since hire, a reduced risk of lung cancer was still associated with cumulative endotoxin when examining person-time between >0 and 50 years of being hired. The results also suggest an increased risk of lung cancer among endotoxin-exposed workers hired longest ago; this finding should be examined further.

The preponderance of epidemiologic evidence of the association between occupational endotoxin and lung cancer supports an inverse relation between endotoxin and lung cancer.[127] Previous analyses tended to focus on the overall dose–response relationship with endotoxin. Changes in the association between endotoxin and lung cancer over time have not been fully explored, despite growing recognition that exposure/disease associations can vary over time.[32] In the present study, we estimated the influence of time since hire in the non-exposed, which allowed us to observe that the risk of lung cancer decreased with longer time since hire, independent of endotoxin exposure. Concerns about downward bias from left truncation were therefore warranted, as left-truncated data represent a greater proportion of workers who had worked longer. Addressing this bias allowed us to observe a possible non-static and potentially paradoxical relationship between endotoxin and lung cancer across time since hire. Given that in any occupational cohort study (eg, even an inception cohort), subjects will remain at work for differing lengths of time and that those who remain at work for longer periods reflect a less susceptible subset,[15] the issue of the relationship changing over time is not limited to left-truncated data at study baseline. If we consider that many previous studies lacked quantitative estimates of endotoxin exposure and therefore used duration of endotoxin exposure as an exposure proxy, it may be that their observed reduced risk of lung cancer is due, in part, to the risk of lung cancer decreasing with time regardless of endotoxin exposure.

Although comprising a minority, there are studies of occupational endotoxin exposure that have reported elevated risks of lung cancer.[236] In addition, Mastrangelo *et al*[30] reported an inverse association between endotoxin and lung cancer disappeared 15 years after leaving dairy farming. They postulated that, because endotoxin does not bioaccumulate, the protection does not persist upon removal from endotoxin exposure. However, our results did not present a clear picture with respect to exposure cessation. Instead, the element of time that was more important was time since hire. Nonetheless, the work by Mastrangelo *et al*[30] and the present paper are consistent in indicating that the association between endotoxin and lung cancer may be time-varying.

There is biological support for a dual role of endotoxin in leading to both early tumour regression followed by later progression.[3738] Both pathways begin with a complex of LPS and LPS-binding protein attaching to CD14 on macrophages. CD14 coupled with the transmember protein toll-like receptor-4 (TLR4) induces intracellular signalling, resulting in production of cytokines, notably tumour necrosis factor-α (TNFα), interleukin (IL)-6 and IL-8, which recruit neutrophils for an innate immune system defence. LPS and components of the subsequent immunologic signalling pathway have long been evaluated as a potential immunotherapeutic agent for cancer. Studies of tumour regression report TNFα induces apoptosis of tumour cells and destruction of tumour vasculature and ILs may be cytotoxic to cancerous cells directly.[4] However, prolonged success of immunotherapy based on this pathway alone or concurrently with other therapies has proven elusive thus far for treating lung cancer. In addition to the association of LPS with tumour regression, evidence supports that tumour progression may also occur. One of the leading theories for the progression pathway is that TLR4 also has an important role in inflammation, which is itself recognised in cancer development, including for lung cancer.[39] Further, TLR4-stimulated TNFα and other cytokines may also promote tumour angiogenesis and activate oncogenes.[39]

Controlling for time since hire as a covariate in a regression model is often used as a way to control for healthy worker survivor effect (HWSE) bias. However, changes in the exposure–disease relationship across categories of time since hire should not be confused with HWSE bias. Within strata defined by time since hire, we observed different exposure–response; in contrast with the inverse exposure–response among more recent prevalent hires, there was no inverse association between endotoxin and lung cancer among those hired longest ago. In general, presenting the exposure–response across time periods can potentially highlight changes over time and identify important associations.[32] Thus, presenting a single exposure–response measure, whether or not time since hire is controlled for, may mask an important observation occurring in a particular time period or patterns in the exposure–response relationship over time.

For Chinese women, lung cancer is among the most common cancers,[40] yet Chinese women rarely smoke.[41] For women in Shanghai, China, it is estimated that only 24% of lung cancer cases are attributable to smoking.[42] Alternative explanations for the elevated lung cancer risk among non-smoking women include exposure to secondhand tobacco smoke,[43] residential radon exposure[44] and exposure to combustion products due to use of biomass or coal for heating and cooking.[45–48] However, it is unlikely that exposure to these risk factors was associated with endotoxin exposure. Another issue for further consideration is competing risks. For example, endotoxin is associated with an increase in chronic obstructive pulmonary disease (COPD),[49–51] which is a risk factor for lung cancer.[5253] Whether decreased lung cancer incidence could be explained by an increase in more severe COPD is an area for future research.

Analyses by time since hire and accounting for left truncation have provided further evidence for an inverse association between endotoxin and lung cancer. Stratification by time periods shed light on how the endotoxin–lung cancer relation varies over time and allowed us to identify time periods when the inverse association was strongest. We conclude that the observed decrease in risk with level of endotoxin exposure is not an artefact of the

study design with a cohort comprised entirely of subjects hired prior to the start of follow-up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What this paper adds

- In a previously published manuscript from this study population of female textile workers in Shanghai, endotoxin, based on quantitative exposure estimates, was associated with a reduced risk of lung cancer. It is possible, however, the explanation for the inverse association was a study cohort consisting entirely of left-truncated data.
- In the present analysis, we accounted for left truncation bias using time since hire as the analytic timeline and examined the endotoxin–lung cancer association within strata of time since hire. Endotoxin exposure was associated with a decreased risk of lung cancer for those hired less than 50 years ago; however, for those hired more than 50 years ago, endotoxin exposure was associated with an elevated risk of lung cancer.
- Our results are consistent with molecular and medical research showing that endotoxin can have a dual role in protecting against cancer and later increasing risk of cancer.
- The analytical strategy used here is easily implemented and allows observation of changes in an exposure–disease relationship over time, which also serves as a way to account for downward bias from left truncation.

Table 1

Distribution of selected characteristics of cases and subcohort members at baseline by endotoxin exposure in the Shanghai female textile workers study

	Never exposed at t_0 N=1102	≤2325 EU/m^3-year at t_0 N=1267	>2325 EU/m^3-year at t_0 N=1268
Age at baseline			
Mean (±SD)	52.8 (±9.7)	51.8 (±10.8)	56.9 (±6.9)
Smoking status (%)			
Never	1035 (93.9%)	1210 (95.5%)	1184 (93.4%)
Former	12 (1.1%)	10 (0.8%)	8 (0.6%)
Current	55 (5.0%)	47 (3.7%)	76 (6.0%)
Age at hire			
Mean (±SD)	24.1 (±7.8)	23.1 (±7.4)	19.2 (±5.5)
Years since hire*			
Mean (±SD)	28.7 (±11.5)	28.7 (±12.0)	37.7 (±8.8)
Current worker (%)	369 (33.5%)	443 (35.0%)	164 (12.9%)
Duration worked			
Mean (±SD)	21.9 (±8.7)	20.7 (±8.1)	28.2 (±6.4)
Lung cancer cases†			
N (%)	186 (16.9%)	209 (16.5%)	207 (16.3%)

*At baseline, the range of years since hire was 0.2–54.0 years.

†Indicates which exposure group the subjects who eventually became cases were at baseline.

Table 2

Overall association between endotoxin and lung cancer incidence in the Shanghai female textile workers study

Cumulative endotoxin (EU/m^3-year)	Cases N (%)	Person-time (%)*	Rate ratio†	95% CI	Rate ratio, adjusted for time since hire‡	95% CI
Never	186 (30.9)	29.7	1.00		1.00	
≤1747	137 (22.8)	22.0	1.05	0.82 to 1.35	1.04	0.81 to 1.34
>1747–3022	140 (23.3)	24.2	0.84	0.65 to 1.07	0.85	0.67 to 1.10
>3022	139 (23.1)	24.0	0.78	0.61 to 1.00	0.83	0.64 to 1.07

*Out of a total of 1 656 830 person-months.

†Controls for smoking and age at baseline.

‡Controls for smoking and age at baseline and time since hire.

Table 3

Combination of cumulative endotoxin exposure and years hired prior to baseline and association with lung cancer risk in the Shanghai female textile workers study

				Joint effects		Stratified	
Hired relative to baseline	**Cumulative endotoxin (EU/m^3-year)**	**Cases N (%)**	**Person-time (%)***	**Rate Ratio†**	**95% CI**	**Rate ratio†**	**95% CI**
>0–35 years before t_0	Never	132 (21.9)	21.9	1.00		1.00	
	≤1747	90 (14.9)	16.6	0.96	0.71 to 1.31	0.96	0.71 to 1.31
	>1747–3022	57 (9.5)	13.3	0.69	0.49 to 0.97	0.69	0.49 to 0.97
	>3022	34 (5.6)	7.9	0.71	0.47 to 1.08	0.71	0.47 to 1.08
>35 years before t_0	Never	54 (9.0)	7.8	0.74	0.51 to 1.07	1.00	
	≤1747	47 (7.8)	5.4	0.93	0.62 to 1.38	1.26	0.80 to 1.96
	>1747–3022	83 (13.8)	11.0	0.81	0.58 to 1.13	1.10	0.74 to 1.62
	>3022	105 (17.4)	16.1	0.71	0.52 to 0.96	0.96	0.66 to 1.38

*Out of a total of 1 656 830 person-months.

†Controls for smoking and age at baseline.

Table 4

Association between lung cancer and endotoxin exposure and cessation by strata of years hired prior to baseline

Years hired before baseline	Time since last exposure	Cumulative endotoxin (EU/m^3-year)	Cases N (%)	Person-time (%)*	Rate ratio†	95% CI
>0–35 years	Never	Never	132 (21.9)	21.9	1.00	
	≤15 years	Ever	108 (17.9)	27.3	0.81	0.61 to 1.07
	>15 years	Ever	73 (12.1)	10.5	0.80	0.57 to 1.12
>35 years	Never	Never	54 (9.0)	7.8	1.00	
	≤15 years	Ever	64 (10.6)	11.8	0.88	0.59 to 1.33
	>15 years	Ever	171 (28.4)	20.7	1.14	0.81 to 1.61

*Out of a total of 1 656 830 person-months.

†Controls for smoking and age at baseline.

Table 5

Change in association between cumulative endotoxin and lung cancer risk with increasing time since hire

Time since hire*	Cumulative endotoxin (EU/m^3-year)	Cases N (%)	Person-time (%)†	Rate ratio‡	95% CI
>0–35 years	Never	84 (41.4)	33.6	1.00	
	≤1747	71 (35.0)	28.2	1.00	0.67 to 1.48
	>1747–3022	29 (14.3)	25.0	0.57	0.35 to 0.94
	>3022	19 (9.4)	13.2	0.71	0.39 to 1.30
>35–50 years	Never	92 (30.1)	26.4	1.00	
	≤1747	49 (16.0)	13.9	0.98	0.61 to 1.56
	>1747–3022	88 (28.8)	27.6	0.52	0.30 to 0.90
	>3022	77 (25.2)	32.1	0.71	0.37 to 1.35
>50 years	Never	10 (10.7)	19.0	1.00	
	≤1747	17 (18.3)	13.1	1.90	0.76 to 4.79
	>1747–3022	23 (24.7)	22.6	1.69	0.72 to 4.01
	>3022	43 (46.2)	45.3	1.77	0.81 to 3.88

*At baseline, the range of years since hire was 0.2–54.0 years.

†Out of a total of 1 656 830 person-months.

‡Models control for smoking and age at baseline and analytic timeline is time since hire.