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Night shift work and lung cancer risk among female textile workers in Shanghai, China

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Abstract

In 2007, the International Agency for Research on Cancer classified *shift work that involves circadian disruption* as a probable human carcinogen. Suppression of the anti-neoplastic hormone, melatonin, is a presumed mechanism of action. We conducted a case-cohort study nested within a cohort of 267,400 female textile workers in Shanghai, China. Newly diagnosed lung cancer cases (n=1451) identified during the study period (1989–2006) were compared with an age-stratified subcohort (n=3040). Adjusting for age, smoking, parity and endotoxin exposure, relative risks [hazard ratios (HRs)] were estimated by Cox regression modeling to assess associations with cumulative years and nights of rotating shift work. Results did not consistently reveal any increased risk of lung cancer among rotating shift work or statistically significant trends for both cumulative years (HR 0.82, 95% CI 0.66 to 1.02; P_{trend} = 0.294) and nights (HR 0.81, 95% CI 0.65 to 1.00; P_{trend} = 0.415). Further analyses imposing 10- and 20-year lag times for disease latency also revealed similar results. Contrary to the initial hypothesis, rotating nighttime shift work appears to be associated with a relatively reduced lung cancer risk although the magnitude of the effect was modest and not statistically significant.

Keywords

Shift Work; Lung Cancer; Textile Workers; Chinese Female; Night shift

INTRODUCTION

With 1.6 million new cases annually, lung cancer is the most common non-skin cancer worldwide and the leading cause of cancer mortality.[1] Tobacco smoke remains the single most influential etiologic factor[2, 3] although 25% of all cases globally occur in never-smokers.[4] Striking differences in epidemiological, clinical and molecular characteristics in never-smokers include female gender, Asian descent, younger age (<40 years), and adenocarcinoma histology.[5]

Historically, cigarette smoking among native Chinese women has been very uncommon (3–5%).[6] A recent study indicated that environmental tobacco smoke accounts for nearly 11% of lung cancer deaths among Chinese non-smoking women.[7] Other known environmental carcinogens include indoor cooking fumes and radon.[8, 9] Occupational exposures to asbestos, chromium, arsenic, and silica are also well-established lung cancer risk factors.[10–12] Furthermore, there is emerging evidence that reproductive and hormonal factors may equally contribute to lung cancer pathogenesis.[13–18] Nonetheless, the etiology of the majority of lung cancer cases in non-smoking women remains unknown.

One possible mechanism by which shift work may increase lung cancer risks involves suppression of melatonin which may have anti-carcinogenic effects. Melatonin is an endogenous hormone synthesized in the pineal gland that exhibits oncostatic activity.[19, 20] There is consistent evidence indicating its effectiveness inhibiting tumor angiogenesis, proliferation and metastasis, and for scavenging free radicals from both animal and *in vitro* models.[21] The rate-limiting step is the catalytic activity of arylalkylamine “N-acetyltransferase (NAT).” The suprachiasmatic nucleus regulates NAT activity and acts as an endogenous oscillator synchronized by light-dark signals via photoreceptors in the eye.[22] Circulating melatonin concentrations are relatively low during daytime, but demonstrate a naturally occurring peak at night (0200–0400).[22] This nocturnal rise was shown to be substantially decreased or even eliminated in animals exposed to constant light.[23] Specifically, external environmental factors such as light at night has shown to alter melatonin secretion.[24] Maladaptation’s can be defined based on the degree of melatonin suppression and phase shifting throughout the body.[25–28]

Maladaptation can result from abnormal day-night sleep patterns typically related to rotating shift work schedules. Shift work is the organization of working time by different continuous sections involving more than the usual 8-hour workday. Its prevalence is consistently rising among industrialized nations in order to maintain increased productivity and economic growth. Occupations in health care, public service, airline, and factory industries commonly employ shift workers. According to a 2000 European Union survey, 76% of the working population was employed during hours beyond the normal daytime work schedule (shift work, compressed work weeks, weekends, irregular work patterns, and split shifts).[29] Nearly 22% of men and 11% of women reported some exposure to night shift work.[29]

Moreover, according to a 2011 Bureau of Labor Statistics report, almost 11% of salaried work included nonstandard work schedules involving approximately 9.4% of male and 11.8% of female employees.[30]

In 2007, the International Agency for Research on Cancer concluded that shift work that involves circadian disruption is a probable human carcinogen.[26] This was based on sufficient evidence from animal models and epidemiological research, primarily focused on breast cancer. However, there is very limited epidemiologic research on shift work and lung cancer risk. Two ecological studies, one that compared lung cancer incidence rates of men in different countries with population-weighted light at night exposure based on several environmental and developmental indicators[31] and a similar study among Israeli women,[32] detected no associations. However, the ecological design is limited by the absence of individual-level data on exposures and potential confounders.

This study was conducted to test the hypothesis that shift work may increase lung cancer risk among a well-characterized cohort of Shanghai female textile workers. The premise was based on this biologic plausibility of melatonin suppression from shift work chronodisruption. Mainly, the purpose of this study was to determine whether there is an increased risk for lung cancer with increased exposure to rotating night shift work.

METHODS

Study Design

Enrollment in the parent study occurred from 1989 to 1991 during an intervention trial for the efficacy of self-breast exam on reducing breast cancer mortality. The cohort included approximately 267,400 female textile workers from 526 factories who were actively employed or retired workers in the “Shanghai Textile Industry Bureau (STIB)” at enrollment and had been born between January 1, 1925 and December 31, 1958. At enrollment, participants completed a baseline questionnaire characterizing demographic data, lifestyle and smoking habits as well as reproductive history.[33, 34]

Cohort Enumeration, Case and Subcohort Ascertainment—Cancer incidence in the parent cohort from 1989 to 1998 was identified through the Cancer and Death Registry maintained by the STIB Station for the Prevention and Treatment of Cancer.[35] Lung cancer diagnosis was confirmed by electronically matching the cohort to the medical records from the “Shanghai Cancer Registry (SCR),” a member of the International Association of Cancer Registries. If the computerized match was not confirmed, then a medical records review was conducted. Cancer incidence from 1999 to 2006 was determined by matching the cohort with the SCR. Lung cancer diagnosis was also confirmed by review of the medical records. A total of 1559 lung cancer cases by “International Classification of Diseases, Ninth revision (ICD-9)” code 162 were identified and confirmed by the tumor and death registry of the STIB and the SCR. Previous analyses of lung cancer risk for the 1989–1998 follow-up focused on dust and chemical exposures. Results of these studies indicated that occupational endotoxin exposures may have had reduced risk for lung cancer.[36–38] A comparison subcohort of 3199 women was randomly selected from the parent cohort frequency matched in 5-year categories to the birth year distribution for all cancer cases.[36]

Study participants were followed from time of enrollment in the original study (January 1, 1989) until the end of the study period (December 31, 2006), the date of lung cancer diagnosis, death, or exit from the STIB. Twenty (20) women in the subcohort were also identified as lung cancer cases. These subjects were included in this study's comparison subcohort and contributed time at risk until date of lung cancer diagnosis.

From the total number of lung cancer cases and the subcohort subjects (n=4738), eleven (11) non-cases and fifty-three (53) cases were excluded due to missing work history. Machinist, wool and sanitation work history excluded fifty (50) more cases and one hundred forty-five (145) non-cases. Exclusions for these work histories were conducted to prevent any misclassifications due to potential endotoxin exposures. Of note, there were four (4) subjects identified as non-cases in this study that were originally excluded for missing endotoxin exposures by Astrakianakas et al.[36] During the follow-up period, endotoxin measurements for these four (4) non-cases were complete and did not meet exclusion criteria. Further exclusions for missing greater than half the shift work history included five (5) cases and three (3) non-cases. There were 4471 total number of subjects remaining for this report's analysis.

Shift Work Exposure Assessment—Each factory had its own history of shift work that was mandated by government policy. Although there were changes in shift work policies over time, these changes have been uniform across factories within the same sector. Trained interviewers collected detailed shift work history for specific jobs by major manufacturing processes. Data for 503 factory profiles were available. Historical shift work profile was fully ascertained for all but three factories. Shift work patterns among three factories (2 textile machinery manufacturing and 1 fabric bleaching and printing factory) involved 11 workers and were estimated from similar factories within that sector. Each subject's work history record was collected through factory personnel record review (80%), supervisor interviews (12%), and in-person employee or close relative interviews (8%). All dates of employment, workshops and job tasks for each occupation held were recorded.

All factory employment records were reviewed and confirmed with a corresponding job exposure matrix based on their entry and end dates.[39] From previous factory visits and review of historical documents, no jobs were exclusively night shift work. The most common shift cycle consisted of two consecutive nights (2200–0600); two consecutive days (0600–1400); then two consecutive evenings (1400–2200). This definition is consistent with the National Institute for Occupational Safety and Health definition of shift work.[40] Therefore, the definition used for night shift exposure is any continuous working hours between the time of 2400 and 0600 and recorded as part of a rotating shift pattern. The basis of this definition is determined by the most probable time of maximum melatonin secretion (approximately 0200). The period of time was restricted to the categorization of ever working night shift (after 2400) as recorded by the shift work data collected. Cumulative number of nights and years of shift work were computed throughout the subject's entire work history.

Statistical Analysis

Cox regression modeling, adapted for the stratified case-cohort design, was used to estimate the relative risk "(hazard ratio [HR])" of lung cancer in relation to dose-response trends of cumulative years and number of night shifts worked.[41] A subject was considered to be at risk from entry into the cohort until a lung cancer diagnosis, death, or end of follow-up on December 31, 2006. Calculations of HRs with 95% confidence intervals included adjustments for age (continuous variable) at the time of the baseline questionnaire, smoking status (ever or never), parity (nulliparous or any parity) and cumulative endotoxin exposure (categorical variable based on approximately equal numbers of cases in 5 strata).[42, 43] Robust variance estimates, incorporating stratum –specific sampling weights for the subcohort, were utilized for calculating standard errors of the hazard ratios.

Risk sets were developed in order to analyze time-dependent exposures. Each risk set consisted of a case and all subcohort women still at risk at the date of the lung cancer diagnosis of the case. Thus, a subcohort subject may have served as a control in multiple risk sets. For each risk set, exposures were computed up to the follow-up time defined by the case in the risk set.

Exposure-response trends were estimated as described by the methods from Langholz and Jiao.[41] Using a group linear model, trend analysis for dose-response of cumulative night shifts or years worked was assessed by comparing median values within each category of the cases for each risk set. Additionally, analyses were performed with 10 and 20-year exposure lag times to account for disease latency. All analyses in the final model were adjusted for age, smoking status, parity, and cumulative endotoxin exposure. The case-cohort risk set construction properly adjusted for length of follow-up. All statistical tests were two-sided and performed with SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Demographic Characteristics

Comparing the cases and non-cases (TABLE I), the average age among the cases (55.7 years) is slightly older than the non-cases (53.2 years). However, both groups appear to have similar proportions of increasing number of cumulative years worked within their respective distributions. As expected, there was a larger percentage of ever smokers among the cases (11.5%) compared to the non-cases (4.6%). As depicted in TABLE II, the prevalence of ever smokers revealed similar distributions among the quartiles of exposures.

Trends for dose-response to cumulative night shift exposure

As shown in TABLES III and IV respectively, years and total number of rotating night shift work were associated with reduced lung cancer risk compared to workers who did not work night shifts; however, trends were modest and not statistically significant unless categorized among the lowest quartiles. Cumulative years of shift work among the lowest exposure quartile (HR=0.76, 95% CI = 0.62 to 0.93; $P_{trend} = 0.294$) and cumulative nights of exposure

(HR=0.74, 95% CI = 0.61 to 0.91; P_{trend} =*0.415*) demonstrated significant moderately reduced risks. These results were similar when exposures were lagged by 10 and 20 years.

DISCUSSION

Contrary to the initial hypothesis, the findings indicate that shiftwork, defined as either number of years or total number of night shifts, was associated with a modestly reduced risk of lung cancer in this cohort, although there was no evidence of inverse dose-response relations. A possible explanation for these observed findings is that the prior hypothesis of increased risk associated with shift work may be more complex than suppression of melatonin alone.

Notably, women in Shanghai play a significant role in the textile and clothing manufacturing industry comprising approximately 40% of the workforce.[37] As a result, parity was considered a potential confounder based on literature supporting its protective effects on lung cancer.[44] Theories involving reproductive and hormonal factors implicate estrogen and estrogen receptors in lung tissue as a plausible effect to lung cancer risk. Circulating estrogens may play a causative role differentiating a more prominent secretory type of lung cancer among females. *In vivo* research has shown that β-estradiol stimulated growth of the non-small cell lung tumor line in SCID mice.[14] Additional studies revealed the expression of mRNA for estrogen receptor α and β *in vitro* cultured human non-small cell lung cancer cells, fibroblasts, and bronchial epithelium linking tumor promotion via receptor-mediated mechanisms.[14, 17] One case-control study demonstrated an increased risk of lung adenocarcinoma (OR=1.7) among women using estrogen replacement therapy.[17, 45] These results suggest that estrogen signaling pathways can play a biological role in lung cancer promotion, either through direct actions on pre-neoplastic or neoplastic cells or indirect actions on lung fibroblasts.

An alternative explanation for the failure to detect any significant and consistent association between lung cancer risk and rotating night shift work might involve probable racial differences in human endogenous circadian suppression, namely melatonin secretion. In one review, it was found that indeed there exists a possible biologic difference in melatonin suppression among Asians. Exposure to both bright unfiltered or filtered light did not seem to suppress nocturnal melatonin levels among Chinese female subjects.[46] Further research discovered that dark eye pigment in Asians had significantly lower melatonin suppression in response to nocturnal light as compared to light eye pigment in Caucasians.[47] Truly, if there are variations in the timing and suppression of melatonin correlated to race or eye pigment, then future consideration may include urine or serum biomarkers for definitive exposures.

Bias can equally influence the results of this analysis. Interviews and surveys can demonstrate a form of information bias; however, covariate information regarding age, smoking, endotoxin exposure and parity were readily available to evaluate for confounding. It is also noteworthy that collection of shift work exposure was based on standardized factory work history and the participant's work records. This would reduce any recall bias typically associated within this study. A more plausible explanation would be the healthy

worker bias among night shift workers. Specifically, particular job descriptions that include night shift work may indeed require a healthier physical profile in order to complete specific tasks. Consequently, the night shift work population would relatively have a decreased risk for lung cancer.

There are several strengths regarding this study. First, this research includes a large, well-defined occupational cohort with detailed work history data and work practices that permitted reconstruction of subjects' shift work history. Secondly, availability of data to include smoking, endotoxin exposure, and reproductive history allow adjustments for any potential confounders in the analysis.

Some limitations should be acknowledged. First, the characteristics of Chinese female textile workers are unique to this study population and lack generalizability to other genders, ethnicities, and occupational histories. Yet, among this population of never smokers, the female Asian descent is a key characteristic in the textile industry and an opportunistic cohort for lung cancer risk.

Second, exposure of night shift work and chronodisruption of the circadian rhythm is used as a surrogate for actual melatonin concentrations in the body. Ascertainment of urinary and serum melatonin biomarkers would prove useful. However, it is reasonable to assume under biologic responses to light-dark cycles that such disruption would occur allowing for decreased melatonin secretion.

Third, exposure status of shift work history was collected as an aggregate at the factory level possibly exposing the data to non-differential misclassification. Although the Shanghai government minimizes this effect by mandating strict factory reporting and uniform shift work policies, individual work schedules would increase internal validity within this study. Similarly, ICD-9 codes are prone to non-differential misclassification if confirmatory data is not available. However, adherence to standardized guidelines under the International Association of Cancer Registries ensures this study's internal validity. Thus obtaining histology type of lung cancer cases should be a goal for future studies.

Lastly, the prevalence of smoking was low in this cohort.[35, 36] It is important to note, however, that smoker status is prone to recall bias and does not account for cumulative exposures of risk. Potential environmental exposures such as second-hand smoke and indoor cooking fumes would be valid covariates for future research. Moreover, all findings did not appreciably differ when adjustments were made with endotoxin exposure, one of the strongest associations to lung cancer risk among this cohort.

CONCLUSIONS

Results from this study provide some insight on one of the most common cancers worldwide for which etiologic factors, other than smoking, are poorly understood. In this study, long-term rotating night shift work appears not to be associated with an increased lung cancer risk. Although these results did not confirm the *a priori* hypothesis of an increased lung cancer risk among rotating night shift workers, there may exist interactions that modify the true association not explored by this study. Research on shift work and lung cancer risk

conducted in other cohorts with different ethnic compositions will be important to clarify potential etiologic relationships.

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References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010
2. Jemal A, Chu KC, Tarone RE. Recent trends in lung cancer mortality in the United States. J Natl Cancer Inst. 2001; 93(4):277–283. [PubMed: 11181774]
3. Giovino GA. The tobacco epidemic in the United States. Am J Prev Med. 2007; 33(6 Suppl):S318–326. [PubMed: 18021906]
4. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55(2):74–108. [PubMed: 15761078]
5. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers--a different disease. Nat Rev Cancer. 2007; 7(10):778–790. [PubMed: 17882278]
6. Chiu YL, Wang XR, Qiu H, Yu IT. Risk factors for lung cancer: a case-control study in Hong Kong women. Cancer Causes Control. 2010; 21(5):777–785. [PubMed: 20084541]
7. Wang JB, Jiang Y, Wei WQ, Yang GH, Qiao YL, Boffetta P. Estimation of cancer incidence and mortality attributable to smoking in China. Cancer Causes Control. 2010; 21(6):959–965. [PubMed: 20217210]
8. Brennan P, Buffler PA, Reynolds P, Wu AH, Wichmann HE, Agudo A, et al. Secondhand smoke exposure in adulthood and risk of lung cancer among never smokers: a pooled analysis of two large studies. Int J Cancer. 2004; 109(1):125–131. [PubMed: 14735478]
9. Nyberg F, Agudo A, Boffetta P, Fortes C, González CA, Pershagen G. A European validation study of smoking and environmental tobacco smoke exposure in nonsmoking lung cancer cases and controls. Cancer Causes Control. 1998; 9(2):173–182. [PubMed: 9578294]
10. Samet JM, Avila-Tang E, Boffetta P, Hannan LM, Olivo-Marston S, Thun MJ, et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clin Cancer Res. 2009; 15(18):5626–5645. [PubMed: 19755391]
11. van Loon AJ, Kant IJ, Swaen GM, Goldbohm RA, Kremer AM, van den Brandt PA. Occupational exposure to carcinogens and risk of lung cancer: results from The Netherlands cohort study. Occup Environ Med. 1997; 54(11):817–824. [PubMed: 9538355]
12. Gottschall EB. Occupational and environmental thoracic malignancies. J Thorac Imaging. 2002; 17(3):189–197. [PubMed: 12082370]
13. Cagle PT, Mody DR, Schwartz MR. Estrogen and progesterone receptors in bronchogenic carcinoma. Cancer Res. 1990; 50(20):6632–6635. [PubMed: 2208126]
14. Stabile LP, Davis AL, Gubish CT, Hopkins TM, Luketich JD, Christie N, et al. Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor alpha and beta

and show biological responses to estrogen. Cancer Res. 2002; 62(7):2141–2150. [PubMed: 11929836]

15. Enmark E, Pelto-Huikko M, Grandien K, Lagercrantz S, Lagercrantz J, Fried G, et al. Human estrogen receptor beta-gene structure, chromosomal localization, and expression pattern. J Clin Endocrinol Metab. 1997; 82(12):4258–4265. [PubMed: 9398750]
16. Kuiper GGJM, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology. 1997; 138(3):863–870. [PubMed: 9048584]
17. Schwartz AG, Prysak GM, Murphy V, Lonardo F, Pass H, Schwartz J, et al. Nuclear estrogen receptor beta in lung cancer: expression and survival differences by sex. Clin Cancer Res. 2005; 11(20):7280–7287. [PubMed: 16243798]
18. Jiang YG, Chen JK, Wu ZL. Promotive effect of diethylstilbestrol on urethan-induced mouse lung tumorigenesis. Chemosphere. 2000; 41(1–2):187–190. [PubMed: 10819200]
19. Cos S, González A, Martínez-Campa C, Mediavilla MD, Alonso-González C, Sánchez-Barceló EJ. Estrogen-signaling pathway: a link between breast cancer and melatonin oncostatic actions. Cancer Detect Prev. 2006; 30(2):118–128. [PubMed: 16647824]
20. Hoang BX, Shaw DG, Pham PT, Levine SA. Neurobiological effects of melatonin as related to cancer. Eur J Cancer Prev. 2007; 16(6):511–516. [PubMed: 18090123]
21. Hardeland R, Reiter RJ, Poeggeler B, Tan DX. The significance of the metabolism of the neurohormone melatonin: antioxidative protection and formation of bioactive substances. Neurosci Biobehav Rev. 1993; 17(3):347–357. [PubMed: 8272286]
22. Brzezinski A. Melatonin in humans. N Engl J Med. 1997; 336(3):186–195. [PubMed: 8988899]
23. Vanecek J. Cellular mechanisms of melatonin action. Physiol Rev. 1998; 78(3):687–721. [PubMed: 9674691]
24. Brainard GC, Sliney D, Hanifin JP, Glickman G, Byrne B, Greeson JM, et al. Sensitivity of the human circadian system to short-wavelength (420-nm) light. J Biol Rhythms. 2008; 23(5):379–386. [PubMed: 18838601]
25. Haus E, Smolensky M. Biological clocks and shift work: circadian dysregulation and potential long-term effects. Cancer Causes Control. 2006; 17(4):489–500. [PubMed: 16596302]
26. Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, et al. Considerations of circadian impact for defining ‘shift work’ in cancer studies: IARC Working Group Report. Occup Environ Med. 2011; 68(2):154–162. [PubMed: 20962033]
27. Hansen J. Increased breast cancer risk among women who work predominantly at night. Epidemiology. 2001; 12(1):74–77. [PubMed: 11138824]
28. Hansen J, Stevens RG. Case-control study of shift-work and breast cancer risk in Danish nurses: Impact of shift systems. Eur J Cancer. 2011
29. Costa G, Haus E, Stevens R. Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. Scand J Work Environ Health. 2010; 36(2):163–179. [PubMed: 20126969]
30. Presser, HB.; Ward, BW. [Accessed May 9, 2013, 2011] Nonstandard work schedules over the life course: a first look [Online]. Available at http://www.stats.bls.gov/opub/mlr/2011/07/art1full.pdf
31. Kloog I, Haim A, Stevens RG, Portnov BA. Global co-distribution of light at night (LAN) and cancers of prostate, colon, and lung in men. Chronobiol Int. 2009; 26(1):108–125. [PubMed: 19142761]
32. Kloog I, Haim A, Stevens RG, Barchana M, Portnov BA. Light at night co-distributes with incident breast but not lung cancer in the female population of Israel. Chronobiol Int. 2008; 25(1): 65–81. [PubMed: 18293150]
33. Thomas DB, Gao DL, Self SG, Allison CJ, Tao Y, Mahloch J, et al. Randomized trial of breast self-examination in Shanghai: methodology and preliminary results. J Natl Cancer Inst. 1997; 89(5):355–365. [PubMed: 9060957]
34. Thomas DB, Gao DL, Ray RM, Wang WW, Allison CJ, Chen FL, et al. Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst. 2002; 94(19):1445–1457. [PubMed: 12359854]

35. Wernli KJ, Ray RM, Gao DL, Thomas DB, Checkoway H. Cancer among women textile workers in Shanghai, China: overall incidence patterns, 1989–1998. Am J Ind Med. 2003; 44(6):595–599. [PubMed: 14635236]
36. Astrakianakis G, Seixas NS, Ray R, Camp JE, Gao DL, Feng Z, et al. Lung cancer risk among female textile workers exposed to endotoxin. J Natl Cancer Inst. 2007; 99(5):357–364. [PubMed: 17341727]
37. Checkoway H, Ray RM, Lundin JI, Astrakianakis G, Seixas NS, Camp JE, et al. Lung cancer and occupational exposures other than cotton dust and endotoxin among women textile workers in Shanghai, China. Occup Environ Med. 2011; 68(6):425–429. [PubMed: 21131604]
38. Astrakianakis G, Seixas NS, Ray R, Camp JE, Gao DL, Feng Z, et al. Re: Lung cancer risk among female textile workers exposed to endotoxin. J Natl Cancer Inst. 2010; 102(12):913–914. [PubMed: 20445162]
39. Wernli KJ, Astrakianakis G, Camp JE, Ray RM, Chang CK, Li GD, et al. Development of a job exposure matrix (JEM) for the textile industry in Shanghai, China. J Occup Environ Hyg. 2006; 3(10):521–529. [PubMed: 16908453]
40. Rosa, RaCM. Plain Language About Shiftwork. Cincinnati, OH: Public Health Service, Centers for Disease Control and Prevention; Jul. 1997
41. Langholz B, Jiao J. Computational methods for case-cohort studies. Computational Statistics & Data Analysis. 2007; 51(8):3737–3748.
42. Astrakianakis G, Seixas NS, Camp JE, Christiani DC, Feng Z, Thomas DB, et al. Modeling, estimation and validation of cotton dust and endotoxin exposures in Chinese textile operations. Ann Occup Hyg. 2006; 50(6):573–582. [PubMed: 16632488]
43. Astrakianakis G, Seixas N, Camp J, Smith TJ, Bartlett K, Checkoway H. Cotton dust and endotoxin levels in three Shanghai textile factories: a comparison of samplers. J Occup Environ Hyg. 2006; 3(8):418–427. [PubMed: 16862712]
44. Paulus JK, Asomaning K, Kraft P, Johnson BE, Lin X, Christiani DC. Parity and risk of lung cancer in women. Am J Epidemiol. 2010; 171(5):557–563. [PubMed: 20123687]
45. Taioli E, Wynder EL. Re: Endocrine factors and adenocarcinoma of the lung in women. J Natl Cancer Inst. 1994; 86(11):869–870. [PubMed: 8182770]
46. Girschik J, Heyworth J, Fritschi L. Re: “Night-Shift Work and Breast Cancer Risk in a Cohort of Chinese Women”. American Journal of Epidemiology. 2010; 172(7):865–U140. [PubMed: 20732936]
47. Higuchi S, Motohashi Y, Ishibashi K, Maeda T. Influence of eye colors of Caucasians and Asians on suppression of melatonin secretion by light. American Journal of Physiology-Regulatory Integrative and Comparative Physiology. 2007; 292(6):R2352–R2356.

TABLE I

Demographic characteristics of cases and the non-cases

Characteristics	Cases (n = 1451)		Non-Cases (n= 3020)	
Age, mean (s.d.)	55.7	(8.3)	53.2	(9.8)
Year of Birth, n (%)				
1925–1929	523	(36.0)	894	(29.6)
1930–1934	486	(33.5)	884	(29.3)
1935–1939	177	(12.2)	340	(11.3)
1940–1944	54	(3.7)	145	(4.8)
1945–1949	88	(6.1)	267	(8.8)
1950–1954	77	(5.3)	303	(10.0)
1955–1958	46	(3.2)	187	(6.2)
Years Worked, n (%)				
<10	33	(2.3)	84	(2.8)
≥ 10 to <20	260	(17.9)	489	(16.2)
≥ 20 to <30	578	(39.8)	1244	(41.2)
≥ 30	580	(40.0)	1203	(39.8)
Smoking status, n (%)				
Never	1284	(88.5)	2880	(95.4)
Ever	167	(11.5)	140	(4.6)
Parity, n (%)				
Nulliparous	78	(5.4)	122	(4.0)
≥ 1 live birth	1373	(94.6)	2898	(96.0)

TABLE II

Prevalence of ever smokers and never-smokers among cases and non-cases

	EVER SMOKERS		NEVER SMOKERS	
Years Shiftwork *Quartiles*	**Cases (n)**	**Non-Cases (n)**	**Cases (n)**	**Non-Cases (n)**
No Lag				
Zero	38	33	373	775
Quartile 1	27	27	232	650
Quartile 2	34	24	227	531
Quartile 3	32	30	227	450
Quartile 4	36	26	225	474
TOTAL	167	140	1284	2880
10-year lag				
Zero	38	33	376	778
Quartile 1	28	27	252	679
Quartile 2	33	25	227	527
Quartile 3	32	29	212	430
Quartile 4	36	26	217	466
TOTAL	167	140	1284	2880
20-year lag				
Zero	38	33	400	813
Quartile 1	38	28	318	781
Quartile 2	28	27	231	520
Quartile 3	33	29	190	358
Quartile 4	30	23	145	408
TOTAL	167	140	1284	2880

TABLE III

Cumulative number years of rotating night shifts in relation to lung cancer risk

Cumulative years	Cases (n)	Non-Cases (n)	HR (95% CI) Crude	HR (95% CI) Adjusted[A]
No Lag				
Zero	411	808	1.0 (ref)	1.0 (ref)
>0 to ≤ 17.1	259	677	0.74 (0.61, 0.90)	0.76 (0.62, 0.93)
17.1 to ≤ 24.9	261	555	0.85 (0.70, 1.04)	0.89 (0.72, 1.09)
24.9 to ≤ 30.6	259	480	0.94 (0.77, 1.15)	0.94 (0.76, 1.17)
>30.6	261	500	0.82 (0.67, 1.00)	0.82 (0.66, 1.02)
P_{trend}			*0.162*	*0.294*
10-year lag				
Zero	414	811	1.0 (ref)	1.0 (ref)
>0 to ≤ 17.1	280	706	0.74 (0.62, 0.90)	0.76 (0.63, 0.93)
17.1 to ≤ 24.9	260	552	0.87 (0.71, 1.05)	0.90 (0.73, 1.10)
24.9 to ≤ 30.6	244	459	0.95 (0.78, 1.17)	0.95 (0.77, 1.18)
>30.6	253	492	0.82 (0.67, 1.00)	0.82 (0.66, 1.03)
P_{trend}			*0.219*	*0.277*
20-year lag				
Zero	438	846	1.0 (ref)	1.0 (ref)
>0 to ≤ 17.1	356	809	0.80 (0.67, 0.94)	0.82 (0.68, 0.98)
17.1 to ≤ 24.9	259	547	0.88 (0.72, 1.06)	0.89 (0.72, 1.09)
24.9 to ≤ 30.6	223	387	0.90 (0.73, 1.10)	0.90 (0.72, 1.12)
>30.6	175	431	0.89 (0.71, 1.12)	0.88 (0.69, 1.12)
P_{trend}			*0.159*	*0.262*

[A] Adjusted for age, smoking, parity, and endotoxin

TABLE IV

Cumulative number nights of rotating night shifts in relation to lung cancer risk

Cumulative nights	Cases (n)	Non-Cases (n)	HR (95% CI) Crude	HR (95% CI) Adjusted[B]
No Lag				
Zero	411	808	1.0 (ref)	1.0 (ref)
>0 to ≤ 1830	260	719	0.72 (0.60, 0.88)	0.74 (0.61, 0.91)
1830 to ≤ 2623	260	537	0.88 (0.72, 1.06)	0.92 (0.75, 1.13)
2623 to ≤ 3480	259	472	0.94 (0.77, 1.14)	0.94 (0.76, 1.17)
>3480	261	484	0.83 (0.67, 1.01)	0.81 (0.65, 1.00)
P_{trend}			*0.180*	*0.415*
10-year lag				
Zero	414	811	1.0 (ref)	1.0 (ref)
>0 to ≤ 1830	282	747	0.74 (0.62, 0.89)	0.74 (0.61, 0.89)
1830 to ≤ 2623	252	519	0.86 (0.71, 1.05)	0.89 (0.72, 1.09)
2623 to ≤ 3480	242	459	0.94 (0.77, 1.15)	0.93 (0.75, 1.16)
>3480	261	484	0.84 (0.68, 1.03)	0.81 (0.65, 1.01)
P_{trend}			*0.197*	*0.474*
20-year lag				
Zero	438	846	1.0 (ref)	1.0 (ref)
>0 to ≤ 1830	346	842	0.77 (0.65, 0.91)	0.79 (0.66, 0.95)
1830 to ≤ 2623	243	488	0.95 (0.78, 1.15)	0.97 (0.79, 1.20)
2623 to ≤ 3480	214	390	0.88 (0.72, 1.09)	0.88 (0.71, 1.10)
>3480	210	454	0.90 (0.72, 1.12)	0.86 (0.68, 1.09)
P_{trend}			*0.105*	*0.322*

[B] Adjusted for age, smoking, parity, and endotoxin