

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

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Abstract

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Background: In 2007, the International Agency for Research on Cancer classified shift work that involves circadian disruption as a probable human carcinogen. Nighttime chronodisruption has been shown to decrease concentrations of melatonin, a presumed antineoplastic hormone. Based on this biologic plausibility, our objective was to investigate an association between night shift work and lung cancer risk among Chinese female textile workers. **Methods:** We conducted a case-cohort study nested within a cohort of 267,400 female textile workers employed by the Shanghai Textile Industry Bureau. Participants were followed for lung cancer incidence from January 1, 1989 through December 31, 2006. The comparison group consisted of a subcohort (n=4807) of non-cases based on a 5-year frequency age-matched to all-cancer cases in the cohort. We examined an association between exposure to cumulative night shift work and lung cancer outcomes (n=1423) adjusting for age, smoking, and parity. Hazard ratios (HRs) using Cox proportional hazards model with robust variance estimated relative risks with 95% confidence intervals (CIs). **Results:** Surprisingly, cumulative years of working rotating night shifts and cumulative nights of rotating shiftwork were both associated with moderately reduced risk of lung cancer risk, although the trends were not statistically significant (P_{trend} of 0.19 and 0.28, respectively). The hazard ratios, adjusted for age and smoking history, for the lowest categories of cumulative years working rotating night shifts (HR = 0.78, 95% CI = 0.64 to 0.95) and cumulative rotating nights worked (HR = 0.79, 95% CI = 0.65 to 0.96) were both statistically significant. Similar results were obtained when exposures were lagged by 20 years to account for disease latency. Parity was not included in the final model as it did not significantly alter the relative risk estimates. **Conclusions:** Long-term rotating nighttime shift work appears to demonstrate a decreased risk of lung cancer among Chinese female textile workers compared to non-exposed although trend was not statistically significant. Further investigation on potential factors not yet measured may elucidate a more definitive association of this effect.

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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 in the development of lung cancer,^{2,3} and yet 25% of all cases globally occur in individuals without a smoking history.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

Smoking among native Chinese women is quite uncommon (3-5%).⁶ A further study revealed second hand or passive smoke was responsible for nearly 11% of lung cancer deaths among Chinese non-smoking women.⁷ Although there are other known carcinogens resulting from certain environmental (e.g. second hand smoke, cooking fumes, and radon)^{8,9} and occupational (e.g. asbestos, chromium, arsenic, and silica)¹⁰⁻¹² exposures, recent research suggests that reproductive and hormonal factors may also contribute to lung tumor genesis.¹³⁻¹⁸ To date, no predominant factor has emerged to explain the major causes of lung cancer arising in never smokers.

Melatonin is a naturally produced cytotoxin that exhibits oncostatic activity.^{19,20} There is consistent evidence indicating its effectiveness to inhibit tumor angiogenesis, proliferation and metastasis, and provide antioxidant action to scavenge free radicals in both animal and *in vitro* models.²¹ Melatonin is mainly secreted by the pineal gland and synthesized from tryptophan through successive steps involving different enzymes.¹⁹ 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 in the body 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 especially light at night is shown to alter the biochemical responses within the body leading to an alteration in melatonin secretion, also known as chronodisruption.²⁴

It is well known that chronodisruption is associated with increased risk of hypertension and coronary heart disease, alterations in lipid, glucose and carbohydrate metabolism, insulin resistance, and melatonin levels.^{25,26} Any particular maladaptation can be defined based on the degree of melatonin suppression and phase shifting throughout the body.²⁷⁻³⁰ There is also epidemiological evidence, albeit not fully consistent, that decreased levels of melatonin among night shift workers are associated

with increased risk of breast and possibly other cancers defining a plausible neuroendocrine pathway.²⁸

Shift work is the organization of working time by different continuous sections to include more than the usual 8-hour workday. Its prevalence is increasing to maintain productivity and economic growth in industrialized nations. 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).²⁶ In general, nearly 22% of men and 11% of women endorsed some exposure to night shift work.²⁶ And according to a 2004 Bureau of Labor Statistics report, almost 15% of salaried work included some nighttime duties, involving approximately 17% of male and 12% of female employees.²⁶

There is growing literature supporting the premise that nighttime dysregulation of melatonin may contribute to cancer promotion. In 2007, the International Agency for Research on Cancer concluded that shift work that involves circadian disruption is a probable human carcinogen.²⁸ This was based on sufficient evidence from animal models but limited epidemiological research, primarily focused on breast cancer outcomes. Currently, there is limited epidemiologic research on lung cancer and night shift work. One study 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 A similar study examined population trends of lung cancer in women in Israel.³² Neither study observed any significant association between light at night and lung cancer; however, individual light at night exposure data were not evaluated. Also, these studies did not adjust for smoking or other potential confounders. Subsequently, we conducted a case-cohort study to examine an association between rotating night shift work and lung cancer risk in a previously enumerated cohort of Shanghai women textile workers.

Methods

Study Design

A case-cohort study of lung cancer and night shift work was designed with identified cases and non-cases nested within a cohort of women employed in the Shanghai Textile Industry Bureau (STIB). Enrollment occurred from 1989 to 1998 during an intervention trial for the efficacy of self-breast exam on reducing breast cancer mortality. The cohort included 267,400 female textile workers from 526 factories who were actively employed or retired at enrollment and had been born between the January 1, 1925 and December 31, 1958. At baseline enrollment, participants completed a questionnaire characterizing demographic data, lifestyle and smoking habits as well as reproductive history. Initially, investigations included occupational exposures and all-cancer incidence patterns.³³

Cohort Enumeration, Case and the Subcohort Ascertainment

Cohort participants in this study were followed from time of enrollment in the original study (January 1, 1989 to December 31, 1998) through the entire follow-up period (January 1, 1999 to December 31, 2006) until date of lung cancer diagnosis, death, or exit from the STIB. Previous studies of lung cancer focusing on dust and chemical exposures have been conducted. Results indicated that endotoxin exposures may reduce risk for lung cancer; whereas, silica and formaldehyde may increase risk.^{34,35} Quality controls were in place during the initial data collection in collaboration with University of Washington and the Fred Hutchinson Cancer Research Center to ensure data integrity.

Cancer incidence from 1989 to 1998 was identified through the Cancer and Death Registry maintained by the STIB Station for the Prevention and Treatment of Cancer. 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 manual records review was conducted. Cancer incidence from 1999 to 2006 was determined by matching the cohort with the SCR. Lung cancer diagnosis was also verified by review of the medical records. A total of 1423 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 SCR. Among these cases, diagnoses were verified by the following data: 563 by histology; 470 by imaging studies; 256 based on cytology or immunological testing; 26 by clinical exams; 4 by death certificate; and 104 verified cases although insufficient medical information was listed.

In this study, the comparison group of non-cases, or the subcohort (n=4807), was defined by the total number of controls originally selected (n=4817) from two different sources: 1) a random sample from the original subcohort (n=3182) set as a 2:1 ratio to breast cancer cases and frequency matched in 5-year categories to the age distribution by birth year of all-cancer cases; plus 2) subjects selected as controls (n=1635) from two prior nested case-control studies based on breast cancer outcomes.^{36,37} From this non-case sample, nineteen (19) subjects were excluded based on missing work history and eight (8) subjects were excluded from missing more than half of the shift work data (Figure 1). Among the remaining non-cases (n=4790), seventeen (17) subjects were also identified as lung cancer cases and only contributed time at risk until date of lung cancer diagnosis. Subsequently, these subjects were included as part of the comparison group, or the subcohort. All factory employment records were reviewed and confirmed with a corresponding job exposure matrix based on their entry and end dates.³⁸

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. Fully trained interviewers collected detailed shift work history for specific jobs by major manufacturing processes per factory. Data for only 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. Subjects recruited for night shift work and the initial breast cancer study worked in 500 out of the 503 factories. Each subject's work history within the Shanghai Textile Industry Bureau (STIB) was collected through factory personnel record review (80%), supervisor interviews (12%), and in-person employee interviews or close relatives (8%). All dates of employment, workshops and job tasks for each occupation held were recorded and validated.

The factory shift work data were linked to each subject's work history data. From previous factory visits, no jobs were exclusively night shift work due to a rotating shift schedule. 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.³⁹ Therefore, our definition of night shift exposure is any continuous working hours between the time of 2400 and 0600 and recorded as part of a rotating shift pattern or any changes of shift policy over time. The basis of our

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 for this study. All shift work data were fully ascertained and reviewed for accuracy by University of Washington occupational epidemiologists in collaboration with the STIB industrial hygienists.

Ethics Approval

The study was approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center (FHCRC), the University of Washington, and the Station for Prevention and Treatment of Cancer of the Shanghai Textile Industry Bureau, in accordance with an assurance filed with the Office for Human Research Protections of the U. S. Department of Health and Human Services. All consents were obtained per FHCRC protocol.

Statistical Analysis

Multivariate analysis using a Cox proportional hazards model was used to estimate the relative risk of lung cancer in relation to dose-response trends of cumulative years and number of night shifts worked. Failure time was defined as time since entry into the cohort until lung cancer diagnosis and a subject was considered to be at risk until diagnosis, death, or end of follow-up on December 31, 2006, whichever came first. Hazard ratios were calculated with 95% confidence intervals adjusting for age (continuous variable) at the time of the baseline questionnaire and smoking status (ever or never) for subjects exposed to night shift work either by cumulative years or nights. Parity (nulliparous or any parity) was added as an additional covariate to the model. Robust variance estimates were utilized for calculating standard errors of the hazard ratios. Based on case-cohort approaches outlined by Kim, Xue and Du,⁴⁰ estimates of statistical power were generated under the assumption that calculations by unmatched case-control methods yield similar results. *A priori* analysis concluded that our sample size had sufficient power (at least 80%) to detect a 10% difference of proportions based on a 0.05 two-sided significance level.

The definition of night shift was considered as any rotating night shift pattern that involved any continuous work schedule between 2400 and 0600 hours. Night shift work was first classified as dichotomous (ever/never). Ever night shift work required at least 12 months of cumulative work

history involving shift work. Cumulative exposures of night shift work during the entire history were categorized into five groups: one that is unexposed (reference) and the four quartiles of exposures based on the distribution of the cases in the exposed group. This analysis was conducted for both cumulative nights and cumulative years worked on a night shift rotation schedule. Note, cumulative nights were calculated by whole number rotating night shift worked within a 24-hour schedule. Whereas, cumulative years worked on rotating night shift was calculated as a fraction of the total number of months per year. Thus, different jobs conducted by a particular worker with multiple night shift exposures can be added to the cumulative number of months per year.

Based on variable periods of risk for each worker, risk sets were developed in order to analyze time-dependent exposures. So, a risk data set included the individually matched case-control risk sets such that each time to failure (date of lung cancer diagnosis of the case) considered all those at risk as controls, or non-cases. Thus, a non-case may have served as a control in multiple risk sets and a potential case may contribute as a non-case if the time to failure has not occurred. Any ties at time to failure were adjusted within the statistical program.

This case-cohort analysis was completed by computational methods designed by 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, 20-year lag times were examined for associations of rotating night shift work and lung cancer diagnosis due to lung cancer's typical long latency period. We determined 20-year lag time analysis by discarding 20 years of night shift exposure of the subcohort; or, in this case, the control group of an identified case. Computation for cases was completed in a similar manner. Initially, statistical analyses were adjusted for potential confounders such as age, smoking history, and parity. All statistical tests were two-sided and were performed with SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

Results

Demographic Characteristics

Comparing the cases and the subcohort (Table 1), the average age among the cases (55.8 years) is older than the subcohort (50.0 years) although the standard deviation is larger in the subcohort group (11.1 years). However, both groups appear to have similar trends of increasing number of cumulative years worked within their respective distributions although cases had proportionally more subjects in the highest category of 30 years or more (35.3%) compared to the subcohort (27.4%). As expected, there is a higher distribution of ever smokers among the cases (11.5%) compared to the subcohort (3.6%). In summary, cases were older, proportionally higher in number of years worked, and more likely to be a smoker compared to the subcohort.

Trends for dose-response to cumulative night shift exposure

At the end of the follow-up period, participants were defined as night shift work exposed based on the pre-set definition of night shift hours (2400-0600). A total of 73 subjects were excluded based on incomplete work history (Figure 1). Crude analysis of the data revealed a reduced risk for lung cancer among cumulative years of shiftwork exposure (Table 2) compared to the non-exposed referent group, especially the lowest quartile group (HR = 0.74, 95% CI = 0.62 to 0.89; $P_{value} < 0.001$) although trend was not statistically significant ($P_{trend} = 0.240$). Similar results were observed with 20-year lag time analysis in the lowest quartile exposure (HR=0.78, 95% CI = 0.67 to 0.93; $P_{value} < 0.001$) with no evidence of a dose-response ($P_{trend} = 0.152$). For cumulative nights of shiftwork exposure (Table 3), there were also reduced risks for lung cancer risk (HR = 0.73, 95% CI = 0.60 to 0.87; $P_{value} < 0.0001$) among the lowest quartile group although trend was not statistically significant ($P_{trend} = 0.239$). Also, the 20-year lag time analysis was also consistent with reduced risks particularly among the lowest quartile group (HR = 0.77, 95% CI = 0.65 to 0.91; $P_{value} < 0.001$) although no signs of trend existed ($P_{trend} = 0.102$). As seen on Tables 4 and 5, adjusted relative risks on smoking and age only demonstrated similar results. Compared to the non-exposed, cumulative years of shift work exposure (Table 4) was associated with reduced lung cancer risk for the lowest quartile group (HR = 0.74, 95% CI = 0.61 to 0.89; $P_{value} = 0.0001$) although trend was not statistically significant ($P_{trend} = 0.19$). Again, reduced risks were observed with 20-year lag time analysis in the lowest quartile exposure (HR = 0.78, 95% CI = 0.66 to 0.92; $P_{value} < 0.001$) with no evidence of a dose-response ($P_{trend} = 0.17$). For cumulative nights of shift work exposure (Table 5), there were also reduced risks for lung cancer risk (HR = 0.72, 95% CI = 0.60 to 0.87; $P_{value} < 0.0001$) among the lowest quartile group although trend was not statistically significant ($P_{trend} = 0.28$). There were consistently similar

results seen for the 20-year lag time analysis (HR = 0.77, 95% CI = 0.65 to 0.91; $P_{value} < 0.001$) with no significant dose-response observed ($P_{trend} = 0.15$). All associations were adjusted for age and smoking. Parity was not included in the final model since it did not significantly alter the relative risk estimates (Tables 6 and 7). Overall, a dose-response was not observed based on trend tests for both cumulative nights and years; and, results were not appreciably different whether a 20-year lag time was evaluated or not. Further, stratified analysis of smoking status (ever vs. never) did not reveal any additional information (Table 8).

Discussion

Among this cohort of Shanghai female textile workers, we found unexpectedly that any exposure to rotating night shift work was associated with a relative decreased risk of lung cancer although no apparent dose-response was concluded. A 20-year lag time analysis did not appreciably change these results even though the effect at a 20-year lag appeared to be less strong. Possible explanations for this inverse relationship may include a more complex immune-mediated interaction between external factors associated with nighttime exposures and lung carcinogenesis.

Women represent an increasing number of laborers in the textile and clothing manufacturing industry, comprising approximately 40% of the workforce.³⁵ Cotton dust exposure has been known to cause adverse non-cancer respiratory effects; yet, numerous occupational cohort studies have consistently revealed an inverse relation to lung cancer risk.^{35,42} The presumption was based on the makeup of endotoxin. The hypothesis was that this heat stable lipopolysaccharide exerted an immune-mediated anti-carcinogenic effect that was protective.^{35,43} Consistent with prior reports, the prevalence of smoking was low in this cohort.^{33,43} Additionally, there was insufficient evidence that occupational exposures to formaldehyde, machine fluids, dyes, solvents, bleaches and finishing agents caused lung cancer within this cohort.^{35,44} Further, the International Agency for Research on Cancer concluded that there is limited evidence that working in the textile industry poses increased risk for cancer.³³ Thus, within these comparison groups, there may be different exposures to other occupational factors such as endotoxin which is known to have protective effects against lung cancer risk. In this study, adjusting for endotoxin was not considered; however, full ascertainment of endotoxin exposure remains an occupational consideration for future research.

Parity was considered as a potential confounder based on literature supporting its protective effects on lung cancer.⁴⁵ However, including this covariate did not significantly change the results of the model. An alternative hypothesis involving reproductive and hormonal factors implicates estrogen and estrogen receptors in lung tissue. 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} 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. One case-control study demonstrated an increased

associated risk of lung adenocarcinoma (OR=1.7) among women using estrogen replacement therapy.⁴⁶ Given these multiple pathways, much additional work is needed to determine mechanistic actions of estrogen on lung tumor genesis and its interaction with other circulating hormones, specifically melatonin.

An alternative explanation of our failure to detect a significant association between lung cancer risk and rotating night shift work may be 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.⁴⁷ 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.⁴⁸ Truly, if there are variations in the timing and suppression of melatonin correlated to race or eye pigment, then future consideration may include biomarkers in urine or serum although race is not factor in this homogenous study population.

Bias can influence the results of this analysis. Interviews and surveys have the potential for information bias; however, covariate information regarding age, smoking, and parity was readily available to evaluate for confounding. It is also worthy to note 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 with this study. Lastly, healthy worker bias may explain the reduced lung cancer risk among night shift workers. Specifically, particular job descriptions that include night shift work may require a healthier physical profile in order to complete necessary tasks compared to non-night shift occupations.

Several strengths in our study include a large, well-defined occupational cohort of highly specific work history and exposure assessment. This well characterized cohort has been studied extensively by researchers from Shanghai, China, the University of Washington, and the Fred Hutchinson Cancer Research Center.^{33,43} Also, detailed shift work on type, schedule times, rotation cycles, and times of shift policy changes allowed us to ascertain a robust exposure classification based on cumulative night shifts.

However, there exist some limitations. First, Chinese female textile workers characteristics are unique to this study population and lack generalizability to other genders, ethnicities, and occupational histories. Second, exposure of night shift work and chronodisruption of the circadian rhythm is used as a surrogate for true melatonin concentrations in the body. Ascertainment of

melatonin urinary and serum biomarkers may prove useful. However, it is plausible to assume under biologic responses to light-dark cycles that such disruption would occur and thus decrease melatonin secretion within this population. Third, exposure status of shift work history was collected as an aggregate at the factory level which may expose the data to non-differential misclassification. Although the Shanghai government minimizes this effect by mandating rigid factory reporting and uniform shift work policies, individual work schedules would increase internal validity in 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 increased the internal validity of this study. Nonetheless, obtaining histology of lung cancer cases should be a goal for future research.

In conclusion, 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 was associated with decreased risk of lung cancer without apparent dose-response. Although these results did not confirm our *a priori* hypothesis of an increased risk among rotating night shift workers, there may exist interactions that modify a true association not explored by this study. Susceptibilities to reproductive factors linked to neuroendocrine chronodisruption not yet measured may elucidate a more definitive association of this effect. Further research is warranted.

Notes

The study data is currently available in SAS 9.1 (SAS Institute Inc., Cary, North Carolina) format and approved by the principal investigator, Dr. Harvey Checkoway PhD MPH, in the University of Washington Department of Environmental and Occupational Health Sciences. I have completed all Institutional Review Board training requirements and approval has been previously obtained by Dr. Harvey Checkoway PhD MPH for shift work studies involving the parent study “Cancer Risk Among Women Textile Workers in China” through National Institute of Health grant (NIH R01CA80180) with approval from the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle. Human subjects’ approval has also previously been obtained both from Fred Hutchinson Cancer Research Center and from Zhong Shan Hospital in Shanghai, China. The authors had full responsibility over the design, analysis and interpretation of the study and any process in the publication of this manuscript.

Table 1. Demographics and characteristics of cases and the subcohort

Characteristics	Case (n = 1423)		Subcohort (n= 4807)*	
Age, mean (s.d.)	55.8	(8.3)	50.0	(11.1)
Year of Birth, n (%)				
1925-1929	506	(35.5)	1095	(22.8)
1930-1934	478	(33.6)	1155	(24.0)
1935-1939	172	(12.1)	513	(10.7)
1940-1944	55	(3.9)	250	(5.2)
1945-1949	92	(6.5)	450	(9.4)
1950-1954	75	(5.3)	627	(13.0)
1955-1958	45	(3.1)	717	(14.9)
Cumulative Years Worked, n (%)				
<10	35	(2.5)	167	(3.5)
≥ 10 to <20	268	(18.8)	1113	(23.1)
≥ 20 to <30	617	(43.4)	2210	(46.0)
≥ 30	503	(35.3)	1317	(27.4)
Smoking status, n (%)				
Never	1259	(88.5)	4632	(96.4)
Ever	164	(11.5)	175	(3.6)
Parity, n (%)				
Nulliparous	78	(5.5)	206	(4.3)
1+ live birth	1345	(94.5)	4601	(95.7)
Cumulative Night Shifts, mean (s.d.)	1827	(1534)	1615	(1417)

**Includes 17 overlapping cases within the subcohort*

Table 2. Cumulative years of rotating night shifts in relation to lung cancer risk (crude)

Cumulative years	Cases n	Subcohort n	HR (95% CI) Crude	<i>P</i> _{value}
Entire employment				
Zero	428	1423	1.0 (ref)	---
>0 to ≤ 16.9	249	1077	0.74 (0.62, 0.89)	<0.001
16.9 to ≤ 24.8	249	942	0.83 (0.69, 1.00)	0.024
24.8 to ≤ 30.5	253	703	0.95 (0.78, 1.11)	0.483
> 30.5	244	662	0.77 (0.63, 0.93)	0.001
<i>P</i> _{trend}				0.240
20-year lag time				
Zero	451	1498	1.0 (ref)	---
>0 to ≤ 16.9	349	1480	0.78 (0.67, 0.93)	<0.001
16.9 to ≤ 24.8	246	771	0.86 (0.72, 1.04)	0.068
24.8 to ≤ 30.5	217	501	0.90 (0.74, 1.10)	0.225
> 30.5	160	557	0.83 (0.66, 1.04)	0.062
<i>P</i> _{trend}				0.152

Table 3. Cumulative number of rotating night shifts in relation to lung cancer risk (crude)

Cumulative nights	Cases n	Subcohort n	HR (95% CI) Crude	<i>P</i> _{value}
Entire employment				
Zero	428	1423	1.0 (ref)	---
>0 to ≤ 1824	248	1210	0.73 (0.60, 0.87)	<0.0001
1824 to ≤ 2610	251	878	0.87 (0.72, 1.05)	0.078
2610 to ≤ 3480	251	686	0.90 (0.75, 1.09)	0.187
> 3480	245	610	0.80 (0.66, 0.97)	0.007
<i>P</i> _{trend}				0.239
20-year lag time				
Zero	451	1498	1.0 (ref)	---
>0 to ≤ 1824	341	1538	0.77 (0.65, 0.91)	<0.001
1824 to ≤ 2610	227	679	0.91 (0.75, 1.10)	0.249
2610 to ≤ 3480	207	518	0.86 (0.71, 1.06)	0.096
> 3480	197	574	0.87 (0.70, 1.07)	0.118
<i>P</i> _{trend}				0.103

Table 4. Cumulative years of rotating night shifts in relation to lung cancer risk (adjusted)

Cumulative years	Cases n	Subcohort n	HR (95% CI) Adjusted*	<i>P</i> _{value}
Entire employment				
Zero	428	1423	1.0 (ref)	---
>0 to ≤ 16.9	249	1077	0.74 (0.61, 0.89)	0.0001
16.9 to ≤ 24.8	249	942	0.83 (0.69, 1.00)	0.019
24.8 to ≤ 30.5	253	703	0.92 (0.76, 1.11)	0.271
> 30.5	244	662	0.78 (0.64, 0.95)	0.003
<i>P</i> _{trend}				0.190
20-year lag time				
Zero	451	1498	1.0 (ref)	---
>0 to ≤ 16.9	349	1480	0.78 (0.66, 0.92)	<0.001
16.9 to ≤ 24.8	246	771	0.84 (0.70, 1.02)	0.038
24.8 to ≤ 30.5	217	501	0.88 (0.72, 1.07)	0.128
> 30.5	160	557	0.84 (0.66, 1.05)	0.069
<i>P</i> _{trend}				0.146

*Adjusted for age and smoking only

Table 5. Cumulative number of rotating night shifts in relation to lung cancer risk (adjusted)

Cumulative nights	Cases n	Subcohort n	HR (95% CI) Adjusted*	<i>P</i> _{value}
Entire employment				
Zero	428	1423	1.0 (ref)	---
>0 to ≤ 1824	248	1210	0.72 (0.60, 0.87)	<0.0001
1824 to ≤ 2610	251	878	0.87 (0.72, 1.05)	0.080
2610 to ≤ 3480	251	686	0.89 (0.73, 1.07)	0.127
> 3480	245	610	0.79 (0.65, 0.96)	0.004
<i>P</i> _{trend}				0.285
20-year lag time				
Zero	451	1498	1.0 (ref)	---
>0 to ≤ 1824	341	1538	0.77 (0.65, 0.91)	<0.001
1824 to ≤ 2610	227	679	0.90 (0.74, 1.09)	0.189
2610 to ≤ 3480	207	518	0.85 (0.69, 1.04)	0.058
> 3480	197	574	0.84 (0.68, 1.05)	0.063
<i>P</i> _{trend}				0.151

*Adjusted for age and smoking only

Table 6. Cumulative years of rotating night shifts in relation to lung cancer risk (adjusted)

Cumulative years	Cases n	Subcohort n	HR (95% CI) Adjusted*	<i>P</i> _{value}
Entire employment				
Zero	428	1423	1.0 (ref)	---
>0 to ≤ 16.9	249	1077	0.73 (0.61, 0.88)	<0.0001
16.9 to ≤ 24.8	249	942	0.83 (0.69, 1.00)	0.021
24.8 to ≤ 30.5	253	703	0.92 (0.76, 1.11)	0.274
> 30.5	244	662	0.78 (0.64, 0.95)	0.003
<i>P</i> _{trend}				0.176
20-year lag time				
Zero	451	1498	1.0 (ref)	---
>0 to ≤ 16.9	349	1480	0.78 (0.66, 0.92)	<0.001
16.9 to ≤ 24.8	246	771	0.85 (0.70, 1.02)	0.039
24.8 to ≤ 30.5	217	501	0.88 (0.72, 1.07)	0.130
> 30.5	160	557	0.84 (0.67, 1.06)	0.073
<i>P</i> _{trend}				0.136

*Adjusted for age, smoking, and parity

Table 7. Cumulative number of rotating night shifts in relation to lung cancer risk (adjusted)

Cumulative nights	Cases n	Subcohort n	HR (95% CI) Adjusted*	<i>P</i> _{value}
Entire employment				
Zero	428	1423	1.0 (ref)	---
>0 to ≤ 1824	248	1210	0.72 (0.60, 0.86)	<0.0001
1824 to ≤ 2610	251	878	0.88 (0.73, 1.06)	0.103
2610 to ≤ 3480	251	686	0.88 (0.73, 1.07)	0.119
> 3480	245	610	0.79 (0.64, 0.96)	0.004
<i>P</i> _{trend}				0.267
20-year lag time				
Zero	451	1498	1.0 (ref)	---
>0 to ≤ 1824	341	1538	0.76 (0.65, 0.90)	<0.001
1824 to ≤ 2610	227	679	0.90 (0.74, 1.09)	0.216
2610 to ≤ 3480	207	518	0.85 (0.69, 1.04)	0.059
> 3480	197	574	0.84 (0.68, 1.05)	0.062
<i>P</i> _{trend}				0.143

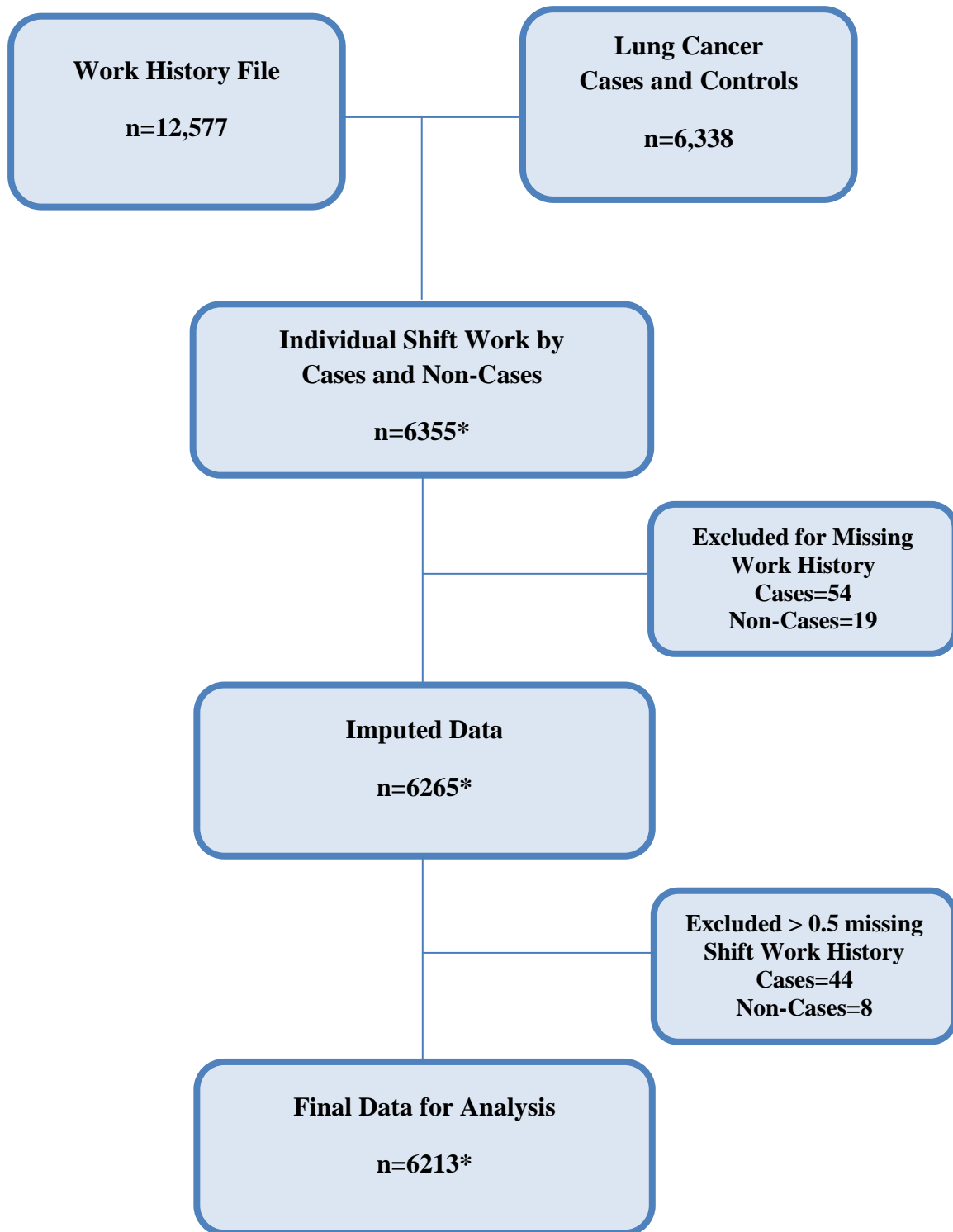
*Adjusted for age, smoking and parity

Table 8. Stratified Analysis of Smoking Status and Hazard Ratios

EXPOSURE	Case n	Subcohort n	EVER SMOKER HR* (95% CI)	NEVER SMOKER HR* (95% CI)
Cumulative Years				
Zero	428	1423	1.0 (ref)	1.0 (ref)
>0 to ≤ 16.9	249	1077	0.63 (0.31, 1.29)	0.75 (0.62, 0.91)
16.9 to ≤ 24.8	249	942	0.81 (0.41, 1.57)	0.83 (0.68, 1.01)
24.8 to ≤ 30.5	253	703	0.72 (0.37, 1.40)	0.95 (0.78, 1.15)
> 30.5	244	662	0.81 (0.41, 1.59)	0.77 (0.63, 0.95)
Cumulative Nights				
Zero	428	1423	1.0 (ref)	1.0 (ref)
>0 to ≤ 1824	248	1210	0.62 (0.30, 1.30)	0.73 (0.61, 0.89)
1824 to ≤ 2610	251	878	0.91 (0.46, 1.79)	0.87 (0.71, 1.05)
2610 to ≤ 3480	251	686	0.74 (0.38, 1.44)	0.90 (0.74, 1.10)
> 3480	245	610	0.71 (0.37, 1.39)	0.80 (0.65, 0.98)

**Adjusted for age*

Figure 1. Schematic of Sample Population after Exclusions



*Total subjects does not include the 17 cases in the subcohort

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