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Reproductive factors and risk of lung cancer in female textile workers in Shanghai, China

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Abstract

Purpose—Hormonal factors may play a role in the development of lung cancer in women. This study examined the relationship between lung cancer and reproductive factors in a large cohort of women, most of whom never smoked (97%).

Methods—A cohort of 267,400 female textile workers in Shanghai, China, enrolled in a trial of breast self-examination provided information on reproductive history, demographic factors and cigarette smoking at enrollment in 1989–91. The cohort was followed until July of 2000 for incidence of lung cancer; 824 cases were identified. Hazard ratios (HR) and 95% confidence intervals (CI) associated with selected reproductive factors were calculated using Cox proportional hazards modeling, adjusting for smoking, age, and also parity when relevant.

Results—Nulliparous women were at increased risk compared to parous women (HR= 1.33, 95% CI 1.00–1.77). Women who had gone through menopause at baseline were at increased risk compared to women of the same age who were still menstruating. Risk was higher in women with a surgical menopause (HR=1.64, 95%CI 0.96–2.79) than in those with a natural menopause (HR=1.35, 95% CI 0.84–2.18), and risk was highest in those postmenopausal women with a hysterectomy and bilateral oophorectomy at baseline (HR=1.39, 95% CI 0.96–2.00), although the risk estimates were not statistically significant.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Conclusions—These results support experimental data that demonstrate a biological role for hormones in lung carcinogenesis.

Background

There is some evidence that gender differences in lung cancer risk may be explained by hormonal factors apart from differences in smoking and environmental factors [1,2]. A higher proportion of lung cancers in women than in men are adenocarcinomas, which are less strongly associated with smoking than other histologic subtypes [1]. Hormone levels fluctuate over a women's reproductive lifetime depending on timing of menarche and menopause, number of pregnancies, lactation, hormone use and other factors. A decreasing trend in risk of lung cancer has been observed with increasing parity in some studies in both Asian [3,4] and Western women [5–7], but others have found no such relationship [8,9]. Older age at first birth or pregnancy has been associated with a decreased lung cancer risk [10,11]. Increased risk of lung cancer has been observed in women who experienced bilateral oophorectomy [9,12,13]. There has generally been inconsistent evidence across studies for relationships to postmenopausal hormone use. The Women's Health Initiative found that combined hormone use (estrogen plus progestin) was associated with increased mortality from lung cancer, but not increased incidence; no increase in either lung cancer mortality or incidence was seen with estrogen use alone [14,15]. Additionally, several studies found no association [16–19] between lung cancer risk and use of hormonal contraceptives, although there is also some evidence of decreased risk [11,20,21].

In the current analysis, we investigate possible relationships between lung cancer risk and selected reproductive factors in a large cohort of female textile workers in Shanghai, China.

Methods

Study Population

Methods for the study have been described in detail elsewhere [22]. Between 1989 and 1991, female workers in 526 textile factories in Shanghai were enrolled in a randomized trial of breast self-examination. The final cohort included 267,400 active and retired workers born between 1925 and 1958 who were followed for cancer incidence and vital status through July, 2000. Specially trained medical workers administered a questionnaire to active and retired textile workers at study enrollment to collect information on their reproductive and contraceptive history, cigarette smoking, and other risk factors. Baseline information was used for analysis and was not updated during the follow-up period.

Outcome Definition

Incident cancer cases were identified through the Shanghai Textile Industry Bureau (STIB) Tumor and Death Registry and periodic reviews of records from the Shanghai Cancer Registry (SCR). For all cancers diagnosed through December 31, 1998, computer matching of the STIB and Shanghai Cancer Registries was performed to confirm diagnoses and medical records were reviewed when records differed, as part of the occupational study of cancers in the cohort. Cases diagnosed from January 1, 1999 to July 31, 2000 were identified only through the STIB registry, but were also included in this analysis because the

number of diagnoses corrected during the matching and record review with SCR was relatively small (~5% for all cancer types combined) [21]. Cohort members contributed person-years from the date of enrollment to date of diagnosis, date of death or last contact, or end of follow-up period (July 31, 2000).

Data Analysis

Cox proportional hazards modeling was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for lung cancer associated with various reproductive factors, while controlling for age, smoking (ever/never) and other potentially confounding variables. Confounding variables were chosen *a priori* based on established associations with lung cancer and plausible biological relationships with reproductive factors of interest. Variables that changed the hazard ratio by more than 10% were retained in final models. Age was adjusted using linear splines with knots at five-year periods, allowing for a change in slope of the relationship between age and cancer at five-year intervals [23]. Trends were estimated by including reproductive factors as continuous variables in final regression models. Several of these variables were ordinal (number of pregnancies and live births, ages at menarche and menopause) and category midpoints were included for others (age at first live birth, duration of breastfeeding and duration of smoking). In several instances, as noted, women in the unexposed group were excluded from trend analyses (nulliparous women, women who did not breastfeed, and never smokers).

Reproductive factors related to pregnancy included ever pregnant, number of live births, age at first live birth and duration of breastfeeding. Factors related to contraception included use of an intrauterine device (IUD) and tubal ligation (ever/never). Reproductive surgical procedures considered were tubal ligation, hysterectomy (ever/never) and oophorectomy (never/one side/two sides/unknown). These procedures often occur together; consequently, combinations were also examined, including hysterectomy or oophorectomy only, both procedures, and by number of ovaries removed. Age at menarche and menopause and type of menopause (natural or surgical) at baseline were also examined. The baseline questionnaire also included information on oral and injectable hormonal contraceptives and induced abortions, and the observed relationships with these factors and the risk of lung cancer have been reported previously [20,21,24].

Six hundred twenty-eight of the lung cancer cases and a randomly selected comparison subcohort of 3,188 textile workers selected from the entire cohort were included in previous studies of lung cancer in relation to endotoxin and other textile industry exposures [25–27] and were included in this analysis to assess possible confounding of the observed associations by occupational factors. Data on occupational exposures are not available for the entire cohort. Cumulative exposure to endotoxin was shown to reduce the risk of lung cancer [25,27] and increased risk for lung cancer was observed for silica and formaldehyde [26]. The latter two exposures were rare with small numbers of exposed cases (n=5 for silica and n=2 for formaldehyde) [26], thus so only endotoxin exposure was evaluated as a confounder. Three of the identified lung cancer cases were among the randomly selected comparison subcohort members and contributed time at risk until their diagnosis date. One subcohort member did not have work history information. Subjects were excluded if they

had unknown endotoxin exposures from jobs in wool processing, metal machining, or sanitation (26 cases and 149 subcohort members). Analyses of the selected reproductive factors was conducted in the subcohort using Cox proportional hazards modeling adapted for the case-cohort design [28] to estimate hazard ratios and 95% confidence intervals using robust variance estimates to compute standard errors [29]. All statistical analyses were completed using SAS 9.3 (SAS Institute, Cary, NC, USA).

The study was approved by the Institutional Review Boards at Fred Hutchinson Cancer Research Center, the University of Washington, and the Station for the Prevention and Treatment of Cancer of the STIB.

Results

The women in the cohort accumulated a total of 2,477,861 person-years of follow-up (mean= 9.3 person-years) and 824 cases of lung cancer were identified. Of the cases diagnosed through 1998, approximately 84% were confirmed by computer matching to the Shanghai Cancer Registry and medical record review. Diagnoses were confirmed histologically (33%) or were based on x-ray and other imaging methods (32%), cytological or immunological testing (16%), clinical records (2%), surgical reports (<1%) or death certificates (<1%). As shown in Table 1, the risk of lung cancer increased with age and duration of smoking. However, only about 3% of the person-years were contributed by smokers, and only 12% of the cases had ever smoked.

Approximately 96% of women reported at baseline that they had ever been pregnant (Table 2). Overall, nulliparous women were at greater increased risk of lung cancer (HR= 1.33, 95% CI 1.00–1.77) than parous women. Women with more than one live birth had marginally lower risks, compared to nulliparous women, but there were no significant trends in risk with numbers of pregnancies or live births among gravid and parous women, respectively. There was little evidence of associations with age at first live birth or duration of breastfeeding. No association was seen with use of an IUD, but a decreased risk of lung cancer was observed in women with a tubal ligation. Adjusting for parity did not change this estimate appreciably. Additionally, prior analyses of this cohort have shown some evidence of decreased risk with ever use of oral contraceptives (RR=0.87, 95%CI 0.69–1.10) and injectable contraceptives (RR=0.61, 95%CI 0.36–1.02), but no association with induced abortion (RR=1.02, 95%CI 0.88–1.18) [20,21,24]. Injectable contraceptive use was rare and could not be evaluated as a confounder, and adjustment for oral contraceptive use did not appreciably change any of the estimates.

There was some suggestion of increasing risk for lung cancer with later age at menarche, but there was no trend when restricted to never smokers. Among ever smokers, there was a significant trend in risk (P=0.03) with increasing age at menarche but the trend was not smooth and none of the point estimates were statistically significant.

The reproductive window, or length of time from age at menarche to age at menopause, did not appear to change the risk of lung cancer. There was some evidence that risk increased with later age at menopause and increased risk of lung cancer was observed among women

who reported being menopausal at baseline, particularly if they had surgical menopause (Table 2). Since earlier age at menopause may indicate surgical menopause, age at natural menopause was examined. Results were similar to when all menopausal women were included. Postmenopausal women who ever had a hysterectomy or an oophorectomy prior to enrollment were at increased risk, particularly when both ovaries were removed. There appeared to be a slightly increasing trend in risk with numbers of ovaries removed among all postmenopausal women and among all postmenopausal women with hysterectomy. No strong associations were seen for hysterectomy only or oophorectomy without hysterectomy, although small numbers of cases limited the statistical precision of these findings.

Restricting the analyses to women who had never smoked did not materially change the results from those observed in the entire cohort. In particular, among never smokers, nulliparous women were at similar increased risk when compared to parous women (HR= 1.28, 95%CI 0.93–1.76) as was ever having an oophorectomy among postmenopausal women (Ever: HR= 1.26, 95% CI 0.90–1.76; Unilateral: HR=0.99, 95% CI 0.52–1.87; Bilateral: HR=1.39, 95% CI 0.94–2.05). Similar decreased risk with tubal ligation (HR= 0.86, 95% CI 0.73–1.01) was also observed in women who had never smoked as in all women combined. Results for the remaining factors were otherwise similar (data not shown).

Controlling for endotoxin exposure did not appreciably change the HRs of lung cancer in relation to any of the reproductive factors of interest in the subcohort. Results for the analyses of parity and reproductive surgeries are shown in Table 3. Notably, the magnitude of the estimates observed in the subcohort is slightly greater for these variables as compared to the results in the entire cohort, but the estimates are also less stable because of the smaller size of the subcohort. For the other reproductive factors, associations with lung cancer were similar in the subcohort and cohort (data not shown).

Discussion

Our findings suggest that altered hormone function and cessation of ovarian function may have influenced the risk of lung cancer in this cohort. There was some suggestion of increased risk for nulliparous women compared to parous women, but there was no trend with increasing parity. No strong associations were observed with age of first live birth, breastfeeding, or IUD use. Some decreased risk was observed with tubal ligation. Increased risk of lung cancer associated with menopause (natural or surgical) and with hysterectomy and bilateral oophorectomy among postmenopausal women was also observed.

A biological role for hormones in lung carcinogenesis is supported by experimental evidence. Estrogen-β and progesterone receptors are present in normal lung tissue and in lung cancer cells [30], and estrogen has been shown *in vitro* and *in vivo* to stimulate the proliferation of non-small cell lung cancer cells while estrogen receptor antagonists inhibit this growth [30–33]. Estrogen-elevating events might then be expected to increase the risk of lung cancer. However, the epidemiological evidence does not fully support this hypothesis. Factors indicative of decreases in hormones such as bilateral oophorectomy, especially at earlier than normal ages, have been found to increase risk as well [9,12].

Mechanisms are likely complex and depend on additional factors, such as duration of exposures, combinations of hormones, and histological subtype of cancer.

Although we did not observe a significant trend in risk with increasing parity, we did observe lower risks in parous than nulliparous women, and most other studies also provide support that childbearing may alter the risk of lung cancer. Studies in Asian women have observed inverse associations and strong decreasing trends in risk of lung cancer in relation to increasing parity. A prospective cohort study of over 35,000 Chinese women in Singapore found a significant decreasing trend in lung cancer risk with increasing parity (RR=0.49 to 0.59, *P* for trend <0.01) with lower risks for adenocarcinomas (RR= 0.32 to 0.42, *P* for trend <0.001) [3]. Another study of over 71,000 non-smoking Chinese women in Shanghai found inverse associations for lung cancer risk with increasing parity (HR=0.79 for 1–3 births, HR=0.45 for >4 births) with a significant trend (*P* <0.01)[4]. One case-control study of Singapore Chinese women also showed reduced risk with increasing parity [34]. However, other case-control studies in China have shown increased risk with parity [35] or no associations [18,36,37], and no association was also observed in a cohort of Japanese women who never smoked [8]. In Western populations, decreased risk of lung cancer with increasing parity has been observed in American women [5– 7], but overall the pattern is less consistent [9,38]. A recent meta-analysis of 11 case-control and 5 cohort studies also found no overall relationship to parity [38], and the results differed little by ethnic group (non-East Asian vs. East Asian). However, there was a weak inverse association with parity when non-small cell lung cancer cases were excluded from the analysis. Although most cases in our cohort were missing histology data, the majority with this information was classified as adenocarcinoma, and our results are thus not inconsistent with those from the meta-analysis. There is a need for additional studies that access the possible relationship of parity to risk for specific histologic types of cancer.

Our findings could indicate an increased risk of lung cancer in nulliparous women, rather than a decreased risk in parous women. This possibility plus the greater risk observed in women who had a surgical or natural menopause at baseline compared to women of the same age who were still menstruating could indicate that ovarian dysfunction, particularly early in reproductive life may results in some hormone imbalance that increase the susceptibility of the pulmonary epithelium to carcinogenesis. These findings for an increased risk of lung cancer in relation to menopause were in agreement with prior studies [9,11,12,15,19]. These observations may reflect use of postmenopausal hormone therapy, which often is prescribed following surgery to counter the sudden decrease in estrogen that occurs [12], but data were not collected on hormone use for this cohort. Other studies have found low percentages of post-menopausal Chinese women with hormone use (4%) [39].

Alternatively, hormonal changes during pregnancy may reduce the risk of lung cancer but the exact mechanism is not completely clear. There is no time during the nine months of pregnancy when an increase in estrogen is not accompanied by an increase in progesterone exposure [40,41]. This pattern is an established mechanism by which pregnancy protects against endometrial cancer [41]. Estrogen has been shown in vitro to stimulate growth of cells from human non-small cell lung tumors [30], and the lack of unopposed estrogen during pregnancy that regularly occurs during menstrual cycles or the overall decline in

circulating estrogens after pregnancy may provide a mechanism for the reduced risk of lung cancer with parity [5].

Similar to this study, other studies have primarily found no relationship between age at first birth and risk of lung cancer [4,5,7,9,12,37,42,43], although both increased risk [6,8,34,36] and decreased risk [10,11] have also been observed. Although there is some interest in the effect of prolonged lactation because it reduces the number of ovulatory cycles [41] and results in very low exposure to estrogen and progesterone [40], no strong association was observed with duration of breastfeeding in this study, in agreement with the few other studies on this factor [8,12].

Another cohort study in Shanghai observed slight decreased risk with ever use of an IUD [17], but we did not find an association in our study. We observed a reduced risk in women who had had a tubal ligation, a common form of sterilization among women in China, but this was not observed in the other Shanghai cohort study [17].

Previous studies in Asian [3,4,8,18,34–37,42,44] and non-Asian populations [5,6,9–12,43,45,46] that have examined age at menarche and age at natural menopause in relation to risk of lung cancer have yielded inconsistent results. We found no clear associations with either of these factors, although we did observe an association with menopausal status. Overall, these results must be interpreted with caution because many of the women classified as still menstruating at baseline subsequently would have gone through the menopause during the follow-up period. The difference between these two ages, a woman's potential reproductive period, has been used as a surrogate for her overall lifetime ovarian hormone exposure. We did not find strong evidence of increased risk with this factor.

There are several important strengths to this study. The cohort is large with prospectively collected outcome information, large numbers of person-years and wide variations in reproductive variables of interest. The prevalence of smoking in this cohort was very low (<3%), giving confidence that the associations observed were unlikely due to uncontrolled confounding by this strong risk factor for lung cancer. However, because of the small percentage of smokers, we were unable to elucidate possible differences in associations between smokers and nonsmokers.

Histology information was missing for most of the lung cancer cases, which precluded assessing histological type specific associations. Also, all reproductive variables were collected at baseline and treated as fixed variables. However, it is unlikely that women in the cohort had more children subsequent to the end of follow-up because most women had been pregnant by the time of enrollment and the one-child-per-family policy in China limited opportunities for additional children. As indicated, many women undoubtedly did go through menopause over the follow-up period and could have obscured a true association between age at menopause and risk of lung cancer.

There are several other environmental exposures common to Chinese women that were not accounted for, such as living with a smoker and heating and cooking practices (coal and wood), that could contribute to increased lung cancer risk [18,47] but these factors are not likely to be associated with the reproductive factors of interest, and therefore unlikely to

have confounded our risk estimates. We also provide evidence that our results are not due to confounding by occupational exposure to endotoxin.

Overall, this study lends support to prior evidence that hormonal factors likely play a role in the risk of women developing lung cancer. In a cohort primarily of women who have never smoked, the strongest evidence was found for factors indicating ovarian dysfunction or cessation, such as nulliparity and surgical menopause. The mechanisms underlying these effects on lung cancer risk may involve either increases or decreases in hormone levels and this may be dependent on timing and duration of exposures and be different for different histologic types of lung cancer. Further study is warranted to more fully elucidate these associations, including differences in associations by smoking status, and their complex underlying mechanisms.

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Table 1

Hazard ratios (HR) for baseline characteristics and lung cancer risk in a cohort of female textile workers, 1989–2000

Characteristic	Person-years at risk	Cases (N=824)	HR	95% CI
Age at baseline (years)[a]				
30–39	946,252	49	1.00	referent
40–49	492,960	67	2.60	(1.80–3.76)
50–59	631,654	345	10.45	(7.75–14.09)
60+	406,995	363	17.18	(12.75–23.15)
Smoking[b]				
Never	2,404,035	723	1.00	referent
Ever (>6 months)	73,478	101	2.19	(1.77–2.70)
Former	11,441	10	1.36	(0.73–2.55)
Current	62,037	91	2.34	(1.88–2.92)
Duration of Smoking (years)[b]				
<10	21,251	13	1.17	(0.67–2.02)
10–19	17,198	18	1.67	(1.05–2.67)
20–29	15,167	21	2.12	(1.37–3.28)
≥30	19,757	49	3.45	(2.57–4.63)
			p trend	0.0002

[a] Adjusted for smoking (ever/never)

[b] Adjusted for age (using linear splines with knots at 5 year periods)

Table 2

Hazard ratios (HR) for reproductive history reported at baseline and lung cancer risk in a cohort of female textile workers, 1989–2000

Reproductive Factor	Person-years at risk	Cases (N=824)	HR[a]	95% CI
Pregnancy				
Never	104,010	42	1.00	referent
Ever	2,373,840	782	0.77	(0.56–1.05)
Number of Pregnancies				
1	426,541	62	1.08	(0.72–1.61)
2	636,989	85	0.70	(0.48–1.02)
3	481,407	149	0.80	(0.56–1.12)
4	362,584	174	0.78	(0.55–1.09)
≥5	466,268	312	0.73	(0.53–1.01)
			p trend*	0.17
Live Birth History				
0 (never pregnant or past pregnancy, no live birth)	121,123	50	1.00	referent
1	1,160,760	112	0.88	(0.61–1.28)
2	407,151	130	0.72	(0.52–1.01)
3	324,115	201	0.80	(0.59–1.10)
4	238,347	156	0.71	(0.51–0.98)
≥5	226,343	175	0.70	(0.51–0.95)
			p trend*	0.15
Age at First Live Birth (years)[a,b]				
<19	118,183	80	1.03	(0.80–1.31)
20–24	691,690	387	1.00	referent
25–29	1,135,467	230	0.92	(0.77–1.10)
30+	411,355	77	0.91	(0.69–1.20)
			p trend	0.29
Duration of Breastfeeding (months)[a,b]				
Never (with live birth)	360,434	69	1.00	referent
<6	331,819	42	0.96	(0.65–1.41)
7–12	686,130	119	1.13	(0.84–1.52)
13–24	369,764	143	1.12	(0.83–1.52)
25–36	238,511	153	1.21	(0.892013;1.65)
37–48	160,534	109	1.11	(0.80–1.55)
≥49	209,525	139	0.87	(0.62–1.21)
			p trend*	0.18
IUD				
Never	1,299,050	675	1.00	referent
Ever	1,178,779	149	1.01	(0.81–1.24)
Tubal Ligation				

Reproductive Factor	Person-years at risk	Cases (N=824)	HR[a]	95% CI
Never	2,023,403	582	1.00	referent
Ever	454,458	242	0.83	(0.72–0.97)
Age at Menarche (years)				
≤13	254,133	60	1.00	referent
14	453,581	107	1.00	(0.73–1.38)
15	550,942	142	0.98	(0.73–1.33)
16	529,477	204	1.22	(0.92–1.63)
≥17	689,107	311	1.16	(0.88–1.53)
			p trend	0.06
Reproductive window (years)				
≤30	195,349	123	1.00	referent
31–33	292,332	206	1.13	(0.90–1.41)
34–36	221,336	153	1.12	(0.88–1.42)
≥37	185,166	126	1.08	(0.84–1.39)
			p trend	0.37
Cause of Menopause				
Premenopausal	1,456,443	121	1.00	referent
Natural	952,215	655	1.35	(0.84–2.18)
Surgical	67,402	48	1.64	(0.96–2.79)
Age at Menopause (years)				
≤48	385,073	235	1.00	referent
49–51	399,116	298	1.22	(1.03–1.46)
≥52	233,042	169	1.16	(0.95–1.42)
			p trend	0.10
Hysterectomy [c]				
Never	947,255	649	1.00	referent
Ever	72,298	54	1.21	(0.91–1.61)
Oophorectomy[c]				
Never	954,705	652	1.00	referent
Ever	56,362	45	1.27	(0.93–1.72)
Unilateral	20,803	13	1.10	(0.63–1.92)
Bilateral	35,558	32	1.35	(0.95–1.93)
Reproductive Surgical Procedure[c,d]				
None	935,048	640	1.00	referent
Hysterectomy only	19,639	12	1.03	(0.57–1.83)
Oophorectomy only	10,290	8	1.14	(0.57–2.30)
Hysterectomy and oophorectomy	46,062	37	1.30	(0.93–1.82)
Hysterectomy and unilateral oophorectomy	13,405	7	1.02	(0.47–2.18)
Hysterectomy and bilateral oophorectomy	32,656	30	1.39	(0.96–2.00)

[a] Adjusted for age (using linear splines with knots at 5 year periods) and smoking (ever/never)

[b] Adjusted for parity

[c] Postmenopausal women only

[d] Excluded subjects missing information for one procedure or for unknown number of ovaries removed

[*] Trend does not include referent group

Table 3

Hazard ratios (HR) for selected reproductive factors reported at baseline and lung cancer risk in subcohort of female textile workers, 1989–1998

Reproductive Factor	Cases (N=602)	Non-cases (N=3035)	MODEL 1 HR (95% CI)[a]		MODEL 2 HR (95% CI)[b]	
Live Birth History						
0 (never pregnant or past pregnancy, no live birth)	33	122	1.00	referent	1.00	referent
1	76	704	0.79	(0.48–1.32)	0.81	(0.48–1.36)
2	93	537	0.69	(0.43–1.11)	0.70	(0.44–1.13)
3	153	608	0.82	(0.53–1.28)	0.84	(0.54–1.32)
4	110	496	0.66	(0.42–1.04)	0.67	(0.43–1.07)
≥5	137	568	0.66	(0.42–1.03)	0.68	(0.43–1.06)
			p trend*	0.24	*p* trend*	0.26
Hysterectomy[c]						
Never	563	2909	1.00	referent	1.00	referent
Ever	38	122	1.26	(0.85–1.85)	1.26	(0.85–1.87)
Oophorectomy[c]						
Never	568	2914	1.00	referent	1.00	referent
Ever	30	101	1.42	(0.92–2.19)	1.39	(0.90–2.16)
Unilateral	6	37	1.14	(0.45–2.88)	1.06	(0.42–2.70)
Bilateral	24	64	1.51	(0.93–2.45)	1.51	(0.92–2.46)

All analyses exclude subjects who ever worked as machinists (n = 114), worked with wool (n = 17), or in sanitation jobs (n = 44)

[a] Adjusted for age at baseline (continuous) and smoking (ever/never)

[b] Adjusted for age at baseline (continuous), smoking (ever/never), and quartile of endotoxin exposure (no lag)

* Trend includes parous women only

[c] Postmenopausal women only