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Reproductive and hormonal factors and the risk of lung cancer: the EAGLE Study

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Abstract

Evidence about the role for reproductive and hormonal factors in the etiology of lung cancer in women is conflicting. To clarify this question, we examined 407 female cases and 499 female controls from the Environment And Genetics in Lung cancer Etiology (EAGLE) population-based case-control study. Subjects were interviewed in person using a computer-assisted personal interview to assess demographics, education, smoking history, medical history, occupational history, reproductive and hormonal factors. Associations of interest were investigated using logistic regression models, adjusted for catchment area and age (matching variables), cigarette smoking (status, pack-years, and time since quitting). Additional confounding variables were investigated but did not substantially affect the results. We observed a reduced risk of lung cancer among women with later age at first live birth (≥31 years: OR=0.57, 95%CI=0.31–1.06, p-trend=0.05), later age at menopause (≥51 years: OR=0.49, 95%CI=0.31–0.79, p-trend=0.003), and longer reproductive periods (≥41 years: OR=0.44, 95%CI=0.25–0.79, p-trend=0.01). A reduced risk was also observed for Hormone Replacement Therapy (OR=0.63, 95%CI=0.42–0.95, p=0.03) and oral contraceptive use (OR=0.67, 95%CI=0.45–1.00, p=0.05), but no trend with duration of use was detected. Menopausal status (both natural and induced) was associated with an augmented risk. No additional associations were identified for other reproductive variables. This study suggests that women who continue to produce estrogens have a lower lung cancer risk. Large studies with great number of never smoking women, biomarkers of estrogen and molecular classification of lung cancer are needed for a more comprehensive view of the association between reproductive factors and lung cancer risk.

Keywords

case-control study; lung cancer; reproductive factors

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INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide. In the last three decades, its risk is dramatically increased in women, for whom is the fourth most common tumor (513,000 cases, 8.5% of all cancers) and the second in number of deaths (427,000 deaths, 12.8% of the total). [1] In contrast, the risk has leveled off or decreased in men. Although different patterns of cigarette smoking over time between the two sexes is likely to account for most of the difference, the hypothesis of a higher female susceptibility to tobacco-related lung cancer has emerged, with conflicting epidemiological results. [2] Still, there is consensus that important biological differences between the sexes exist in non-small-lung cancer risk. In particular, women are more likely to develop adenocarcinomas, and experience younger age at onset. [3] Moreover, a reduced DNA repair capacity has been showed in females tumors compared to men and the hypothesis that estrogens can play a role in lung cancer carcinogenesis has gained attention. [4] Estrogen effects are likely to be mediated by the estrogen receptors (ER) α and β. ERα mRNA are expressed at low levels in the lung, whereas ERβ, the less active in inducing transcriptional activation, has been shown to be expressed in both normal and tumor pulmonary tissue.[5–7] Estrogens could also interact with cigarette smoking by accelerating the metabolism of smoking derived carcinogens.[8]

The first clue of a potential role for estrogens and reproductive factors came from a study of women in China that showed increased lung cancer risk with shorter menstrual cycle length.[9] Afterwards, numerous observational studies examined the relationship between lung cancer and reproductive factors including: parity, age at first live birth, age at menarche, and age at menopause.[10–25] However the findings across studies are far from being consistent. Most studies are small and examined only a few reproductive factors. The three most recent cohort studies, the Shanghai Women's Health Study.[19] the Nurses' Health Study,[24] and the NIH-AARP Diet and Health Study,[10] suggested a possible protective role of endogenous estrogens showing reduced lung cancer risk with later age at menopause[10,19,24] and longer reproductive periods.[19]

In a small hospital-based case-control study, Taioli and Wynder [18], showed a positive association between hormone replacement therapy (HRT) and risk of lung cancer, but most subsequent case-control[12,14,15,26–30] and cohort studies[10,11,13,16,19,24,31–35] did not support this hypothesis. Also investigations on oral contraceptive (OC) use and lung cancer risk failed to show a clear association.[11,12,14–16,18,19,24,28,36,37]

The purpose of our study was to examine whether reproductive or hormonal factors are associated with the risk of lung cancer in a population-based case-control study conducted in Italy, with a relatively large number of female cases and population controls.

MATERIAL AND METHODS

Study population

EAGLE (Environment And Genetics in Lung cancer Etiology) is a population based case-control study primarily designed to investigate the genetic and environmental determinants of lung cancer. The study protocol has been extensively described elsewhere.[38] Incident lung cancer cases (2,100) and 2,120 population controls were enrolled between 2002 and 2005 from a catchment area including 216 municipalities in the Lombardy region of Italy. Lung cancer cases were enrolled in 13 hospitals and population controls were randomly sampled from the catchment area to frequency match the cases by residence, gender, and age. Subjects were 35–79 years at diagnosis or at sampling. Participation rates were 86.6% for cases and 72.4% for controls. Extensive clinical data were collected for lung cancer cases including morphology coded according to the *International Classification of Diseases*

for Oncology, Third Edition.[39] The study was approved by the institutional review boards and all participants signed a written informed consent. Our study population includes the EAGLE females study subjects (448 cases and 500 controls).

Exposure assessment

All cases and controls underwent a Computer Assisted Personal Interview and completed a self-administered questionnaire (both questionnaires are available on the EAGLE website (http://eagle.cancer.gov/). The interview included questions on demographics, education, current and past smoking behavior, environmental tobacco smoke (ETS) at home (during childhood and adulthood) and at the workplace, alcohol consumption, medical history, family history of cancer and occupational history. For women, the questionnaire also included a detailed section on reproductive history. Information on age at menarche, age at menopause, average length of menstrual cycle, age at first pregnancy, number of full term pregnancies, breast-feeding, and history of ovariectomy, and use of oral contraceptives (OC) was recorded. Menopausal women were asked on the type of menopause (natural, or induced by surgery, radiation or chemotherapy), on age at start and duration, and on use of hormone replacement therapy (HRT). No information was collected on type of hormones or dosage. The self-administered questionnaire investigated behavioral aspects related to smoking habits and diet.

Statistical analyses

Odds ratios (ORs), 95% confidence intervals (CI), and tests for trend were calculated using unconditional logistic regression. All models included the matching variables: area (five categories including 5 large cities and their surrounding municipalities) and age (five-year categories). Additional potential confounders or effect modifiers examined in the models were: smoking status (ever/never); pack-years (continuous, mean-centered: linear, quadratic, and cubic terms); time since quitting (0 for never/current smokers, 0.5, 1, 2, 5, 10, 20, ≥30 years),[40] education, body mass index (BMI), and environmental tobacco smoke (ETS) at home (during childhood and/or adulthood) and at work. Risk estimates were little affected by the inclusion of other covariates such as alcohol consumption, occupational exposure to lung carcinogens, personal history of other cancers, and family history of lung cancer, so they were not included in the final model.

Several reproductive characteristics were investigated as independent variables: age at menarche (<13, 13–14, ≥15 years), cycle duration (<27, 27–28, ≥29 days), parity (0, 1, 2, ≥3 live-births), age at first live-birth (<22, 22–25, 26–30, ≥31 years), breastfeeding (ever/never), menopausal status (no, natural menopause, induced menopause), age at menopause (<46, 46–50, ≥51 years), ovariectomy (both ovaries removed yes/no), oral contraceptives (OC) and hormone replacement therapy (HRT) (ever, never, and duration of use in years). We also calculated duration of the reproductive period – time from age at menarche to age at menopause (if in menopause) or from age at menarche to age at diagnosis/enrollment (if not in menopause) – and duration of menopause – time between age at menopause and age at diagnosis/enrollment.

When adequate, we also ran all models including the independent variables as continuous.

To evaluate interaction between reproductive variables and smoking or BMI, we compared the log-likelihood of models with and without product terms.

Multinomial logistic regression models were performed to test the homogeneity of the association between reproductive variables and lung cancer risk across histological types.

All tests were two-sided. Statistical analyses were performed using Stata 11 (Stata Corporation, College Station, TX).

RESULTS

Out of 448 female cases and 500 female controls enrolled in the study, interviews or questionnaire information were available for 407 cases (90.8%) and 499 controls (99.8%) (Table 1). Cases and controls did not differ for residential area, and age (the effect of matching), education, environmental tobacco smoke, or alcohol consumption, and occupational exposure to known (list A) or suspected (list B) lung carcinogens according to the International Agency for Research on Cancer (IARC) evaluations.[40] Almost half of the cases (46%) were current smokers compared with 21% of the controls; cases had smoked a greater number of cigarettes. The proportion of subjects underweight was higher among cases and that of obese higher in controls. Cases had a higher frequency of primary cancer other than lung cancer and reported more frequently a positive family history of lung cancer. As expected, the majority of lung cancers were adenocarcinomas.

Table 2 shows associations between lung cancer and each exposure variable. After adjusting for area, age and smoking, reduced risk of lung cancer was observed among women with later age at first live birth (OR=0.57; 95% CI 0.31–1.06 for ≥31 vs. <22 years, p-trend=0.05), later age at menopause (OR=0.49; 95% CI 0.31–0.79 for ≥51 vs. <46 years, p-trend=0.003), and longer reproductive duration (OR=0.44; 95% CI 0.25–0.79 for ≥41 vs. <33 years, p-trend=0.01). Menopausal status (both natural and induced) was associated with an augmented risk which increased with menopause duration (p-trend=0.002); exclusion of women who declared to be in surgical menopause but not to have undergone bilateral ovariectomy (thus, potentially, maintaining their ovarian function unaltered) did not substantially modify the effect estimates (i.e. about 5%, data not shown).

Hormone replacement therapy and the use of oral contraceptives were associated with a reduced lung cancer risk (OR=0.63; 95% CI: 0.42–0.95 and OR=0.67; 95 CI%: 0.45–1.00, respectively). The risk did not substantially change among women with longer duration of HRT or OC use.

Lung cancer risk was not associated with age at menarche, cycle duration, breastfeeding and parity.

Further adjustment for passive smoking, education, and BMI did not substantially change the risk estimates of each exposure variable.

We also examined the results separately for never and ever smokers (current and former) and we found no evidence of interaction between the reproductive variables and smoking status. Although based on small numbers, the direction of the associations was similar in the two groups for most of the examined variables (Table S1; Supplementary).

Since the residual sources of estrogen production in menopausal women are related to the production of estrone from androstenedione in adipose tissue, the risks for menopause status and menopause duration were separately examined for women with BMI < 25 and ≥ 25. OR estimates did not differ (p for interaction = 0.68 and 0.93, respectively; Table S2; Supplementary)

We also examined the increasing risk of lung cancer with menopause duration separately in never and ever users of HRT: the pattern of increasing risk did not differ (p for interaction = 0.33; Table S3; Supplementary). In the same way, when we considered lung cancer risk for

reproductive duration stratified by OC use (ever, never) a similar decreasing risk was observed in the two groups (p for interaction =0.79).

Similar OR patterns were observed across histological types (adenocarcinoma versus other morphologies, Table 3).

DISCUSSION

In a population-based case-control study conducted in Italy (EAGLE), endogenous hormones during premenopausal years appear to have a protective role in lung cancer development. Specifically, we found a reduced risk of lung cancer with later age at menopause (and, correspondingly, increasing risk with menopause), later age at first live birth and longer reproductive period. These findings were consistent across the major lung cancer histology groups. In contrast, lung cancer risk was not associated with age at menarche, cycle duration, breastfeeding or parity. These findings suggest a complex pattern of hormone-related factors in association with lung cancer risk.

Our results on the protective effect of later menopause or longer reproductive periods, support previous findings from large prospective studies (the Nurses' Health study and the NIH-AARP Diet and Health Study, respectively),[24,10] which found increased risk of lung cancer with younger age at menopause. Similarly, a prospective study in lifetime nonsmokers Chinese women showed an inverse association between age at menopause and the risk of lung cancer.[19] Similar results, although not statistically significant, were observed in three case-control studies from Canada,[25] Czechoslovakia,[21] and China.[41] However, other studies showed positive associations with lung cancer risk[9,18,20,22] or null results.[12–16]

Age at first live birth was not associated with lung cancer risk in most studies.[13–15,17–19,25] A few [2422] reported an increased risk with older age at first live birth, while others [11,12] reported an inverse association.

The only study which examined the length of the reproductive period[19] showed a pattern consistent with ours.

The use of OC and HRT in our population was associated with a reduced lung cancer risk, however no trend in risk was found with increasing duration of use. Observational studies that investigated the association between HRT and lung cancer risk have shown mixed results. After the increased risk reported by Taioli et al.[18], only one study found a doubled risk limited to induced menopausal women treated with HRT.[13] No effect,[11,14,16,19,24,28,33] or reduced risk were found in other studies.[12,15,29,30,34,42] A recent review of 18 studies (15 observational studies and 3 randomized clinical trials) found mixed results,[43] however the authors cautioned the interpretation of these findings since most studies did not report smoking status and HRT type. The findings of another meta-analysis of 11 studies published between 1968 and April 2008 (8 case-control studies and 3 cohort studies)[44] do not support the hypothesis of an association between HRT and lung cancer risk. Slatore et al.[35] examined a large cohort of menopausal women and found that the use of combined (estrogen + progestin) hormone therapy was associated with an increased risk of lung cancer in a duration-dependent manner with a 50% increase in women using HRT for a period longer than ten years. In the Women's Health Initiative randomized controlled trial study, the use of estrogen alone was not associated with increased incidence or mortality from lung cancer[32] whereas estrogen plus progestin therapy was associated with an increased mortality, but not incidence, from lung cancer.[31] In our study population we did not collect information on HRT type and therefore cannot address this issue.

With regard to oral contraceptive use, most observational studies found no association with lung cancer risk.[11,14–16,18,19,24,28] Kreuzer et al.[12] observed a reduction in lung cancer risk, but no trend in risk with increasing duration as in our study. On the contrary, in the Nurses' Health Study[24] duration of OC use longer than 5 years was associated with a slightly increased risk. Two other large cohort studies in UK, the Royal College of General Practitioners cohort study and the Oxford FPA cohort study, compared long-term mortality in ever *versus* never-users of OC and did not find major differences across the two groups.[36,37]

We found no association with cycle duration, breastfeeding or parity. These findings appear in contrast with the quite consistent pattern of an inverse association of estrogen-related variables with lung cancer risk in our study. A possible explanation is that reproductive factors may not be consistently associated with estrogen levels. A recent study in premenopausal women reported no association between 15 different estrogens measured in the urine and age at menarche, OC use, parity, or breastfeeding [45], but showed a significant association with menstrual cycle length and regularity and age at first birth. This suggests a complex association between estrogen levels and reproductive factors. Moreover, the effects of these hormones are likely to be tissue-specific, as the different patterns of association between breast and lung cancer risk seem to indicate[46].

Studies on the role of estrogen receptor (ER) expression in lung cancer have been inconclusive with high levels of ER expression in some studies, but very low levels in others.[47,48] Schwartz et al.[15] found that postmenopausal hormone use was associated with reduced lung cancer risk only in non-small cell lung cancers characterized as ER α and/or β positive. In addition, Chleboswski et al.[32] hypothesized that the stimulation of estrogen receptor alone is not sufficient to increase lung cancer growth but stimulation of progesterone receptor is also needed. Additional evidences suggest that estrogens can interact with growth factors, in particular Epidermal Growth Factor (EGF). Although EGF is known to be involved in cell growth, protection from apoptosis and angiogenesis, it is possible that ER and EGF pathways are alternatively activated, since EGFR protein expression was shown to be down-regulated in response to estrogens.[49] It is also possible that specific subgroups of lung cancer may be differentially associated with estrogens, as it appears for ER positive vs. ER negative or basal-like breast cancer types. [50] Our results were consistent across histology groups of lung cancer, but more subtle, molecularly-related subgroups may be present and account for some of these differences.

Moreover, different study designs, modest sample sizes, and populations with different ethnicities, life styles, diet or proportion of smokers could have contributed to the disparate findings across the studies. Our study is a population-based case-control investigation conducted in Caucasians, with life style and diet typical of a Western population. Confounding by smoking is often raised as a possible explanation of the inconsistent findings. Although the analyses in never smoking women in our study were limited by the small sample size, EAGLE benefitted from comprehensive and detailed data on smoking, which allowed for tight adjustment by smoking status, intensity, duration and time since quitting. Although residual confounding by smoking can never be completely ruled out, it is unlikely that smoking can substantially explain our results.

Additional strengths of our study were a quite large sample size as a whole, the high participation rates, which reduces the likelihood of selection bias, and the detailed and comprehensive assessment of reproductive factors and major confounding variables. Study limitations include lack of data on hormone therapy type. In addition, analyses by smoking status were limited by the small number of cases in each category.

In conclusion, in a population-based study of lung cancer, we found that women who continue to produce endogenous hormones have a lower lung cancer risk. Larger studies (or pooled datasets) with rigorously defined reproductive variables, large number of never smoking women, biomarkers of estrogen and molecular classification of lung cancer are needed for a more comprehensive view of the association between reproductive factors and lung cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

EAGLE	Environment And Genetics in Lung cancer Etiology
OR	Odds ratio
CI	Confidence Interval
ER	estrogen receptor
HRT	hormone replacement therapy
OC	oral contraceptives
ETS	environmental tobacco smoke
BMI	body mass index
EGF	epidermal growth factor

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Novelty and impact of the work

The EAGLE population-based case-control study finds a consistent pattern of reduced lung cancer risk among women with later age at first live birth, at menopause, and longer reproductive period. Together with recent reports from large cohort studies, our study supports that women who continue to produce estrogens have a lower lung cancer risk.

Table 1

Distribution of Selected Characteristics for Cases and Controls, EAGLE Study (2002 – 2005) [a]

	Cases (n = 407)		Controls (n = 499)	
	N	**%**	**N**	**%**
Area				
MI	289	*71.0*	349	*69.9*
MZ	24	*5.9*	23	*4.6*
BS	47	*11.6*	53	*10.6*
PV	21	*5.2*	37	*7.4*
VA	26	*6.4*	37	*7.4*
	p = 0.55			
Age at Study [mean (SD)]	65 (10)		64 (10)	
	p = 0.31			
Education				
None/Elementary	149	*36.6*	167	*33.5*
Middle	135	*33.2*	158	*31.7*
High/University	123	*30.2*	174	*34.9*
	p = 0.32			
Smoking Status				
Never	104	*25.6*	282	*56.5*
Former	116	*28.5*	110	*22.0*
Current	187	*46.0*	107	*21.4*
	p < 0.001			
Pack/Years [mean (SD)]	32.6 (21.1)		16.4 (16.4)	
	p < 0.001			
Years Since Quitting [mean (SD)]	11 (10)		18 (13)	
	p < 0.001			
ETS Home (Child)				
Never	125	*30.7*	158	*31.7*
Ever	277	*68.1*	334	*66.9*
Missing	5	*1.2*	7	*1.4*

	Cases (n = 407)		Controls (n = 499)	
	N	**%**	**N**	**%**
		p = 0.74		
ETS Home (Adult)				
Never	96	*23.6*	145	*29.1*
Ever	268	*65.9*	327	*65.5*
Missing	43	*10.6*	27	*5.4*
		p = 0.17		
ETS Work				
Never	186	*45.7*	219	*43.9*
Ever	215	*52.8*	270	*54.1*
Missing	6	*1.5*	10	*2.0*
		p = 0.63		
BMI				
Underweight (<20)	61	*15.0*	46	*9.2*
Normal (≥20)	170	*41.8*	237	*47.5*
Overweight (≥25)	135	*33.2*	141	*28.3*
Obese (≥30)	41	*10.1*	75	*15.0*
		p = 0.003		
Alcohol Consumption				
Never	57	*14.0*	58	*11.6*
Former	18	*4.4*	33	*6.6*
Current	316	*77.6*	401	*80.4*
Missing	16	*3.9*	7	*1.4*
		p = 0.23		
Occupational Exposure				
No	379	*93.1*	471	*94.4*
List A	3	*0.7*	2	*0.4*
List B	24	*5.9*	26	*5.2*
Missing	1	*0.3*	0	-
		p = 0.70		
Other Cancers				

	Cases (n = 407)		Controls (n = 499)	
	N	**%**	**N**	**%**
No	337	*82.8*	448	*89.8*
Yes	70	*17.2*	51	*10.2*
		p = 0.002		
Family History of Lung Cancer				
No	282	*69.3*	395	*79.2*
Yes	74	*18.2*	56	*11.2*
Missing	51	*12.5*	48	*9.6*
		p = 0.001		
Histological Type				
ADK	221	*54.3*		
Squamous	45	*11.1*		
Large Cells	28	*6.9*		
NSCLS, NOS	34	*8.4*		
SCLC	38	*9.3*		
Others	26	*6.4*		
NA	15	*3.7*		

[a]Percentages may not add to 100.0 because of rounding;

ETS = Environmental Tobacco Smoking;

p = Pearson's chi-squared/Fisher's exact test for categorical variables, and t-test for continuous variables, after excluding subjects without available information.

Table 2

Adjusted Odds Ratios (OR) and 95% Confidence Intervals (95%CI) for Lung Cancer by Reproductive and Hormonal Factors [a]

	Cases (n = 407)		Controls (n = 499)		Model 1*			Model 2**		
	N	%	N	%	OR	95% CI	p [b]	OR	95% CI	p [b]
Age at Menarche										
< 13	179	*44.0*	209	*41.9*	1			1		
13 – 14	157	*38.6*	215	*43.1*	0.82	(0.59 – 1.15)		0.82	(0.58 – 1.18)	
≥ 15	62	*15.2*	67	*13.4*	1.08	(0.67 – 1.73)	*0.85*	1.10	(0.66 – 1.82)	*0.90*
Missing	9	*2.2*	8	*1.6*						
Continuous					0.99	(0.90 – 1.08)	*0.77*	0.98	(0.89 – 1.09)	*0.73*
Cycle Duration (Days)										
< 27	83	*20.4*	119	*23.9*	1			1		
27 – 28	234	*57.5*	292	*58.5*	1.07	(0.73 – 1.56)		1.25	(0.83 – 1.89)	
≥ 29	79	*19.4*	78	*15.6*	1.38	(0.85 – 2.24)	*0.20*	1.53	(0.91 – 2.56)	*0.10*
Missing	11	*2.7*	10	*2.0*						
Continuous					1.04	(0.99 – 1.09)	*0.14*	1.05	(1.00 – 1.10)	*0.08*
Parity (Number of Livebirths)										
0	78	*19.2*	88	*17.6*	1			1		
1	112	*27.5*	117	*23.5*	1.29	(0.80 – 2.06)		1.33	(0.78 – 2.29)	
2	148	*36.4*	205	*41.1*	1.28	(0.82 – 1.99)		1.33	(0.79 – 2.22)	
≥3	69	*17.0*	89	*17.8*	1.07	(0.64 – 1.80)	*0.74*	1.23	(0.67 – 2.24)	*0.57*
Continuous					1.03	(0.91 – 1.18)	*0.63*	1.07	(0.92 – 1.24)	*0.40*
Age at 1st Livebirth										
< 22	67	*20.4*	52	*12.7*	1			1		
22 – 25	103	*31.3*	122	*29.7*	0.92	(0.54 – 1.56)		0.95	(0.54 – 1.65)	
26 – 30	116	*35.3*	165	*40.2*	0.77	(0.46 – 1.29)		0.73	(0.42 – 1.27)	
≥ 31	41	*12.5*	70	*17.0*	0.57	(0.31 – 1.06)	*0.05*	0.52	(0.26 – 1.01)	*0.03*
Missing	2	*0.6*	2	*0.5*						
Continuous					0.95	(0.92 – 0.99)	*0.01*	0.95	(0.91 – 0.99)	*0.01*
Breastfeeding										
Never	78	*23.7*	94	*22.9*	1			1		

	Cases (n = 407)		Controls (n = 499)		Model 1*			Model 2**		
	N	%	N	%	OR	95% CI	p b	OR	95% CI	p b
Ever	248	*75.4*	316	*76.9*	1.00	(0.67 – 1.50)	*0.99*	0.98	(0.64 – 1.49)	*0.92*
Missing	3	*0.9*	1	*0.2*						
Menopause Status										
Premenopausal	38	*9.3*	64	*12.8*	1			1		
Natural Menopausal	285	*70.0*	336	*67.3*	2.06	(0.84 – 5.08)	*0.12*	2.50	(0.97 – 6.45)	*0.06*
Induced Menopausal	83	*20.4*	98	*19.6*	2.58	(1.02 – 6.56)	*0.05*	2.87	(1.08 – 7.66)	*0.04*
Missing	1	*0.3*	1	*0.2*						
Age at Menopause										
< 46	95	*25.8*	78	*18.0*	1			1		
46 – 50	124	*33.6*	144	*33.2*	0.65	(0.41 – 1.02)		0.70	(0.43 – 1.14)	
≥ 51	90	*24.4*	168	*38.7*	0.49	(0.31 – 0.79)	*0.003*	0.51	(0.31 – 0.84)	*0.01*
Missing	60	*16.3*	44	*10.1*						
Continuous					0.96	(0.93 – 0.99)	*0.003*	0.96	(0.93 – 0.99)	*0.01*
Ovariectomy										
No	363	*89.2*	442	*88.6*	1			1		
Yes	44	*10.8*	57	*11.4*	1.08	(0.67 – 1.74)	*0.76*	1.03	(0.62 – 1.71)	*0.91*
Reproductive Duration										
< 33	107	*26.3*	102	*20.4*	1			1		
33 – 36	98	*24.1*	106	*21.2*	0.77	(0.48 – 1.24)		0.84	(0.51 – 1.40)	
37 – 40	98	*24.1*	158	*31.7*	0.67	(0.43 – 1.06)		0.76	(0.47 – 1.25)	
≥ 41	41	*10.1*	84	*16.8*	0.44	(0.25 – 0.79)	*0.01*	0.46	(0.25 – 0.85)	*0.02*
Missing	63	*15.5*	49	*9.8*						
Continuous					0.96	(0.93 – 0.98)	*0.002*	0.96	(0.93 – 0.99)	*0.01*
Menopause Duration										
< 10	65	*17.6*	105	*24.2*	1			1		
10 – 17	77	*20.9*	103	*23.7*	1.50	(0.75 – 3.02)		1.42	(0.67 – 3.03)	
18 – 24	68	*18.4*	92	*21.2*	1.90	(0.84 – 4.29)		1.80	(0.75 – 4.32)	
≥ 25	99	*26.8*	90	*20.7*	3.74	(1.56 – 8.97)	*0.002*	3.69	(1.43 – 9.48)	*0.003*
Missing	60	*16.3*	44	*10.1*						
Continuous					1.05	(1.02 – 1.08)	*0.001*	1.06	(1.02 – 1.09)	*0.001*

	Cases (n = 407)		Controls (n = 499)		Model 1*			Model 2**		
	N	%	N	%	OR	95% CI	p b	OR	95% CI	p b
HRT c										
Never	305	*82.7*	322	*74.2*	1			1		
Ever	63	*17.1*	112	*25.8*	0.63	(0.42 – 0.95)	*0.03*	0.61	(0.39 – 0.95)	*0.03*
Missing	1	0.3	0	-						
HRT Duration c										
Never Users	305	*74.9*	322	*64.5*	1			1		
< 4	32	*7.9*	58	*11.6*	0.58	(0.34 – 0.99)		0.53	(0.29 – 0.94)	
≥ 4	29	*7.1*	51	*10.2*	0.70	(0.39 – 1.24)	*0.07*	0.75	(0.40 – 1.37)	*0.11*
Missing	41	*10.1*	68	*13.6*						
Continuous					0.97	(0.92 – 1.02)	*0.24*	0.97	(0.92 – 1.03)	*0.33*
OC										
Never	306	*75.2*	367	*73.6*	1			1		
Ever	101	*24.8*	132	*26.5*	0.67	(0.45 – 1.00)	*0.05*	0.60	(0.39 – 0.93)	*0.02*
OC Duration										
Never Users	306	*75.2*	367	*73.6*	1			1		
< 2	41	*10.1*	61	*12.2*	0.57	(0.33 – 0.96)		0.49	(0.28 – 0.87)	
≥ 2	49	*12.0*	61	*12.2*	0.72	(0.43 – 1.22)	*0.10*	0.71	(0.41 – 1.26)	*0.09*
Missing	11	*2.7*	10	*2.0*						
Continuous					0.98	(0.92 – 1.03)	*0.39*	0.98	(0.93 – 1.04)	*0.54*
HRT/OC Combined										
HRT Never/OC Never	253	*62.2*	259	*51.9*	1			1		
HRT Ever/OC Never	42	*10.3*	82	*16.4*	0.49	(0.30 – 0.80)	*0.004*	0.45	(0.26 – 0.76)	*0.003*
HRT Never/OC Ever	52	*12.8*	63	*12.6*	0.44	(0.26 – 0.75)	*0.002*	0.38	(0.21 – 0.67)	*0.001*
HRT Ever/OC Ever	21	*5.2*	30	*6.0*	0.60	(0.29 – 1.26)	*0.18*	0.59	(0.27 – 1.31)	*0.20*
Missing	39	*9.6*	65	*13.0*						

[a] Percentages may not add to 100.0 because of rounding.

[b] For ordinal variables, test for trend was performed.

[c] In menopausal women only.

HRT = Hormone Replacement Therapy.

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OC = Oral Contraceptives.

* **Model 1**: adjusted for area, age at study, smoking (ever/never, pack-years, time since quitting).

** **Model 2**: adjusted for area, age at study, smoking (ever/never, pack-years, time since quitting), ETS, education, BMI.

Table 3

Adjusted Odds Ratios (OR) and 95% Confidence Intervals (95%CI) for Lung Cancer by Histological Type [a]

	Cases		Model 2**		
	N	%	OR	95% CI	p [b]
Age at Menopause					
Adenocarcinoma					
< 46	49	*22.2*	1		
46 – 50	61	*27.6*	0.64	(0.37 – 1.10)	
≥ 51	50	*22.6*	0.50	(0.28 – 0.88)	*0.02*
Missing	61	*27.6*			
Other Cancers					
< 46	46	*24.7*	1		
46 – 50	63	*33.9*	0.81	(0.43 – 1.52)	
≥ 51	40	*21.5*	0.52	(0.27 – 1.01)	*0.05*
Missing	37	*19.9*			
Test for homogeneity					*0.71*
Menopause Status					
Adenocarcinoma					
Premenopausal	28	*12.7*	1		
Natural Menopausal	142	*64.3*	1.81	(0.66 – 5.02)	*0.25*
Induced Menopausal	50	*22.6*	2.42	(0.85 – 6.90)	*0.10*
Missing	1	*0.5*			
Other Cancers					
Premenopausal	10	*5.4*	1		
Natural Menopausal	143	*76.9*	5.87	(1.28 – 26.96)	*0.02*
Induced Menopausal	33	*17.7*	5.28	(1.10 – 25.41)	*0.04*
Missing	0	-			
Test for homogeneity					*0.17*
Age at 1st Livebirth					
Adenocarcinoma					
< 22	35	*15.8*	1		

	Cases		Model 2**		
	N	%	OR	95% CI	p b
22 – 25	57	*25.8*	0.93	(0.50 – 1.73)	
26 – 30	69	*31.2*	0.73	(0.39 – 1.34)	
≥ 31	20	*9.1*	0.41	(0.18 – 0.90)	*0.02*
Missing	40	*18.1*			
Other Cancers					
< 22	32	*17.2*	1		
22 – 25	46	*24.7*	0.89	(0.43 – 1.83)	
26 – 30	47	*25.3*	0.71	(0.35 – 1.44)	
≥ 31	21	*11.3*	0.67	(0.28 – 1.59)	*0.23*
Missing	40	*21.5*			
Test for homogeneity					*0.65*
Menopause Duration					
Adenocarcinoma					
< 10	38	*17.2*	1		
10 – 17	43	*19.5*	1.55	(0.67 – 3.59)	
18 – 24	32	*14.5*	1.71	(0.64 – 4.59)	
≥ 25	47	*21.3*	3.85	(1.34 – 11.09)	*0.01*
Missing	61	*27.6*			
Other Cancers					
< 10	27	*14.5*	1		
10 – 17	34	*18.3*	1.22	(0.45 – 3.30)	
18 – 24	36	*19.4*	1.93	(0.62 – 6.05)	
≥ 25	52	*28.0*	3.53	(1.03 – 12.08)	*0.02*
Missing	37	*19.9*			
Test for homogeneity					*0.84*
Reproductive Duration					
Adenocarcinoma					
< 33	56	*25.3*	1		
33 – 36	55	*24.9*	0.82	(0.46 – 1.46)	
37 – 40	59	*26.7*	0.81	(0.47 – 1.40)	

	Cases		Model 2**		
	N	%	OR	95% CI	p [b]
≥ 41	18	*8.1*	0.41	(0.20 – 0.84)	*0.03*
Missing	33	*14.9*			
Other Cancers					
< 33	51	*27.4*	1		
33 – 36	43	*23.1*	0.88	(0.45 – 1.70)	
37 – 40	39	*21.0*	0.68	(0.35 – 1.33)	
≥ 41	23	*12.4*	0.54	(0.25 – 1.17)	*0.09*
Missing	30	*16.1*			
Test for homogeneity					*0.76*

[a] Percentages may not add to 100.0 because of rounding.

[b] For ordinal variables, test for trend was performed.

** **Model 2**: adjusted for area, age at study, smoking (ever/never, pack-years, time since quitting), ETS, education, BMI.