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Menstrual and reproductive factors and lung cancer risk: a pooled analysis from the International Lung Cancer consortium (ILCCO)

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The authors declare that they have no conflict of interest.

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Abstract

Many clinical features of lung cancer are different in women and men. Sex steroid hormones exert effects in non-reproductive organs, such as the lungs. The association between menstrual and childbearing factors and the risk of lung cancer among women is still debated. We performed a pooled analysis of eight studies contributing to the International Lung Cancer Consortium (ILCCO; 4,386 cases and 4,177 controls). Pooled associations between menstrual or reproductive factors and lung cancer were estimated using multivariable unconditional logistic regression. Subgroup analyses were done for menopause status, smoking habits and histology. We found no strong support for an association of age at menarche and at menopause with lung cancer, but peri/postmenopausal women were at higher risk compared to premenopausal (OR 1.47, 95% CI 1.11–1.93). Premenopausal women showed increased risks associated with parity (OR 1.74, 95% CI 1.03–2.93) and number of children (OR 2.88 95% CI 1.21–6.93 for more than 3 children; P for trend 0.01) and decreased with breastfeeding (OR 0.54, 95% CI 0.30–0.98). In contrast, peri/postmenopausal subjects had ORs around unity for the same exposures. No major effect modification was exerted by smoking status or cancer histology. Menstrual and reproductive factors may play a role in the genesis of lung cancer, yet the mechanisms are unclear, and smoking remains the most important modifiable risk factor. More investigations in large well-designed studies are needed to confirm these findings and to clarify the underlying mechanisms of gender differences in lung cancer risk.

Keywords

Case-control studies; Lung neoplasms; Menopause; Reproductive History; Women

Introduction

Lung cancer in women was a rare disease until the 1970s: clinical and etiological knowledge has been therefore acquired from studies that included mainly men. Clinical features are different between genders and have led some researchers to consider lung cancer in women as a distinct biological entity [1, 2]. Tumours are more often localised in women than in men. Squamous cell carcinoma has been the predominant subtype among men for decades, but it has been overtaken by adenocarcinoma in many countries in the new millennium, while among women the latter has always been to most common histotype, irrespective of smoking status[3]. Women have better survival rates than men, a fact that is still poorly understood [4, 5]. A Scandinavian study conducted on over 40,000 lung cancer cases showed that this difference is independent of lung cancer stage at diagnosis, age at diagnosis, period of diagnosis, and histological type [6], while a French study demonstrated that 1-year mortality has significantly decreased in both genders over ten years, but less so in men than in women, leading to an increased difference [7].

There is increasing evidence for the effects of sex steroid hormones in non-reproductive organs such as the lungs. Acknowledgment of this kind of interplay is fundamental for innovative integrated health care approaches like systems medicine, that consider the individual's complexity for the best therapeutic and preventive strategies [8]. Recent reports suggest that sex hormones may play a role in many chronic respiratory diseases, including asthma, lung fibrosis, COPD and lung cancer. Sex steroid receptors have been reported in human bronchial epithelium, airway smooth muscle and alveolar epithelium. Most studies have focused on estrogen receptors (ER α and ER β), but some evidence exists also for progesterone and androgen receptors. Local metabolism of sex steroids may also be important, as suggested by the presence of sex steroids synthesising enzymes in lung parenchyma [9, 10].

A possible role of hormonal factors in the aetiology of lung cancer in women was first suggested after the finding of an increased risk of lung adenocarcinoma in association with shorter menstrual cycle lengths [11]. Since then, several studies have evaluated the association of lung cancer risk with menstrual and reproductive factors, with findings generally inconsistent. Increased, null or decreased risks have been reported to be associated with the factors investigated, possibly reflecting differences in study populations and design, or random associations due to small sample size and multiple comparisons. Two meta-analyses have summarized some of these heterogeneous results, showing a protective effect of longer menstrual cycles and no association for parity, number of pregnancies, or age at menarche, at first live birth, and at menopause [12, 13].

Previous studies investigating the association between lung cancer risk and hormone therapy after menopause and/or for contraceptive purposes have shown conflicting results [12], while a pooled analysis conducted in the International Lung Cancer Consortium (ILCCO) dataset based on six studies has found that hormone use was inversely associated with lung cancer [14]. To investigate the role of menstrual and reproductive factors in the onset of lung cancer, we conducted a pooled analysis based on 8 studies from the ILCCO, with a total of 4,386 lung cancer patients and 4,177 controls.

Methods

Study design and population

A pooled analysis was conducted from 8 independent case-control studies participating in ILCCO, a consortium established in 2004 with the aim to pool comparable data and maximize statistical power of lung cancer epidemiological studies. Further details regarding the aims, guidelines and policies are described in Hung et al. [15] and available on the consortium portal (http://ilcco.iarc.fr). A de-identified dataset was provided by each study and was checked for inconsistencies, before harmonizing variables and coding data uniformly across studies.

Eight case-control studies that included hormonal and reproductive variables agreed to participate and were pooled, including one case-control study nested in a cohort (ESTHER[16]) (table 1). Six out of the 8 individual studies were conducted in North America (i.e., LCSS[17], MLCS[18], TORONTO[19], WELD[20], NELCS[21], MLCCCS[22]) and two came

from Europe (EAGLE-Italy[23], ESTHER-Germany). Two case-control studies included both hospital and population-based control groups (MLCS and TORONTO), while the others had only population-based controls. Enrollment periods dated back to the early 1990s and were quite comparable. All studies except the TORONTO study frequency matched controls to cases on age. Moreover, the TORONTO study performed matching on ethnicity and residential area, and the MLCS study additionally matched hospital controls on smoking status. Finally, the pooled analysis included eight studies with 4,386 cases and 4,177 controls. Institutional approval and written informed consent from all subjects was obtained by the investigators at each study site.

Study variables

From each study participating in ILCCO, we obtained data on case/control status, age at interview, ethnicity, education level, smoking status and cancer histology. In each study, ever smokers were defined as subjects who reported having smoked at least 100 cigarettes in their lifetime, and former smokers as subjects who declared smoking cessation at least 2 years prior to interview. Lifetime smoking history was estimated in each study by the Comprehensive Smoking Index (CSI) that has been previously used in other case-control studies on lung cancer [24, 25]. CSI incorporates measures of smoking duration, time since cessation, and smoking intensity into one aggregate measure. The lung cancer histological subtypes were classified according to the International Classification of Diseases in Oncology, Third Edition [26].

Women were asked about their reproductive histories. Information available included menstrual factors (age of menarche, menopause status and reason, age at natural menopause, oophorectomy status), and childbearing factors (age at first child, parity, number of children, breastfeeding).

The variable “Age at menopause” was built on the replies to questions like “At what age was your last menstrual period?” among subjects that declared not to be menstruating anymore. In addition, women experiencing episodic amenorrhea could have self-attributed a definite menopausal status even if they were rather in perimenopause. Consequently, mean age at menopause was relatively early (47 years, rather similar in the various studies collecting this information) and menopause status was defined as “premenopausal” or “peri/postmenopausal”.

Menopause was considered as non-natural if both ovaries were surgically removed or ovarian function was abolished by radiation or drugs. Oophorectomy was defined as the surgical removal of the two ovaries. Missing values for oophorectomy were considered as no oophorectomy.

Single datasets were eligible for a specific analysis only if information on reproductive factors was available for at least 70% of the subjects. For a given variable, data were pooled according to its availability in each study.

Statistical analysis

All data were quality checked for inadmissible values, inconsistencies and missing variables. Questions regarding data were resolved by the original study principal investigators.

To estimate differences between cases and controls in socio-demographic characteristics, a single pooled database was built from all studies. Pooled odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated using unconditional logistic regression models that included study center, age at interview or diagnosis (categorized into 4 groups, ≤53, 54–62, 63–70 and >70 years based on the distribution among the control population), ethnicity (Caucasians, non Caucasians), education level (categorized into 3 groups: primary, secondary, university) and CSI (as a continuous variable). We conducted analyses stratified by menopause (pre- or peri/post-) and smoking status (never, ex- and current smokers), and tests of interaction were assessed using log-likelihood test statistics, comparing models with and without the interaction term. We also performed multinomial logistic regression to test homogeneity of the association between the menstrual and reproductive factors and lung cancer risk across histological types (adenocarcinoma, squamous cell carcinoma and small cell carcinoma), using Wald test.

In addition we calculated I^2, the percentage of the variability across studies in effect that is due to heterogeneity [27], using the Cochrane Handbook for systematic Review interventions [28]. The influence of each study on the overall analysis estimate was evaluated by an influence analysis, where the analysis estimates are computed before and after omitting each study that was found to be a source of heterogeneity.

Statistical analyses were performed with SAS (© SAS Institute Inc.; North Carolina, USA; version 9.3). All p values were two-sided, and a p value ≤ 0.05 was the threshold for statistical significance.

Results

ILCCO pooled analysis

Table 2 describes demographic and lifestyle characteristics of cases and controls included in the analysis. Mean ages of cases and controls were 63.3 years (range: 26–93) and 59.6 years (range: 20–97) respectively. The majority of the population was Caucasian (more than 80%). Compared with controls, cases had lower education levels and were more likely to be smokers. Regarding histological subtypes of lung cancer cases, 47% of the tumors were classified as adenocarcinomas, followed by squamous cell carcinomas (14%), while small cell lung cancers represented 7% of all cases.

Pooled ORs of lung cancer associated with menstrual and reproductive factors are shown in table 3. No association was observed with age of menarche. Late age at natural menopause (>51 years) was associated with significantly decreased odds ratio, but this association was lost when the EAGLE study was removed because of high heterogeneity (I^2=61%).

Peri/postmenopausal women had a 90% higher risk of lung cancer as compared to premenopausal women (statistically significant). After removing the TORONTO study in

order to eliminate significant heterogeneity (I^2=65%), the risk estimate was reduced, but still significant (Pooled OR = 1.47, 95% CI 1.11 – 1.93). Figure 1a shows the study-specific ORs for menopause status, along with the overall estimate. When accounting for menopause reason, the association was slightly stronger for non-natural than natural menopause. The positive association was confirmed in the subgroup of studies that reported on oophorectomy, as is shown in Figure 1b.

No association with lung cancer was found for age at first child. Pooled ORs for parity and for number of children were around unity, even after removing the MLCS and LCSS studies, that gave a high heterogeneity (I^2=67%). Figure 1c is dedicated to parity and shows the ORs with confidence intervals of the single studies, together with the pooled results.

Breastfeeding was associated with a slightly decreased lung cancer risk, although without reaching statistical significance.

Subgroup analyses

The associations with menstrual and reproductive factors were stratified by menopausal status, as is shown in table 4.

Age at menarche was not related to lung cancer, neither in pre- nor in peri/postmenopausal women.

The reproductive factors appeared to exert a different, stronger influence on lung cancer risk among the premenopausal women than the peri/postmenopausal, as confirmed by the statistically significant interactions that have been found for all the variables considered.

In particular, the risk of lung cancer seemed to decrease with age at first child among premenopausal women, although no clear trend could be demonstrated, but it was null for women that were not menstruating anymore. In comparison to nulliparity, the risk associated with parity was 74% higher among premenopausal women (statistically significant), while it was slightly decreased in peri/postmenopausal subjects, showing a highly significant interaction. In addition, among premenopausal women the risk increased with the number of children (p for trend <0.002 and <0.01 respectively in analysis with and without heterogeneity), up to an almost triple risk for women with 3 children or more, whereas borderline decreased risks were observed among peri/postmenopausal women in the same categories (p for interaction 0.0002). After removing heterogeneous studies (LCSS and MLCS), a significant increased risk was confirmed only among women with more than 3 children (Pooled OR = 2.88, 95% CI 1.21 – 6.93), while no clear trend was found among peri/postmenopausal women. Finally, breastfeeding was associated with half the risk of lung cancer among the women still menstruating at interview, but showed no major effect among those after menopause.

The results according to histology of lung cancer are presented in table 5. We did not observe any major difference with respect to the overall results presented in table 3. Oophorectomy was negatively associated with small cell lung cancer and positively associated with the other histologies. However, even in this case, histological types were statistically homogeneous. Test of homogeneity was significant (P=0.04) only for

menopause status, which was more strongly associated with small cell lung cancer than with adenocarcinoma and squamous cell carcinoma histotypes.

We also examined the possibility of effect modification by smoking status, and the results are reported in supplementary materials. No significant interaction could be demonstrated.

Moreover, there were no major influences of smoking status on the associations between lung cancer and the menstrual variables, except for oophorectomy, whose positive association with lung cancer was statistically significant only among current smokers. For most reproductive factors, never smokers showed somehow increased risks with respect to smokers, namely for age at first children, parity and number of children.

Four studies never caused any statistically significant heterogeneity in our analysis, namely MLCCCS, ESTHER,WELD and NELCS. After excluding the NELCS study, due to its relatively low participation rate, we run a sensitivity analysis with the three remaining studies, and we found that the results were in line with those presented above.

Discussion

We explored whether menstrual and reproductive factors might be associated with the risk of lung cancer among women, using data pooled from eight studies in the framework of the ILCCO collaboration. Menopausal status represented a risk factor, while we found no strong support for an association of age at menarche and age at menopause with lung cancer. A statistically significant association with reproductive factors was found among premenopausal women, who showed increased risks for parity and number of children. Premenopausal women who breastfed had lower risks, compared to those who did not. In contrast, peri/postmenopausal subjects had ORs around unity for the same exposures. No major effect modification was exerted by smoking status or cancer histology.

Biology of sex hormones in women is undoubtedly complex, and includes the enzymes involved in their metabolism, their receptors, their regulation and the cross-talk with other signalling pathways. The interplays of these factors in normal and neoplastic lung have not been fully clarified yet, but in vitro data, animal models, and functional or physiologic evidence provide support for a role of steroid hormones in lung carcinogenesis. The presence of receptors for both estrogen (ER α, ER β and GPER) and progesterone in lung cells[29, 30], the pulmonary physiologic abnormalities associated with the targeted inactivation of ER β receptors in female mice [31], the ER β receptor most often expressed in human non-small cell lung cancer cell lines and in normal pulmonary tissue of sick patients [30], illustrate the plausibility of the role of steroid hormones in lung carcinogenesis. Furthermore, some studies have indicated differences in the expression of ERs depending on the sex of the subject and the cancer histology [10].

Tens of studies have evaluated the association of lung cancer risk with several menstrual and reproductive factors, but their results have been generally inconsistent.

Late age of menarche resulted in a slightly, non significantly decreased risk of lung cancer in the meta-analysis of 19 studies (including LCSS, MLCCCS, MLCS and WELD), conducted

by Zhang and colleagues [12]. No association was shown in four studies published thereafter [14, 20, 31, 32] and in the present pooled analysis. Tan and colleagues recently found a doubling of risk limited to lung adenocarcinoma in Chinese women [33], a result that we did not confirm in our study population, which predominantly included Caucasian women.

Summary results for *late age at menopause* pointed to a weak protective or null effect in a meta-analysis of 15 studies[12], and so did both our pooled analysis and the Singapore cohort [33]. Among the other recent studies, two gave an indication of an increased risk in Chinese women [31, 32], and two of a protective effect in Caucasians [14, 20].

Menopausal status was associated with a statistically significant 50% increased risk of lung cancer in our analysis, with minor differences according to menopause reason (natural, induced, oophorectomy), smoking behaviour or cancer histology. The risk was similar or even higher in the subset of women from the EAGLE study [14] and from MLCCCS [22] and in two other study groups that were included in this analysis, namely MLCS and WELD (partially published in [18] and [34] respectively), but an inverse association was found in two smaller datasets (ESTHER and NELCS).

Our pooled result is particularly important because menopausal status has been rarely examined in previous studies with adequate statistical power. Lung cancer is diagnosed typically at late ages and many published studies included only (e.g. Schwartz 2015) [20] or almost exclusively peri/postmenopausal women (e.g. Tan 2015) [31, 33]. In the case-control studies that examined this issue [14, 18, 22, 34–38], the number of premenopausal cases was less than 50, with one exception [37]. As a consequence, even if they consistently reported higher risks for peri/postmenopausal with respect to premenopausal women, particularly in the case of induced menopause, their results rarely reached statistical significance [22, 37]. In the cohort studies, menopausal status is often recorded only at entry, and no information at time of cancer diagnosis is generally available. An exception is represented by a study on a cohort that was updated every two years and whose results pointed once more to a positive association of peri/postmenopausal status with lung cancer [39].

Our result should be interpreted cautiously, because residual confounding by smoking was still possible after adjustment by CSI, however the OR was increased even among the never smokers. Some peculiarities in smoking patterns of pre- and peri/postmenopausal women in our pooled dataset may have influenced the results. The premenopausal women reported smoking less than the peri/postmenopausal, and the proportion of never smokers was higher (43% vs. 31%). Moreover in the premenopausal there was a shift towards low CSI levels, an index that includes a duration term and is therefore linked to the subjects' age. In addition, the age of menopause has been shown to be 1 to 2 years earlier among current and former smokers with respect to never smokers[40]. The anti-estrogenic effect of smoking was confirmed in our study, with a mean age at natural menopause of 50.3, 48.9 and 48.6 years respectively for never, former and current smokers.

Bilateral *oophorectomy* is known to be associated with lower risks of ovarian and breast cancers, but few studies have examined its association with lung cancer. Our results are consistent with some previous studies that have observed an increased lung cancer risk

among women with oophorectomies [37, 41, 42], while one study showed no statistically significant association [43]. The effect of a sudden and rapid decrease in circulating estrogen levels that occurs after a bilateral oophorectomy has been proposed as a possible hypothesis to justify the increased risk [22]. Some studies hypothesized that the association could be explained by long-term use of hormone replacement therapy prescribed to oophorectomized women [22, 44]. However, this explanation seems to be unlikely, as a previously published ILCCO pooled study demonstrated a protective effect of exogenous hormones, either oral contraceptives or hormone replacement therapy [45].

Parity was not associated with lung cancer in our analysis, when considering the whole pooled dataset. However, after stratifying by menopausal status, a statistically significant 74% increased risk was found among premenopausal women, and was corroborated by a significant trend with the *number of children*, with an almost tripling risk for those who had had 3 children or more. On the contrary, a weak inverse association between lung cancer and parity was shown among peri/postmenopausal subjects, with no dose-response trend. Moreover, the tests for interaction were highly significant. The effect exerted by parity was more evident in premenopausal women, who were younger and smoked less, while it seemed to be masked in subjects not menstruating anymore, who were already at higher risk because of their menopausal status. However, our results in women still menstruating must be interpreted cautiously, because they appeared to be mainly driven by two of the pooled studies (WELD and MLCS). Should this association be confirmed in other studies, mechanisms are likely complex and may depend on many different factors. At each childbirth, parous women experience a multitude of changes that may have a transient influence on their risk of cancer: first of all a huge hormonal derangement, but also radical changes in smoking habits, exposure to infectious agents and occupational hazards, diet, hours of sleep and other lifestyle or biological conditions.

The lack of association of parity with lung cancer in the whole study population, and the weak inverse association among peri/postmenopausal women that we observed in the present pooled analysis confirm most of the existing literature, considering that the studies published to date included mainly peri/postmenopausal women, as explained above. It should be noted, however, that the endpoints may differ among studies (e.g., pregnancies instead of parity, or different categorizations of the number of children), therefore any comparison should be cautious. Non-significant inverse associations were reported in a recent cohort study [32] and in the meta-analysis of 19 studies performed by Zhang and co-workers [12]. The relative risk per livebirth was close to unity in a meta-analysis of 16 studies [13] (including LCSS, MLCCCS, MLCS and WELD), and in the EAGLE study [14]. Statistically significant inverse associations were shown instead in two recent Singaporean studies [31, 33].

Regarding the studies conducted exclusively on peri/postmenopausal women, three studies have found no association with parity [44, 46], with a modest significantly increased risk in those with five children or more [20].

Two studies examined the association between lung cancer and parity after stratifying by age, which might be a proxy of menopausal status: a Canadian cohort study did not observe

any difference by age (40–49 vs. 50–59 years) [47], while a preliminary analysis of the LCSS case-control study (performed on half the subjects that have been included in the present pooled analysis) found no risk in the subgroup of women aged less than 50 years, and a statistically significant negative association in those 50 years old or more [17].

Only one published study to date carefully examined the effect of parity by menopausal status. It reported on a part of the WELD subjects included in the present pooled analysis, and found a statistically significant positive association with lung cancer in premenopausal women, with no effect in peri/postmenopausal women [34].

In our analysis, *breastfeeding* was associated with a slightly reduced risk, when considering the whole study population, but the risk was halved, and statistically significant, in the subgroup of premenopausal women. Few studies have examined this issue to date, and they found no significant association, in substantial agreement with the result we obtained in the whole group [32, 44 22, 36].

Some associations seemed to be slightly strengthened when attention was restricted to never smokers, in particular those with menopause reason, parity and number of children, although no significant interaction could be demonstrated according to *smoking status*. It is unclear whether this result could be related to the fact that about 20% of never smokers were premenopausal. On the other hand, the positive association with oophorectomy was statistically significant only in current smokers. No major differences were found in our analysis according to *cancer histology* as well. Sparse and inconsistent results have been shown in the published literature, when stratifying by smoking habits or cancer histology.

In conclusion, the effects of gynecologic and obstetric factors on lung cancer development are difficult to disentangle, possibly due to their complex interactions with other host or environmental factors. For example, cigarette smoking decreases hormone levels and causes early menopause, while estrogens produced in adipose tissue after menopause may partly explain the relationship between BMI and lung cancer. Multiple pathways of estrogen action exist and estrogen levels have never been measured in lung cancer patients, so that their role remains an open question[20]. The pattern that we found in lung cancer is in contrast with what has been demonstrated for breast cancer, for which late menopause and low parity are well-established risk factors. On the other hand, it appears to be similar to what has been observed among thyroid cancer patients: the risk decreased with increasing age at menopause and ovariectomy, and decreased with breastfeeding[48].

Biological mechanisms are far from being elucidated, but it is possible that exposure to fluctuating levels of hormones for decades plaid different roles in different tissues, according to their specific hormone receptors.

Strengths and limitations of the study

The main strength of our study lies in its size: 4386 cases and 4177 controls were pooled from eight different studies. This allowed us to have considerable statistical power to conduct separate analyses by menopausal status and by lung cancer histological type and to examine potential effect modification by smoking status.

Bias due to differential reporting of hormonal and reproductive factors by cases and controls was unlikely, because a potential role for these factors in lung cancer risk has rarely been mentioned in popular media, and questionnaires investigated a variety of factors.

Another major strength of this study was the detailed assessment of smoking history across studies. This is important in an analysis of hormonal factors and lung cancer, as women smokers generally have lower estrogen levels [49]. We used one parsimonious measure (i.e., the CSI), which incorporates various measures of smoking: duration, intensity and time since cessation. Nonetheless, residual confounding by smoking is still possible.

The principal limitation of data from epidemiological studies by using pooled analysis is heterogeneity [50]. One of the main potential sources of heterogeneity is the design of studies to be combined, however almost all those in our sample had a case-control design, except one case-control study nested in a cohort, and no cohort study has been included. The exposure under investigation and the covariables may also vary across studies, most commonly because of differing approaches to definition or measurement. To overcome this potential heterogeneity, we performed a careful standardization of the original data and we excluded studies which had not precisely collected the information we needed.

Another limitation of our study was the inclusion of studies conducted exclusively in North American and European countries, where the population is largely of Caucasian descent and tobacco consumption levels among women were typically higher than in other parts of the world.

Lastly, we lacked information regarding occupational exposures. However, this did not seem a great concern, because occupational exposures possibly posing an increased lung cancer risk have generally a very low prevalence among women.

In summary, there is evidence that menstrual and reproductive factors may play a role in the genesis of lung cancer, yet the mechanisms are unclear. While smoking remains the most important modifiable factor associated with lung cancer, understanding the role of hormones and the potential effect modification by smoking in lung carcinogenesis may provide further insights into the etiology of the disease, particularly for women. Our results suggest that menopause may increase the risk, while a positive association of parity with lung cancer is suggested among premenopausal women. Nonetheless, more investigations in large well-designed studies are needed to confirm these findings and to clarify the underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

OR	odds ratio
CI	confidence interval
CSI	comprehensive smoking index

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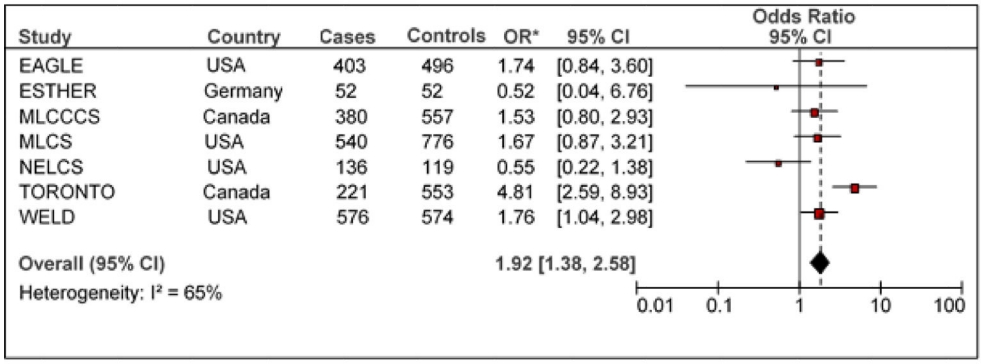
Novelty and Impact

There is increasing evidence for the effects of sex steroid hormones in non-reproductive organs. Our study suggests that menstrual and reproductive factors may play a role in lung carcinogenesis. In particular, menopausal status represented a risk factor, while premenopausal women showed increased risks with parity and number of children.

a



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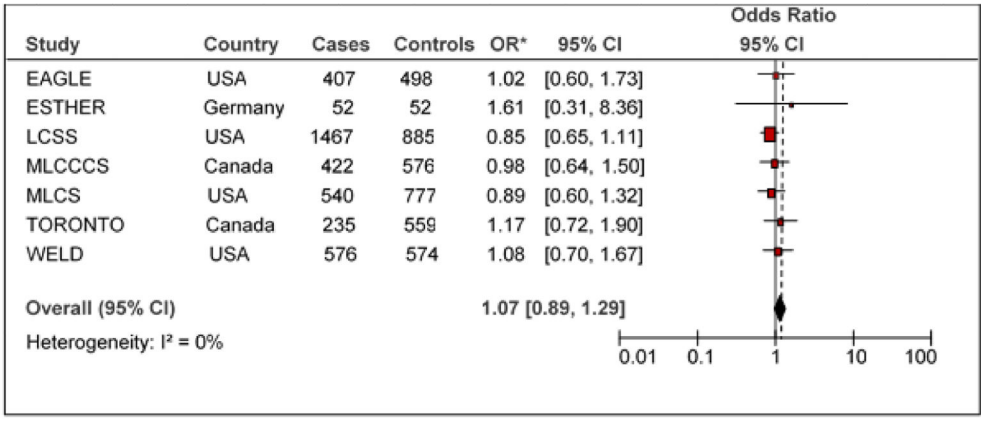

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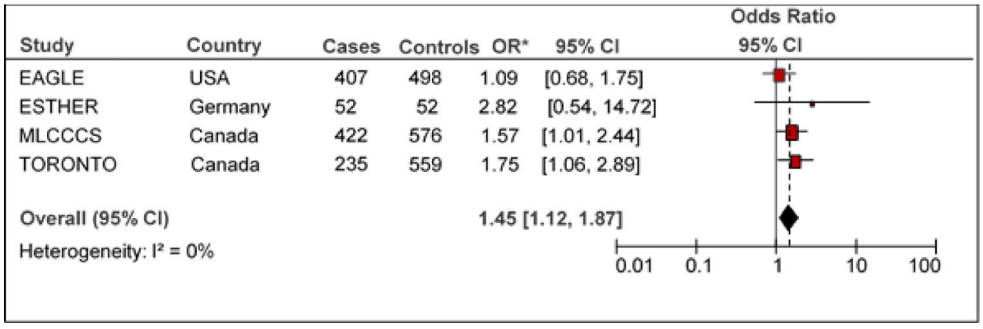

Figure 1.

*Odds ratios for lung cancer were adjusted for age at interview, ethnicity, education and CSI using multivariable unconditional logistic regression models.

I^2 were calculated using the Cochrane Handbook for systematic Review interventions

TABLE 1

Characteristics of ILCOO studies

Study name Principal investigator	Country (location)	Controls	Period of enrolment	Cases		Controls		Age range (years) in protocol
				n	Participation Rate* (%)	n	Participation Rate * (%)	
EAGLE *MT Landi*	Italy (Lombardy region)	Population	2002–2005	407	86.6	498	72.4	35–79
ESTHER *H Brenner*	Germany (Saarland)	Population	2000–2003	52	Nested case-control study	52	Nested case-control study	50–75
LCSS *D Christiani*	USA (Boston, Massachusetts)	Population	1992–2009	2005	85	993	80	More than 18[A]
MLCCCS *A Koushik*	Canada (Montreal area)	Population	1996–1997	422	81.7	576	69.4	More than 35[B]
MLCS *CC Harris*	USA (Baltimore City and Eastern Shore of Maryland)	Population/Hospital	1998–2010	540	80	777	80	No age restriction[C]
NELCS *E Duell*	USA (New Hampshire and Vermont)	Population	2005–2008	149	61	148	46	30–74
TORONTO *RJ Hung; J McLaughlin*	Canada (Metropolitan Toronto)	Population/Hospital	1997–2002	235	62	559	60	20–84
WELD *AG Schwartz*	USA (Wayne, Macomb and Oakland counties)	Population	1984–2005	576	83	574	70.6	18–74
Total				4386		4177		

*Participation Rate as mentioned in the published study protocols.

[A]Age range (years) in ILCCO: (23–93).

[B]Age range (years) in ILCCO: (33–75).

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$C_{\text{Age range (years) in ILCCO: (27–97).}}$

TABLE 2

Demographic characteristics of the study population among cases and controls and distribution of histological subtypes of lung cancer

Characteristics	Cases (n=4386)		Controls (n=4177)		OR	95%CI	P_{χ^2}*
	n	%	n	%			
Age at interview (years)[A]							
≤ 53	834	19.0	1202	28.8	0.71	(0.61–0.82)	
54–62	1100	25.1	1098	26.3	0.81	(0.70–0.93)	
63–70	1226	28.0	1096	26.2	1.0	Reference	
>70	1218	27.8	778	18.6	1.62	(1.40–1.87)	<0.0001
Missing	8	0.2	3	0.1	-	-	
Mean (SD)	63.3 (10.7)		59.6 (11.8)			P<0.0001	
Ethnicity[B]							
Caucasian	3837	87.5	3400	81.4	1.0	Reference	
No-Caucasian	536	12.2	761	18.2	1.14	(0.98–1.32)	<0.0001
Missing	13	0.3	16	0.4	-	-	
Education[C E]							
Primary	584	24.5	564	17.7	1.23	(1.03–1.47)	
Secondary	1143	48.0	1238	38.9	1.0	Reference	
University	632	26.5	1330	41.8	0.68	(0.58–0.79)	<0.0001
Missing	22	0.9	52	1.6	-	-	
Smoking status[D]							
Never smoker	636	14.5	1923	46.0	1.0	Reference	
Former smoker	1684	38.4	1210	29.0	3.58	(3.17–4.05)	
Current smoker	2030	46.3	993	23.8	6.64	(5.86–7.52)	<0.0001
Missing	36	0.8	51	1.2	-	-	
CSI[D]							

Characteristics	Cases (n=4386)		Controls (n=4177)		OR	95%CI	P_{χ^2}*
	n	%	n	%			
0	636	14.5	1923	46.0	1.0	Reference	
≤0.92	474	10.8	949	22.7	1.44	(1.24–1.67)	
0.93–1.56	839	19.1	594	14.2	4.17	(3.61–4.82)	
1.57–2.03	1025	23.4	398	9.5	8.30	(7.11–9.69)	
>2.03	1137	25.9	226	5.4	14.6	(12.2–17.44)	<0.0001
Missing	275	6.3	87	2.1	-	-	
Histological type							
SCLC	322	7.3	-	-			
NSCLC	2901	66.1	-	-			
Squamous cell	605	13.8	-	-			
Large cell	223	5.1	-	-			
Adenocarcinoma	2073	47.3	-	-			
Others[F]	1011	23.1	-	-			
Missing	152	3.5	-	-			

Abbreviations: CI = Confidence interval; CSI = Comprehensive Smoking Index

*P values are derived from the χ^2 test for categorical variables.

*A*Adjustment for center, ethnicity, education and CSI

*B*Adjustment for center, age at interview, education and CSI

*C*Adjustment for center, age at interview, ethnicity and CSI

*D*Adjustment for center, age at interview, education and ethnicity

*E*Not available in LCSS

*F*carcinoid/Barrett's carcinoma/not otherwise specified/information not available

TABLE 3

Pooled analysis of the association of menstrual and reproductive factors with lung cancer

Factors (cases/controls)[A]	Cases		Controls		Pooled OR[B]	95%CI	*P trend*[C]
Studies	**n**	**%**	**n**	**%**			
MENSTRUAL FACTORS							
Age of menarche (years) (2381/3184)							
EAGLE - ESTHER - MLCCCS - MLCS - NELCS - TORONTO - WELD							
≤ 12	983	41.3	1384	43.5	1.0	Reference	0.9
]12–13]	556	23.4	823	25.9	0.99	(0.84–1.16)	
]13–14]	357	15.0	476	15.0	1.11	(0.92–1.35)	
> 14	346	14.5	447	14.0	0.98	(0.81–1.2)	
Missing	139	5.8	54	1.7			
Age at natural menopause (years)[D] (1575/1901)							
EAGLE - ESTHER - MLCS - WELD							
≤ 43	507	32.2	492	25.9	1.0	Reference	0.1
]44–48]	358	22.7	372	19.6	0.98	(0.78–1.22)	
]48–51]	257	16.3	323	17.0	0.97	(0.76–1.24)	
> 51	243	15.4	422	22.2	0.78	(0.62–0.99)	
Missing	210	13.3	292	15.4			
Menopause status (2381/3184)[E]							
EAGLE - ESTHER - MLCCCS - MLCS - NELCS - TORONTO - WELD							
Premenopausal	230	9.7	604	19.0	1.0	Reference	
Peri/Postmenopausal	2078	87.3	2523	79.2	1.92	(1.5–2.46)	
Missing	73	3.1	57	1.8			
Menopause reason (1945/2425)							
EAGLE - MLCCCS - MLCS - WELD							

Factors (cases/controls)[A]	Cases		Controls		Pooled OR[B]	95%CI	*P trend*[C]
Studies	**n**	**%**	**n**	**%**			
Premenopausal	152	7.8	308	12.7	1.0	Reference	
Peri/Postmenopausal							
natural	1078	55.4	1358	56.0	1.64	(1.2–2.23)	
non natural	666	34.2	734	30.3	1.89	(1.38–2.58)	
Missing	49	2.5	25	1.0			
Oophorectomy (1116/1685)[F]							
EAGLE - ESTHER - MLCCCS - TORONTO							
No	934	83.7	1483	88.0	1.0	Reference	
Yes	182	16.3	202	12.0	1.45	(1.12–1.87)	
REPRODUCTIVE FACTORS							
Age at first child (years) (2232/3036)							
EAGLE - ESTHER - MLCCCS - MLCS - TORONTO – WELD							
≤ 20	647	29.0	645	21.3	1.0	Reference	0.6
]20–23]	493	22.1	575	18.9	1.16	(0.95–1.41)	
]23–27]	428	19.2	668	22.0	1.05	(0.56–1.28)	
> 27	318	14.3	624	20.6	0.94	(0.75–1.17)	
Missing	346	15.5	524	17.3			
Parity (4237/4029)							
EAGLE - ESTHER - LCSS - MLCCCS - MLCS - TORONTO - WELD							
No	563	13.3	650	16.1	1.0	Reference	0.42
Yes	3489	82.3	3319	82.4	1.07	(0.89–1.29)	
Missing	185	4.4	60	1.5			
Number of children[G] (4237/4029)							
EAGLE - ESTHER - LCSS - MLCCCS - MLCS - TORONTO - WELD							
0	563	13.3	650	16.1	1.0	Reference	

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Factors (cases/controls)[A]	Cases		Controls		Pooled OR[B]	95%CI	*P trend*[C]
Studies	**n**	**%**	**n**	**%**			
1	528	12.5	569	14.1	1.1	(0.88–1.4)	
2	1053	24.9	1142	28.3	1.19	(0.97–1.45)	
3	739	17.4	795	19.7	0.95	(0.76–1.2)	
>3	803	19.0	739	18.3	0.98	(0.78–1.23)	
Missing	551	13.0	134	3.3			
Breastfeeding (1997/2477)[H]							
EAGLE - ESTHER - MLCCCS - MLCS - WELD							
No	1049	52.5	1111	44.9	1	Reference	
yes	670	33.6	1021	41.2	0.88	(0.74–1.04)	
Missing	278	13.9	345	13.9			

Abbreviations: CI = Confidence interval; OR = odds ratio

[A](Number of cases/number of controls) included in the logistic regression

[B]Adjustment for center, age at interview, ethnicity, education and CSI

[C]Test for ordinal variables was performed only when the assumption of linearity was satisfied.

[D]Heterogeneity: I^2=61%

[E]Heterogeneity: I^2=65%

[F]Missing was considered as No Oophorectomy

[G]Heterogeneity: I^2=67%

[H]Adjustment for center, age at interview, ethnicity, education, CSI and number of children

TABLE 4

Pooled analysis of the association of menstrual and reproductive factors with lung cancer stratified by menopause status

Factors (cases/controls)[A]	*Premenopausal*						*Peri/Postmenopausal*						
	Cases		Controls		Pooled OR[B]	95%CI	Cases		Controls		Pooled OR[B]	95%CI	*P for interaction*[C]
Studies	**n**	**%**	**n**	**%**			**n**	**%**	**n**	**%**			
MENSTRUAL FACTORS													
Age of menarche (years)(230/604)							**(2078/2523)**						
EAGLE - ESTHER - MLCCCS - MLCS - NELCS - TORONTO - WELD													
≤ 12	110	47.8	266	44.0	1.0		858	41.3	1091	43.2	1.0		
]12–13]	49	21.3	181	30.0	0.74	(0.46–1.2)	497	23.9	636	25.2	1.02	(0.86–1.21)	
]13–14]	37	16.1	87	14.4	0.97	(0.55–1.7)	313	15.1	382	15.1	1.13	(0.92–1.38)	
> 14	27	11.7	64	10.6	1.23	(0.65–2.36)	313	15.1	379	15.0	0.98	(0.8–1.20)	0.3
Missing	7	3.0	6	1.0			97	4.7	35	1.4			
			p trend[E]*=0.9*							*p trend*[E]*=0.9*			
REPRODUCTIVE FACTORS													
Age at first child (years) (180/568)							**(1992/2440)**						
EAGLE - ESTHER - MLCCCS - MLCS - TORONTO - WELD													
≤ 20	56	31.1	69	12.2	1.0	Reference	576	28.9	570	23.4	1.0	Reference	
]20–23]	34	18.9	45	7.9	1.2	(0.6–2.38)	455	22.8	528	21.6	1.17	(0.96–1.44)	
]23–27]	26	14.5	125	22.0	0.49	(0.26–0.94)	391	19.6	542	22.2	1.16	(0.93–1.45)	
> 27	38	21.1	161	28.4	0.73	(0.38–1.41)	272	13.7	461	18.9	1.01	(0.79–1.28)	0.006
Missing	26	14.4	168	29.6			298	15.0	339	13.9			
										p trend[E]*=0.8*			
Parity (272/606)							**(2634/2491)**						
EAGLE - ESTHER - LCSS - MLCCCS - MLCS - TORONTO - WELD													
No	48	17.7	192	31.7	1.0	Reference	349	13	331	13.3	1.0	Reference	
Yes	223	82.0	405	66.8	1.74	(1.03–2.93)	2266	86	2147	86.2	0.92	(0.75–1.12)	0.001

Factors (cases/controls)[A]	Premenopausal						Peri/Postmenopausal						
	Cases		Controls		Pooled OR[B]	95%CI	Cases		Controls		Pooled OR[B]	95%CI	*P for interaction*[C]
Studies	**n**	**%**	**n**	**%**			**n**	**%**	**n**	**%**			
Missing	1	0.4	9	1.5			19	0.7	13	0.5			
Number of children (272/606)							**(2634/2491)**						
EAGLE - ESTHER - LCSS - MLCCCS - MLCS - TORONTO - WELD													
0	48	17.7	192	31.7	1.0	Reference	349	13.3	331	13.3	1.0	Reference	
1	50	18.4	122	20.1	1.41	(0.75–2.67)	390	14.8	358	14.4	1.01	(0.78–1.3)	
2	93	34.2	188	31.0	1.55	(0.87–2.76)	775	29.4	735	29.5	1.03	(0.82–1.3)	
3	48	17.7	61	10.1	2.63	(1.3–5.34)	530	20.1	529	21.2	0.78	(0.61–0.99)	0.0002
>3	32	11.8	34	5.6	2.87	(1.28–6.44)	571	21.7	525	21.1	0.82	(0.64–1.05)	
Missing	1	0.4	9	1.5			19	0.7	13	0.5			
			p trend[E]*=0.002*										
Breastfeeding[D] (154/311)							**(1797/2144)**						
EAGLE - ESTHER - MLCCCS - MLCS - WELD													
No	86	55.8	97	31.2	1.0	Reference	936	52.1	1007	47.0	1.0	Reference	
yes	50	32.5	147	47.3	0.54	(0.3–0.98)	614	34.2	870	40.6	0.94	(0.78–1.12)	0.04
Missing	18	11.7	67	21.5			247	13.8	267	12.5			

Abbreviations: Cl = Confidence interval; OR = odds ratio

A(Number of cases/number of controls) included in the logistic regression.

*B*Adjustment for center, age at interview, ethnicity, education and CSI.

*C*P-value for interaction between the corresponding variable and menopause status using the likelihood ratio test.

*D*Adjustment for center, age at interview, ethnicity, education, CSI and number of children.

*E*Test for ordinal variables was performed only when the assumption of linearity was satisfied.

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TABLE 5

Association between menstrual and reproductive factors and lung cancer risk by histologic types

		Small cell carcinoma			*Adenocarcinoma*			*Squamous cell carcinoma*			
Factors (cases/controls)[A]	**Controls**	**Cases**	**Pooled**	**95%CI**	**Cases**	**Pooled**	**95%CI**	**Cases**	**Pooled**	**95%CI**	***p***[C]
Studies	**n**	**n**			**n**			**n**			
MENSTRUAL FACTORS											
Age of menarche (years) (3184/157)					**(1188)**			**(349)**			
EAGLE - ESTHER - MLCCCS - MLCS - NELCS - TORONTO - WELD											
≤ 12	1384	60	1	Reference	501	1	Reference	131	1	Reference	
]12–13]	823	33	1.03	(0.63–1.69)	273	0.97	(0.81–1.17)	84	1.08	(0.79–1.49)	
]13–14]	476	17	0.8	(0.44–1.47)	193	1.19	(0.96–1.49)	53	1.12	(0.77–1.63)	**0.9**
> 14	447	21	0.83	(0.45–1.51)	172	0.97	(0.80–1.17)	49	0.92	(0.62–1.34)	
Missing	54	26			49			32			
Age at natural menopause (years) (1901/51)					**(843)**			**(206)**			
EAGLE - ESTHER - MLCS - WELD											
≤ 43	492	6	1	Reference	273	1	Reference	59	1	Reference	
]44–48]	372	9	1.85	(0.56–6.06)	170	0.84	(0.65–1.09)	63	1.65	(1.09–2.51)	
]48–51]	323	14	4.14	(1.33–12.84)	144	0.98	(0.74–1.28)	33	1.24	(0.76–2.03)	**0.25**
> 51	422	13	3.67	(1.15–11.67)	126	0.7	(0.53–0.93)	28	0.91	(0.55–1.51)	
Missing	292	9			130			23			
***Menopause status* (3184/157)**					**(1188)**			**(349)**			
EAGLE - ESTHER - MLCCCS - MLCS - NELCS - TORONTO - WELD											
Premenopausal	604	12	1	Reference	129	1	Reference	22	1	Reference	
Peri/Postmenopausal	2523	133	2.9	(1.31–6.4)	1027	1.82	(1.36–2.43)	313	1.83	(0.98–3.44)	**0.04**
Missing	57	12			32			14			
Menopause reason (2425/112)					**(1019)**			**(278)**			
EAGLE - MLCCCS - MLCS - WELD											

		Small cell carcinoma			*Adenocarcinoma*			*Squamous cell carcinoma*			
Factors (cases/controls)[A]	**Controls**	**Cases**	**Pooled**	**95%CI**	**Cases**	**Pooled**	**95%CI**	**Cases**	**Pooled**	**95%CI**	***p*[C]**
Studies	**n**	**n**			**n**			**n**			
Premenopausal	308	6	1	Reference	100	1	Reference	9	1	Reference	
Peri/Postmenopausal											
natural	1358	78	4.41	(1.57–12.38)	544	1.47	(1.05–2.08)	174	2.06	(0.9–4.71)	**0.2**
non natural	734	16	3.06	(1.01–9.36)	352	1.75	(1.23–2.48)	85	1.92	(0.83–4.46)	
Missing	25	12			23			10			
Oophorectomy[D] (1483/140)					**(540)**			**(172)**			
EAGLE - ESTHER - MLCCCS - TORONTO											
No	1483	129	1	Reference	451	1	Reference	141	1	Reference	
yes	202	11	0.56	(0.28–1.11)	89	1.5	(1.1–2.01)	31	1.35	(0.85–2.14)	**0.2**
REPRODUCTIVE FACTORS											
Age at first child (years) (3036/141)					**(1137)**			**(322)**			
EAGLE - ESTHER - MLCCCS - MLCS - TORONTO - WELD											
≤ 20	645	31	1	Reference	297	1	Reference	107	1	Reference	
]20–23]	575	28	1.02	(0.57–1.82)	257	1.34	(1.06–1.68)	71	0.95	(0.66–1.37)	
]23–27]	668	26	0.92	(0.5–1.68)	231	1.22	(0.96–1.55)	62	0.95	(0.64–1.4)	**0.3**
> 27	624	25	1.05	(0.57–1.94)	184	1.15	(0.88–1.5)	36	0.67	(0.43–1.06)	
Missing	*524*	31			168			46			
Parity (4029/306)					**(2022)**			**(578)**			
EAGLE - ESTHER- LCSS - MLCCCS - MLCS - TORONTO - WELD											
No	650	43	1	Reference	265	1	Reference	68	1	Reference	
yes	3319	250	1.02	(0.62–1.69)	1671	1.15	(0.92–1.43)	483	1.07	(0.74–1.56)	**0.83**
Missing	60	13			86			27			
Number of children (4029/306)					**(2022)**			**(578)**			
EAGLE - ESTHER- LCSS - MLCCCS - MLCS - TORONTO - WELD											

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		Small cell carcinoma			*Adenocarcinoma*			*Squamous cell carcinoma*			
Factors (cases/controls)[A]	**Controls**	**Cases**	**Pooled**	**95%CI**	**Cases**	**Pooled**	**95%CI**	**Cases**	**Pooled**	**95%CI**	***P*[C]**
Studies	**n**	**n**			**n**			**n**			
0	650	43	1	Reference	265	1	Reference	68	1	Reference	
1	569	35	0.99	(0.53–1.85)	267	1.18	(0.9–1.55)	73	1.02	(0.64–1.62)	
2	1142	68	0.86	(0.47–1.55)	534	1.3	(1.01–1.64)	124	1.21	(0.8–1.84)	
3	795	50	1.04	(0.55–1.97)	362	1.05	(0.8–1.37)	106	0.86	(0.54–1.37)	**0.93**
>3	739	70	1.31	(0.71–2.43)	368	0.97	(0.74–1.28)	133	1.11	(0.71–1.72)	
Missing	134	40			226			74			
Breastfeeding[E] **(2477/124)** *EAGLE - ESTHER - MLCCCS - MLCS - WELD*					**(1044)**			**(289)**			
No	1111	63	1	Reference	541	1	Reference	160	1	Reference	
yes	1021	36	0.73	(0.41–1.31)	367	0.88	(0.73–1.07)	95	0.94	(0.68–1.31)	**0.3**
Missing	345	25			136			34			

Abbreviations: Cl = Confidence interval; OR = odds ratio

[A](Number of controls/number of cases) included in the logistic regression.

[B]Adjustment for center, age at interview, ethnicity, education and CSI using multinomial logistic regression models.

[C]P-value for homogeneity using the Wald test

[D]Missing was considered as no oophorectomy

[E]Adjustment for center, age at interview, ethnicity, education, CSI and number of children.