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Hormone use and risk for lung cancer: a pooled analysis from the International Lung Cancer Consortium (ILCCO)

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Background: The association between oral contraceptive (OC) use, hormone replacement therapy (HRT) and lung cancer risk in women is still debated.

Methods: We performed a pooled analysis of six case–control studies (1961 cases and 2609 controls) contributing to the International Lung Cancer Consortium. Potential associations were investigated with multivariable unconditional logistic regression and meta-analytic models. Multinomial logistic regressions were performed to investigate lung cancer risk across histologic types.

Results: A reduced lung cancer risk was found for OC (odds ratio (OR)=0.81; 95% confidence interval (CI): 0.68–0.97) and HRT ever users (OR=0.77; 95% CI: 0.66–0.90). Both oestrogen only and oestrogen + progestin HRT were associated with decreased risk (OR=0.76; 95% CI: 0.61–0.94, and OR=0.66; 95% CI: 0.49–0.88, respectively). No dose–response relationship was observed with years of OC/HRT use. The greatest risk reduction was seen for squamous cell carcinoma (OR=0.53; 95% CI: 0.37–0.76) in OC users and in both adenocarcinoma (OR=0.79; 95% CI: 0.66–0.95) and small cell carcinoma (OR=0.37; 95% CI: 0.19–0.71) in HRT users. No interaction with smoking status or BMI was observed.

Conclusion: Our findings suggest that exogenous hormones can play a protective role in lung cancer aetiology. However, given inconsistencies with epidemiological evidence from cohort studies, further and larger investigations are needed for a more comprehensive view of lung cancer development in women.

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Lung cancer is the second leading cause of cancer mortality in women worldwide. In the past decades, lung cancer incidence rates have decreased or leveled off among men, whereas they are increasing among women, reflecting differences in pattern of smoking habits, with women starting smoking several decades later than males. Tobacco smoking is the major cause of lung cancer, accounting for 80% of the worldwide lung cancer burden in males and 50% in females (Jemal *et al*, 2011). There is increasing evidence that women present different clinical patterns of lung cancer from men: they are more likely to develop adenocarcinoma, tend to be younger than men and experience better survival rates (Kiyohara and Ohno, 2010; Donington and Colson, 2011). These gender differences raised the question of the possible role of female hormones in lung cancer carcinogenesis and found support by studies that have identified steroid receptors in lung cancer cell lines and tumour tissue (Chen *et al*, 2008). However, the significance of oestrogens and progesterone receptor expression in lung cells is still unknown as these receptors are expressed in many other organs (Greiser *et al*, 2010). Oestrogens could also interact with cigarette smoking by accelerating the metabolism of smoking-derived carcinogens (Meireles *et al*, 2010; Siegfried, 2010). Despite the growing number of studies evaluating the biological plausibility of hormonal factors in lung cancer carcinogenesis, the mechanisms through which they could contribute to lung cancer risk are still not fully clarified and are likely to be more complex than originally thought. Oestrogens directly promote cellular proliferation in the lung and can induce direct DNA damage (supporting a role in lung cancer development). However, they can also increase apoptosis, reduce cell proliferation through oestrogen receptor- β -mediated mechanisms and stimulate the immune system (thus playing a protective role). Progesterone seems to act as a growth-inhibiting factor on malignant lung cells. In addition, the crosstalk between different pathways involved in oestrogen response, such as interactions with epidermal growth factor or insulin-like growth factor, enhances the complexity of the regulatory mechanisms promoting tumour growth.

The evidence deriving from epidemiological studies is conflicting too. The first clue of a possible role of hormone replacement therapy (HRT) in lung cancer risk was from a small case-control study (Taioli and Wynder, 1994) that showed an increased risk in women ever using HRT. Numerous subsequent studies gave mixed results (Blackman *et al*, 2002; Kreuzer *et al*, 2003; Schabath *et al*, 2004; Liu *et al*, 2005; Elliott and Hannaford, 2006; Chen *et al*, 2007; Kabat *et al*, 2007; Ramnath *et al*, 2007; Schwartz *et al*, 2007; Rodriguez *et al*, 2008; Weiss *et al*, 2008; Chlebowski, 2009; Seow *et al*, 2009; Baik *et al*, 2010; Chlebowski *et al*, 2010; Slatore *et al*, 2010; Brinton *et al*, 2011; Clague *et al*, 2011; Meinhold *et al*, 2011). Most case-control studies (excluding those included in the present analysis) observed a reduced risk (Blackman *et al*, 2002; Kreuzer *et al*, 2003; Schabath *et al*, 2004; Elliott and Hannaford, 2006; Chen *et al*, 2007; Ramnath *et al*, 2007), whereas cohort studies failed to show a clear association between HRT and lung cancer risk. Three cohort studies were conducted among nonsmoking women in China (Weiss *et al*, 2008; Seow *et al*, 2009) and Japan (Liu *et al*, 2005), thus avoiding the possible residual confounding by smoking, but the number of cases who ever used HRT was too small (4, 12 and 24, respectively) to allow interpretation of the findings. Two case-control studies (Blackman *et al*, 2002; Schabath *et al*, 2004) and four cohort studies (Rodriguez *et al*, 2008; Baik *et al*, 2010; Slatore *et al*, 2010; Clague *et al*, 2011) were able to examine the risk by HRT type (oestrogen only and oestrogen plus progestin). The use of oestrogen only was not associated with an increased lung cancer risk consistently across studies; only in the VITAL study (Slatore *et al*, 2010), women using combined (oestrogen + progestin) hormone therapy for >10 years showed an ~50% increased risk.

Two randomised clinical trial evaluated HRT type and lung cancer risk. The Heart and Estrogen/Progestin Replacement Study

(HERS) (Hulley *et al*, 1998), a randomised trial of oestrogen plus progestin therapy in postmenopausal women with coronary diseases at enrollment, is limited by the modest number of lung cancer cases observed, the short duration of follow-up and the old age of study participants. In the Women Health Initiative randomised controlled trial, the use of oestrogen alone was not associated with increased lung cancer incidence or mortality (Chlebowski *et al*, 2010), whereas oestrogen plus progestin therapy was associated with an increased lung cancer mortality but not incidence (Chlebowski, 2009). However, the limited number of observed cases precluded firm conclusions.

Most of the scientific literature on oral contraceptive use (OC) points to no association with lung cancer risk (Taioli and Wynder, 1994; Elliott and Hannaford, 2006; Kabat *et al*, 2007; Schwartz *et al*, 2007; Weiss *et al*, 2008; Seow *et al*, 2009; Hannaford *et al*, 2010; Vessey *et al*, 2010; Meinhold *et al*, 2011), with two possible exceptions showing, however, opposite results: a reduced lung cancer risk among ever OC users in a case-control study (Kreuzer *et al*, 2003) and a slightly increased risk among women using OC for >5 years in a cohort study (Baik *et al*, 2010).

To shed light on the role of hormonal factors in lung cancer aetiology, we evaluated the association between hormone use (OC and HRT) and lung cancer risk in women, by performing a pooled analysis of data from six case-control studies from the International Lung Cancer Consortium (ILCCO). The large sample size allowed to examine the risk by type of HRT, smoking status and histology.

MATERIALS AND METHODS

Study population. The International Lung Cancer Consortium (<http://ilcco.iarc.fr>) was established in 2004 with the aim of sharing comparable data from ongoing lung cancer case-control and cohort studies. The individual-level data across studies have been pooled. Data were checked for inconsistency, inadmissible values, aberrant distributions and outliers before being standardised into a common data set. To be included in the present pooled analysis, studies had to have data on reproductive and hormonal factors in women. Seven case-control studies were eligible. One of them (MSKCC), however, had both cases and controls represented by lung cancer patients (multiple and single non-small-cell lung cancers, respectively) and it was excluded. Finally, the analysis included a total of six studies, with 1961 cases and 2609 controls overall (Table 1). Three studies were conducted in the United States (MLCS, NELCS and WELD), two in Europe (EAGLE and ESTHER) and one in Canada (TORONTO). Most studies recruited population controls only, whereas two studies recruited also hospital controls (319 and 353 in the MLCS and TORONTO study, respectively). Controls were frequency matched to cases on age in all studies but the TORONTO study, some were also matched on ethnicity, one on residential area and in the MLCS study an additional matching variable for hospital controls was smoking status.

The pooled data set included the following clinical and sociodemographic data: case status (case or control), age at diagnosis (cases) and at interview (cases and controls), ethnicity, education, body mass index (BMI), lifetime cigarette smoking history and lung cancer histology (coded according to the *International Classification of Diseases for Oncology*, Third Edition; Fritz *et al*, 2000). Institutional approval and written informed consent from participants had been collected at each study site.

Reproductive and hormonal factors. Reproductive variables of interest were: menopause status (postmenopausal defined as 'no menstrual periods for at least 1 year' before the time of diagnosis or interview), menopause reason (natural vs induced: surgery/

Table 1. Characteristics of the included studies

Study name Principal investigator	Country	Enrolment period	Matching variables	Cases	Controls Source	Total
EAGLE MT Landi (Pesatori <i>et al</i> , 2013)	Italy	2002–2005	Age, residential area	407	499 Population	906
ESTHER H Brenner	Germany	2000–2003	Age	52	52 Population	104
MLCS CC Harris (Meinhold <i>et al</i> , 2011)	USA	1998–2010	Age, ethnicity, pack-years, hospital	540	777 Population + hospital	1317
NELCS EJ Duell (Heck <i>et al</i> , 2009)	USA	2005–2008	Age	150	148 Population	298
TORONTO JR McLaughlin (Brenner <i>et al</i> , 2010)	Canada	1997–2002	Ethnicity	235	558 Population + hospital	793
WELD AG Schwartz (Schwartz <i>et al</i> , 2007)	USA	2002–2007	Age, ethnicity	577	575 Population	1152
Total				1961	2609	4570

chemotherapy or radiation therapy/other) and menopause age. Information on ovariectomy (defined as bilateral ovary removal) and hysterectomy was collected in four (EAGLE, ESTHER, MLCS and TORONTO) and three (ESTHER, MLCS and TORONTO) studies, respectively.

Main exposures of interest were OC use and HRT. We defined OCs as ‘pills for birth control’, and HRT as ‘any use of hormones (pills or patches) just before, during or after menopause’ (as suggested by Meinhold *et al*, 2011), with ‘just before’ delimited to 1 year before menopause.

The durations of OC/HRT were defined as the difference between OC/HRT quitting and starting ages (or between age at diagnosis and starting age if quitting age fell beyond age at diagnosis), or the declared years of total consumption. When the information was available (MLCS, TORONTO and WELD), periods (years or months) of suspension from hormone use were considered in calculating therapy duration.

Three studies (MLCS, TORONTO and WELD) provided information on HRT type as well. We categorised HRT type as: ‘Oestrogen (E) Only’ or ‘Progesterone (P) Only’ if a woman used only oestrogens or only progesterone as HRT in her entire life; ‘E + P Only’ if a woman used combined oestrogens and progesterone as HRT in her entire life; and ‘E + P Mixed’ if a woman used unopposed oestrogens, progesterone or combined HRT in different moments of her life. The HRT type-specific durations were calculated for the ‘E Only’ and ‘E + P Only’ categories (the most represented ones), following the same criteria as previously defined.

Statistical analysis. Potential differences between cases and controls were evaluated with the Mann–Whitney *U*-test for ordinal and continuous variables and the Pearson’s χ^2 test for categorical variables, after excluding subjects without available information. We excluded 43 subjects because of missing information on smoking, reproductive and hormonal variables (41 cases and 2 controls).

To model information on smoking habits, we first used a common variable on smoking status (never/former/current) from the pooling data set. Never smokers were individuals who reported smoking <100 cigarettes in their lifetime. Former smokers reported smoking cessation at least 2 years before interview. We then represented most of the relevant aspects of smoking history (duration, time as cessation and cigarettes/day) by a single aggregate measure, the Comprehensive Smoking Index (CSI), as originally proposed by Hoffmann *et al* (2001), and subsequently modified by Leffondré *et al* (2006).

To investigate potential associations between lung cancer and the independent variables of interest, we performed unconditional logistic regression models, adjusted for age (<55; 55–62; 63–69; and ≥ 70 years) at diagnosis or interview (for cases and controls respectively), ethnicity (Caucasian/non-Caucasian), smoking status (ever/never), CSI (continuous), BMI (continuous), education (low, medium, high) and study (categorical). Further adjustment for age at menopause, number of livebirths and environmental tobacco smoke (at home during childhood or adulthood and at work) did not change the results.

For categorical exposure variables with more than two levels, we performed tests for trend (both including and excluding ‘non-exposed subjects’ as reference category) by assigning a unit score to each category.

To evaluate interaction on a multiplicative scale between the main variables of interest (OC, HRT and HRT type) and smoking or BMI, we ran logistic regression models stratifying by smoking status (never/former/current) and BMI (underweight/normal weight/overweight/obese), and compared the log-likelihood of models with and without product terms. In three studies, BMI clearly referred to at least 1 year before diagnosis or interview, whereas current BMI was collected in the remaining studies. As findings did not differ between the two groups, we considered BMI as a unique variable independently from the collection time (data not shown). For smoking, we also evaluated interaction on an additive scale, calculating the ‘Relative Excess Risk due to Interaction’ (RERI) (Andersson *et al*, 2005). The lowest risk category of OC/HRT use in never smokers was used as reference (Rothman, 2002).

Meta-analyses of study-specific odds ratios (ORs) and 95% confidence intervals (95% CIs) were performed as well. Test for homogeneity based on Cochran’s *Q* (Cochran, 1954) and I^2 (Higgins *et al*, 2003) statistics were calculated. If no substantial heterogeneity was detected, we ran a fixed effect meta-analysis using inverse-variance weighting (Egger *et al*, 2001) to calculate summary estimates. When there was evidence of some heterogeneity, we conducted an influence analysis, evaluating the impact of each single study on the meta-analytic estimate. As a sensitivity analysis, we re-ran the fixed effect meta-analysis after excluding the study contributing the most to the heterogeneity.

Finally, we performed multinomial logistic regression models to test the homogeneity (using Wald test) of the association between the main hormonal variables (OC/HRT) and lung cancer risk across main histologic types (adenocarcinoma, squamous cell carcinoma and small cell carcinoma).

All tests were two sided. Statistical analyses were performed using Stata 12 (Stata Corp 2011, College Station, TX, USA).

RESULTS

Table 2 reports the demographic and hormonal factor distributions for cases and controls. The majority of the population was Caucasian, cases had lower education, a greater proportion of normal or underweight women and, as expected, a higher proportion of smokers. Adenocarcinoma was the predominant histologic subtype of lung cancer followed by squamous cell carcinoma. With regard to reproductive and hormonal factors, cases included a higher proportion of women who were postmenopausal. Data on bilateral ovariectomy were collected in four studies (1234 cases, 63%, and 1886 controls, 72%). Information on hysterectomy was available in three studies (827 cases, 42%, and 1387 controls, 53%).

The proportion of women who ever used OC did not differ between cases and controls, whereas HRT was more frequent among controls. In the subgroup of women for whom data on HRT type were available, approximately half of the study population used oestrogen only therapy, whereas 24.9% of cases and 29.4% of controls had combined HRT (E + P Only).

Table 3 shows the pooled ORs (adjusted for age at interview, ethnicity, smoking status, CSI, BMI, education and study) for each exposure variable. We found a reduced risk of lung cancer for women who ever used OC and no evidence of a dose-response relationship associated with the duration of OC use among users (P -trend excluding never users as reference category = 0.2). The same held for HRT, with a decreased lung cancer risk among ever users and no trend with treatment duration. Similar results emerged when analysing HRT type: both the use of oestrogen only and combined HRT were associated with decreased risks (OR = 0.76; 95% CI: 0.61–0.94 and OR = 0.66; 95% CI: 0.49–0.88, respectively), without a clear dose-response relationship with years of use. The exclusion of hospital controls did not change the results (data not shown).

Women having ever used both OC and HRT showed the greatest reduction in risk when compared with never users (OR = 0.61; 95% CI: 0.47–0.78).

Study-specific ORs and meta-analytic estimates for OC use, HRT and HRT type are shown in Figure 1. The inverse-variance fixed-effect ORs for each variable examined were quite similar to those obtained with the logistic regression model. No heterogeneity across studies was detected for OC ($I^2 = 0.0\%$), whereas HRT study-specific estimates showed a low heterogeneity ($I^2 = 35.9\%$). The influence analysis to detect the study-specific contribution to the meta-analytic estimate of HRT showed the NELCS study as contributing the most to the interstudy variability (Supplementary Figure 1). We thus re-ran the meta-analysis after excluding NELCS, and found no heterogeneity ($I^2 = 0.0\%$) with a slightly lower OR (0.74; 95% CI: 0.63–0.88).

We examined the results for OC, HRT and HRT type (Table 4) by smoking status (never/former/current). The point estimates associated with all three variables were generally reduced across the smoking strata. For OC the greatest risk reduction was seen in former smokers; HRT showed a statistically significant decreased risk among never smokers. Looking at HRT type, the use of oestrogen only showed the lowest reduced risk among former smokers, whereas the combined HRT was associated with the greatest reduction in risk among never smokers.

No interaction between hormonal factors and smoking status was detected on both multiplicative (OC P for interaction = 0.4; HRT P for interaction = 0.3; oestrogen only P for interaction = 0.6; E + P only P for interaction = 0.2) and additive scale

(Supplementary Table 1: the lower CIs of all calculated RERIs fell below zero).

The association between hormone use and lung cancer risk did not change across BMI categories (Supplementary Table 2).

When assessed by histologic subtypes (Table 5), the greatest reduction in risk associated with the ever use of OC was seen for squamous cell carcinoma (OR = 0.53; 95% CI: 0.37–0.76), whereas HRT was associated with a significant reduction in lung cancer risk in both adenocarcinoma and small cell carcinoma (OR = 0.79; 95% CI: 0.66–0.95 and OR = 0.37; 95% CI: 0.19–0.71, respectively). When stratifying by smoking status across histologic subtypes (Supplementary Table 3) the findings, although hampered by small numbers in some cells, basically confirmed what was observed in the entire study population (Table 5).

The analysis on HRT type in women with adenocarcinoma confirmed what was observed in the whole population: OR = 0.76 (95% CI: 0.59–0.98) for oestrogen only and OR = 0.59 (95% CI: 0.41–0.83) for combined E + P. Similarly, no relevant differences were observed in the stratum-specific estimates of smoking status categories.

DISCUSSION

Our study is one of the largest investigations conducted to date to evaluate the association between HRT and OC use with lung cancer risk in women. Only one cohort study (Brinton *et al*, 2011) included a larger number of cases but did not collect information on HRT type.

Overall, we found a reduced lung cancer risk for both OC use and HRT. The reduction in lung cancer risk appeared only marginally, if not at all, influenced by the duration of OC use or HRT. The greatest reduction in risk was seen among women using both OC and HRT during their whole life. The inverse association between HRT and lung cancer was found in both women who ever used E only and women who ever used E + P formulation. The associations were not modified by BMI. When we stratified by smoking status, there was no evidence of interaction on both multiplicative and additive scales between hormone use and smoking. However, the risk reduction was somehow attenuated among smokers. It is well recognised that smoking can interact with oestrogen metabolism through the induction of phase-I enzymes (e.g., CYP1A1 and CYP1B1), leading to both the activation of cigarette smoke carcinogens and the production of highly reactive catechols that form DNA adducts and activate ER (Meireles *et al*, 2010; Siegfried, 2010). Smoking is associated with a lower total body fat mass and therefore reduces the major source of oestrogens in postmenopausal women (i.e., the adipose tissue, where androgens are converted to oestrogens) (Tanko and Christiansen, 2004). All these mechanisms might be invoked as a possible explanation of the attenuation of the observed risk reduction among smokers.

The protective effect of OC use was more evident for squamous cell histology, whereas the greatest reduction in risk for HRT was found for small cell carcinoma; however, the small number of cases in these histology subtypes prevents any firm conclusion.

Our findings suggest that exogenous hormones may have a protective effect in lung cancer development consistently with a meta-analysis of previously published case-control studies showing a reduced lung cancer risk in HRT ever users (OR 0.81; 95% CI 0.68–0.97) (Oh *et al*, 2010).

The evidence emerging from cohort studies is murkier. Three cohort studies in Asian non-smoking women lacked statistical power (Liu *et al*, 2005; Weiss *et al*, 2008; Seow *et al*, 2009). The findings in the Cancer Prevention Study II Nutrition Cohort support our results (Rodriguez *et al*, 2008), whereas other cohort

Table 2. Demographic, reproductive and hormonal characteristics of the study population among cases and controls

Characteristic	Cases		Controls	
Age at interview (years)				
<55	436	(22.2)	733	(28.1)
55–62	457	(23.3)	609	(23.3)
63–69	495	(25.2)	636	(24.4)
≥70	573	(29.2)	631	(24.2)
	<i>P</i> < 0.001			
Ethnicity				
Caucasian	1590	(81.1)	2057	(78.8)
Non-Caucasian	367	(18.7)	549	(21.1)
African-American	135	(6.9)	132	(5.1)
Mexican	161	(8.2)	304	(11.7)
Asian	45	(2.3)	61	(2.3)
Mixed ^a	26	(1.3)	52	(2.0)
Missing	4	(0.2)	3	(0.1)
	<i>P</i> = 0.05			
Education (years of attendance)				
Low (1–9)	362	(18.5)	344	(13.2)
Medium (10–15)	969	(49.4)	964	(37.0)
High (≥ 16)	608	(31.0)	1250	(47.9)
Missing	22	(1.1)	51	(2.0)
	<i>P</i> < 0.001			
Smoking status				
Never	344	(17.5)	1251	(48.0)
Former	671	(34.2)	665	(25.5)
Current	935	(47.7)	658	(25.2)
Missing	11	(0.6)	35	(1.3)
	<i>P</i> < 0.001			
Comprehensive smoking index (CSI)	1.35	(0.59–1.74)	0.02	(0–0.93)
	<i>P</i> < 0.001			
BMI (kg m⁻²)				
Underweight (< 18.5)	111	(5.7)	53	(2.0)
Normal (18.5–24.9)	887	(45.2)	1049	(40.2)
Overweight (25.0–29.9)	587	(29.9)	762	(29.2)
Obese (≥ 30.0)	349	(17.8)	714	(27.4)
Missing	27	(1.4)	31	(1.2)
	<i>P</i> < 0.001			
Histology				
SCLC	84	(4.2)	–	–
NSCLC	1643	(83.8)	–	–
Squamous cell	266	(13.6)	–	–
Large cell	67	(3.4)	–	–
Adenocarcinoma	1074	(54.8)	–	–
Non-small-cell carcinoma/ NOS	236	(12.0)	–	–
Carcinoma/NOS	52	(2.7)	–	–
Carcinoid	4	(0.2)	–	–
Other/missing/info NA	178	(9.1)	–	–
Menopause status				
Premenopausal	156	(8.0)	508	(19.5)
Postmenopausal	1792	(91.4)	2093	(80.2)
Missing	13	(0.7)	8	(0.3)
	<i>P</i> < 0.001			
Number of livebirths				
Nulliparous	270	(13.8)	439	(16.8)
1	341	(17.4)	415	(15.9)
2	582	(29.7)	815	(31.2)
3+	766	(39.1)	926	(35.5)
Missing	2	(0.1)	14	(0.5)

Table 2. (Continued)

Characteristic	Cases		Controls	
	<i>P</i> < 0.001			
Menopause reason				
Natural	1080	(60.3)	1307	(62.5)
Induced	703	(39.2)	779	(37.2)
Surgery	558	(31.1)	679	(32.4)
Chemo-/radiotherapy	86	(4.8)	51	(2.4)
Other	59	(3.3)	49	(2.4)
Missing	9	(0.5)	7	(0.3)
	<i>P</i> = 0.2			
Menopause age (years)	47	(40–50)	48	(42–52)
	<i>P</i> < 0.001			
Natural	49	(46–52)	50	(48–53)
	<i>P</i> < 0.001			
Induced	40	(34–46)	41	(36–47)
	<i>P</i> = 0.01			
Ovariectomy^b				
No	1027	(83.2)	1615	(85.6)
Yes	204	(16.5)	271	(14.4)
Missing	3	(0.3)	0	–
	<i>P</i> = 0.09			
Hysterectomy^c				
No hysterectomy/no ovariectomy	530	(64.1)	966	(69.7)
No hysterectomy/ovariectomy	18	(2.2)	20	(1.4)
No hysterectomy/ovariectomy unknown	1	(0.1)	0	–
Hysterectomy/no ovariectomy	127	(15.4)	197	(14.2)
Hysterectomy/ovariectomy	142	(17.2)	194	(14.0)
Hysterectomy/ovariectomy unknown	9	(1.1)	10	(0.7)
	<i>P</i> = 0.06			
Oral contraceptives (OC)				
Never	818	(41.7)	1020	(39.1)
Ever	958	(48.9)	1322	(50.7)
Missing	185	(9.4)	267	(10.2)
	<i>P</i> = 0.1			
OC duration (years)	4	(1–9)	4.9	(1.5–9.8)
	<i>P</i> = 0.02			
Hormone replacement therapy (HRT)^d				
Never	1078	(60.2)	1094	(52.3)
Ever	699	(39.0)	995	(47.5)
Missing	15	(0.8)	4	(0.2)
	<i>P</i> < 0.001			
HRT duration (years) ^d	7	(2.5–13.9)	6.1	(2–13)
	<i>P</i> = 0.5			
HRT type^e				
Oestrogen (E) only	271	(49.0)	397	(49.2)
Progesterone (P) only	7	(1.3)	14	(1.7)
E + P only	138	(24.9)	237	(29.4)
E + P mixed	33	6.0	56	(6.9)
Missing	104	(18.8)	103	(12.8)
	<i>P</i> = 0.6			

Abbreviations: BMI = body mass index; info NA = information not available; NOS = not otherwise specified; NSCLC = non-small-cell lung carcinoma; SCLC = small-cell lung carcinoma. Characteristics are summarised as absolute and relative frequencies, that is, *N* (%), except for CSI, menopause age and OC/HRT durations where medians and (25th–75th percentiles) were used; percentages may not add up to 100.0 because of rounding. *P* = Mann–Whitney *U*-test after excluding subjects without available information; for ethnicity (Caucasian vs non-Caucasian), menopause reason (natural vs induced) and other categorical variables, χ^2 test was performed.

^aOther Latino, Native American, Other.

^bDefined as bilateral ovary removal (only available in EAGLE, ESTHER, MLCS and TORONTO).

^cOnly available in ESTHER, MLCS and TORONTO.

Table 3. Association between main hormonal factors and lung cancer risk

Hormonal factor	Cases	Controls	OR	95% CI	p ^a
OC					
Never	818	1020	1		
Ever	958	1322	0.81	(0.68–0.97)	0.02
Missing	185	267			
OC duration					
Never users	818	1020	1		
≤1 year	262	316	0.85	(0.67–1.09)	
1–5 years	287	421	0.81	(0.65–1.03)	
5–10 years	230	330	0.78	(0.61–1.00)	
>10 years	156	238	0.70	(0.53–0.93)	0.007
Missing	208	284			0.2 ^b
HRT^c					
Never	1078	1094	1		
Ever	699	995	0.77	(0.66–0.90)	0.001
Missing	15	4			
HRT duration^c					
Never users	1078	1094	1		
≤2 years	157	257	0.61	(0.47–0.78)	
2–7 years	166	227	0.84	(0.65–1.09)	
7–14 years	156	220	0.79	(0.60–1.03)	
>14 years	142	209	0.70	(0.53–0.92)	0.004
Missing	93	86			0.7 ^b
HRT type^d					
Never users	676	685	1		
Oestrogen Only	271	397	0.76	(0.61–0.94)	0.01
E + P only	138	237	0.66	(0.49–0.88)	0.005
Missing	120	119			
HRT type-specific duration^d					
Oestrogen only					
Never users	676	685	1		
≤2 years	67	101	0.67	(0.47–0.98)	
2–8 years	66	92	0.81	(0.56–1.19)	
8–16 years	61	91	0.80	(0.54–1.18)	
>16 years	70	105	0.71	(0.49–1.02)	0.03
					0.9 ^b
E + P only					
Never users	676	685	1		
≤2 years	30	60	0.55	(0.33–0.93)	
2–5 years	35	60	0.69	(0.41–1.16)	
5–10 years	32	67	0.52	(0.31–0.87)	
>10 years	39	47	0.94	(0.56–1.57)	0.04
					0.5 ^b
OC/HRT combined^c					
OC never/HRT never	539	552	1		
OC ever/HRT never	426	390	0.80	(0.62–1.03)	0.09
OC never/HRT ever	224	327	0.74	(0.57–0.96)	0.02
OC ever/HRT ever	417	566	0.61	(0.47–0.78)	<0.001
Missing	186	258			

Abbreviations: CI = confidence interval; E + P = oestrogen + progesterone; HRT = hormone replacement therapy; OC = oral contraceptive; OR = odds ratio. Effect estimates are expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs) Logistic regression model adjusted for age at interview (categorical), ethnicity (Caucasian/non-Caucasian), smoking status (ever/never), comprehensive smoking index (CSI; continuous), body mass index (BMI; continuous), education (categorical) and study.

^aFor ordinal variables, test for trend was performed.

^bP-trend after excluding reference category.

^cIn postmenopausal women only.

^dOnly available in MLCS, TORONTO and WELD.

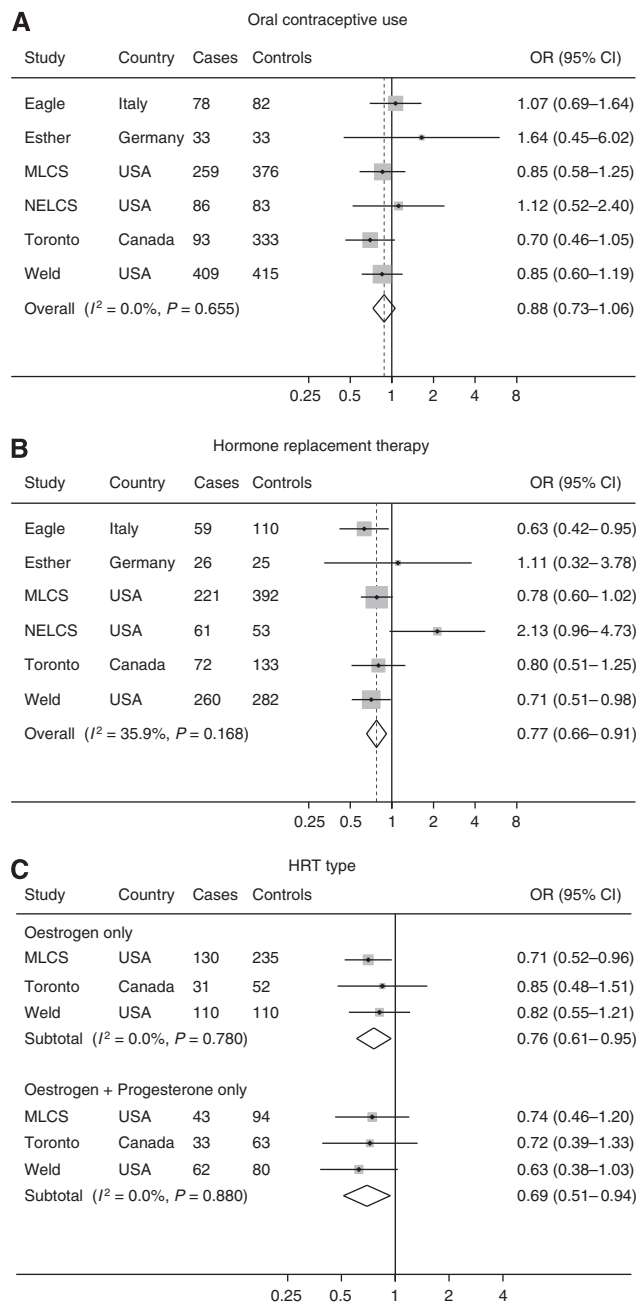


Figure 1. Study-specific odds ratios and meta-analytic estimates for oral contraceptive use (A), hormone replacement therapy (B) and HRT Type (C). Inverse-variance fixed-effect ORs adjusted for age at interview, ethnicity, smoking status, CSI, BMI and education. The number of cases and controls refers to OC/HRT/HRT Type ever users.

studies (Kabat *et al*, 2007; Slatore *et al*, 2010; Brinton *et al*, 2011; Clague *et al*, 2011) showed no association between HRT and lung cancer risk.

Considering HRT type, oestrogen only was not associated with an increased lung cancer risk in either observational studies (Blackman *et al*, 2002; Rodriguez *et al*, 2008; Baik *et al*, 2010; Slatore *et al*, 2010; Clague *et al*, 2011) or a randomised clinical trial (Chlebowski *et al*, 2010), whereas the use of combined oestrogen + progestin HRT was associated with an increased risk in two studies: long-term users (> 10 years) showed a modest augmented risk in the VITAL study (Slatore *et al*, 2010), whereas the Women Health Initiative randomised trial (Chlebowski, 2009) reported an

association with increased lung cancer mortality but not incidence (although based on a small number of deaths).

Inconsistent findings between studies might depend on study design (case-control vs cohort studies). Case-control studies are possibly more prone to selection and sometimes to recall bias. On the other hand, cohort studies may be affected by low respondent rates at enrollment and poorer information on hormone use history (Slatore *et al*, 2010; Brinton *et al*, 2011).

Our study has several strengths: we could rely on a large sample size that allowed us to investigate duration of OC and HRT over a long period of time; we were also able to analyse HRT type and to control for major confounders. All the studies included in our analysis enrolled incident lung cancer cases from well-defined source populations. One study (WELD) excluded women with a previous history of breast cancer because of the association between reproductive factors and this tumour. The number of subjects with previous breast cancer diagnosis was only 76 (30 cases and 46 controls). Analyses excluding these subjects yielded almost identical results. Therefore, the associations observed in our study between exogenous hormones and lung cancer are not driven by risk factors of or treatment for breast cancer.

One of the key issues in case-control studies is the appropriate choice of controls. In this pooled analysis, four out of six studies enrolled only controls sampled from the underlying populations. Two studies used a mix of population and hospital controls. Risk estimates remained virtually the same after excluding hospital controls. Hence, a major source of selection bias was taken into account. Another potential important source of selection bias is differential participation among cases and controls. Selection bias could occur if participation was associated with both exposure and outcome. Even if its occurrence cannot be completely ruled out, we chose to adjust for education (a strong determinant of hormone use, lung cancer and participation), thus substantially reducing nonresponse bias (Richiardi *et al*, 2008).

Although information on hormone use was self-reported, recall is unlikely to have occurred differentially for cases and controls because of the lack of knowledge regarding the possible link with lung cancer at the time the studies were conducted.

Data on HRT type were available only for a portion of the study population, and some subgroup analyses might have been influenced by small sample size in a few categories. Finally, although in theory residual confounding by smoking can never be completely excluded, a detailed smoking history was collected that allowed us to adjust for smoking status, intensity, duration and time since quitting.

The OC use has been previously investigated in five case-control (Taioli and Wynder, 1994; Kreuzer *et al*, 2003; Elliott and Hannaford, 2006; Schwartz *et al*, 2007; Meinhold *et al*, 2011) and five cohort (Kabat *et al*, 2007; Weiss *et al*, 2008; Seow *et al*, 2009; Baik *et al*, 2010; Brinton *et al*, 2011) studies, and most of them did not show an association with lung cancer risk. A reduction in lung cancer risk was observed by Kreuzer *et al* (2003), but a selection bias due to a particularly poor response among controls cannot be excluded. In the Nurses' Health Study (Baik *et al*, 2010) the use of OC for > 5 years was associated with a slightly increased risk mainly among smokers. In the United Kingdom, two large prospective studies have been established in the 1970s to evaluate health effects among women who have used OC (the RCGP and the Oxford FPA cohort studies). In both studies, the most recent updated mortality (Hannaford *et al*, 2010; Vessey *et al*, 2010) and cancer incidence did not reveal increased lung cancer risk when OC ever users were compared with never users.

Oestrogens may be involved in lung carcinogenesis through multiple pathways not yet completely clarified. Oestrogen effects are likely to be mediated by the oestrogen receptors (ERs) α and β . Oestrogen receptor- α mRNA is expressed at low levels in the lung,

Table 4. Association between main hormonal factors and lung cancer risk: analyses stratified by smoking status

	Never smokers					Former smokers					Current smokers					P for interaction
	Cases	Controls	OR	95% CI	P	Cases	Controls	OR	95% CI	P	Cases	Controls	OR	95% CI	P	
OC																
Never	195	585	1			253	230	1			363	193	1			
Ever	128	585	0.89	(0.65–1.21)	0.5	338	368	0.72	(0.52–1.00)	0.05	489	347	0.88	(0.65–1.20)	0.4	0.4
Missing	21	81				80	67				83	118				
HRT^a																
Never	194	527	1			349	270	1			527	284	1			
Ever	104	438	0.73	(0.54–0.98)	0.04	268	292	0.77	(0.59–1.01)	0.06	326	258	0.85	(0.65–1.12)	0.2	0.3
Missing	3	2				5	2				7	0				
HRT type^b																
Never Users	105	292	1			250	170	1			313	211	1			
Oestrogen only	45	154	0.94	(0.61–1.46)	0.8	111	119	0.65	(0.46–0.94)	0.02	115	124	0.78	(0.54–1.12)	0.2	0.6
E + P only	20	100	0.52	(0.28–0.95)	0.03	45	63	0.61	(0.35–1.04)	0.07	72	68	0.97	(0.60–1.55)	0.9	0.2
Missing	12	54				45	38				63	27				

Abbreviations: CI = confidence interval; E + P = oestrogen + progesterone; HRT = hormone replacement therapy; OC = oral contraceptive; OR = odds ratio. Effect estimates are expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). Logistic regression model adjusted for age at interview (categorical), ethnicity (Caucasian/non-Caucasian), comprehensive smoking index (CSI; continuous), body mass index (BMI; continuous), education (categorical) and study.

^aIn postmenopausal women only.

^bOnly available in MLCS, TORONTO and WELD.

Table 5. Association between main hormonal factors and lung cancer risk across histologic types

	Adenocarcinoma					Squamous cell carcinoma				Small cell carcinoma				Test for homogeneity ^a	
	Controls	Cases	OR	95% CI	P	Cases	OR	95% CI	P	Cases	OR	95% CI	P		
OC															
Never	1020	410	1			122	1			49	1				
Ever	1322	585	0.97	(0.79–1.19)	0.8	97	0.53	(0.37–0.76)	0.001	35	0.91	(0.50–1.65)	0.8	0.004	
Missing	267	79				47				0					
HRT^b															
Never	1094	545	1			160	1			62	1				
Ever	995	407	0.79	(0.66–0.95)	0.01	90	0.79	(0.58–1.09)	0.2	15	0.37	(0.19–0.71)	0.003	0.07	
Missing	4	10				2				2					

Abbreviations: CI = confidence interval; HRT = hormone replacement therapy; OC = oral contraceptive; OR = odds ratio. Effect estimates are expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). Multinomial logistic regression model adjusted for age at interview (categorical), ethnicity (Caucasian/non-Caucasian), smoking status (ever/never), comprehensive smoking index (CSI; continuous), body mass index (BMI; continuous), education (categorical) and study.

^aWald test.

^bIn postmenopausal women only.

whereas ERβ has been shown to be expressed in both normal and tumour pulmonary tissue (Kaiser *et al*, 1996; Omoto *et al*, 2001). The AF-1 domain of ERβ is truncated compared with ERα, and ERβ is thus less active in inducing transcriptional activation (Delaunay *et al*, 2000).

Moreover, the oestrogen receptors α and β are expressed in a wide range of immune cells involved in both the innate and adaptive immune response (Cutolo *et al*, 2010). Oestrogens might

therefore be involved in strengthening the immune response against neoplastic cells.

An additional hypothesis is that part of the protective effect exerted by oestrogens might be mediated by interaction 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, as the expression of the EGF

receptor protein was shown to be downregulated in response to oestrogens (Stabile *et al*, 2005).

Hormone replacement therapy has been shown to decrease insulin-like growth factor 1 (IGF1) (Yu *et al*, 1999), and low levels of IGF1 have been associated with a reduced risk of lung cancer (Schabath *et al*, 2004).

In conclusion, our results suggest that exogenous hormones could play a protective role in lung cancer aetiology and find some support from the biological mechanisms underlying lung cancer development. At the same time, the absence of a clear dose-response relationship urges cautiousness in interpreting the observed association. Moreover, the complex crosstalk between different pathways requires further and large studies to clarify the role of exogenous hormones and the involved mechanisms in lung cancer aetiology.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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