RESEARCH ARTICLE

Association of Oral Contraceptives Use and Lung Cancer Risk among Women: an Updated Meta-analysis Based on Cohort and Case-control Studies

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Abstract

Background: Previous studies on the association of oral contraceptives (OC) use and lung cancer generated inconsistent findings. The aim of this study was to confirm any definite correlation between OC use and lung cancer risk. Methods: Publications were reviewed and obtained through PubMed and EMBASE databases literature search up to November, 2013. Reference lists from retrieved articles were also reviewed. The language of publication was restricted to English. A meta-analysis was performed to evaluate the association by calculating pooled odds ratios (ORs) and 95% confidence intervals (CIs). Results: A total of 14 studies consisting of 9 case-control studies and 5 cohort studies were finally included in this meta-analysis. There was no significant association observed between OC use and lung cancer risk in the overall analysis (OR=0.91; 95% CI=0.81-1.03). There was a significant protective effect in Europe (OR=0.74; 95% CI=0.60-0.91) and a borderline significant protective effect with an adenocarcinoma histology (OR=0.90; 95% CI=0.80-1.01) in subgroup analyses. No association was observed for methodological quality of study, study design, smoking status and case number of study. Conclusion: This meta-analysis suggests that OC use is not likely to be associated with the risk of lung cancer at all. While a significant protective effect of OC use on lung cancer was observed in Europe, interpretation should be cautious because of the potential biases of low-quality studies. At the same time, more attention should be paid to the possible association of OC use with adenocarcinoma of lung. Our findings require further research, with well-conducted and large-scale epidemiological studies to confirm effects of OC use on lung cancer.

Keywords: Oral contraceptives - meta-analysis - lung cancer - adenocarcinoma

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Introduction

Lung cancer is the leading cause of cancer mortality worldwide (Edwards et al., 2005). The incidence rates of male lung cancer have been declining for the past two decades, while the increasing incidence rates for females have only begun to stabilize in recent years (Jemal et al., 2009). The differences between male and female are mostly thought to be attributable to the long term trend in cigarette smoking (Jemal et al., 2009). The hypothesis that women who smoke have a higher susceptibility to lung cancer than men has emerged, though with conflicting epidemiological results (Twombly, 2004). A lot of studies found that female smokers have higher relative risks for lung cancer than male smokers (Brownson et al., 1992; Risch et al., 1993; Zang and Wynder, 1996). They speculated that sex hormones might influence the metabolism of tobacco carcinogens by cytochrome p450 in the liver (Zang and Wynder, 1996). Meanwhile, estrogen receptors or estrogen binding sites were found to be present in non-small cell lung cancer tissues (Kawai et al., 2005; Schwartz et al., 2005; Wu et al., 2005). All these clues indicated that sex hormones might play an important role in lung carcinogenesis.

Oral contraceptives (OC) which comprised different types of estrogen and progesterone is one of the world-wide used and effective contraceptive measures. Since the introduction of OC in the early 1960s more than 300 million women are thought to have used it (Cogliano et al., 2005). Many studies have examined the potential association between OC use and cancer. The evidence indicates that current users of combined OC have been associated with an increased risk of cancer of the breast, cervix, and liver compared with non-users (La Vecchia et al., 2001; Smith et al., 2003; Tehranian et al., 2010; Lodha et al., 2011; Anothaisintawee et al., 2013). Long term (>5 years) consumption of oral contraceptive pills was identified as one of the most important risk factors for the occurrence of premenopausal breast cancer (Bidgoli et al., 2011). Nevertheless, current users of combined OC have a reduced risk of cancer of the endometrium, ovaries, and colorectum (Fernandez et al., 2001; La Vecchia et al., 2001; Cogliano et al., 2005).

Nowadays, a lot of studies have reported the

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association of OC use and lung cancer, but the results were still inconsistent. Kreuzer et al. (2003) and Pesatori et al. (2013) observed a reduction in lung cancer risk. On the contrary, in the Nurse's Health Study (Baik et al., 2010) duration of OC use longer than 5 years was associated with a slightly increased risk. Chen et al. (2009) conducted a meta-analysis and found there was no statistical relationship between lung cancer risk and OC use (OR = 0.95; 95% CI: 0.83-1.20). Nevertheless, Pesatori et al. (2013) performed a pooled analysis from the International Lung Cancer Consortium, a reduced lung cancer risk was found for OC use (OR = 0.81; 95% CI: 0.68-0.97). In order to confirm a definite correlation between OC use and lung cancer risk, we performed a literature search and conducted an update meta-analysis of available studies.

Materials and Methods

Search Strategy

We searched PubMed and EMBASE databases from their inception to November 2013 and systematically identified studies that evaluated the effect of OC use on the risk of lung cancer in human populations. Various combinations of the following terms were used in the search: "lung cancer", "lung neoplasm", "lung carcinoma", "birth control pills", "oral contraceptive*", "OC", "OCs", "oral contraceptive pills", "OCPs", "hormone", "contraceptive*", "estrogen*" and "oestrogen*". Only English language papers were included in the search. We also retrieved the references cited in the original articles or review articles concerning the relevant topic so as to potentially broaden the search for additional relevant publications.

Inclusion and Exclusion Criteria

The following criteria were used to select the articles for the meta-analysis: (a) case-control study or cohort study methodology was used; (b) evaluated the association between OC use and lung cancer risk; (c) reported the adjusted odds ratio (OR), relative risk (RR) or hazard risk (HR) and its 95% confidence interval (CI), for OC users versus OC never-users. The exclusion criteria used were: (a) had no available data for outcome measures or only provided the crude estimates; (b) data on mortality only or those only reported standardized incidence ratios (SIR); (c) the same population as another study (in this case, the most recent publication was included in the analysis).

Data Extraction

Two investigators (Wei Wu, Zhihua Yin) independently evaluated the eligibility of all retrieved publications and carefully extracted the relevant information from each included study with a standard protocol and data-collecting form based on the inclusion criteria. The original extraction data were checked by another investigator (Peng Guan), and disagreements were resolved by discussion among the three investigators. The items included in the data-collecting form were as follows: name of first author, year of publication, country, study design, participants, cases, age of participants, results of studies (adjusted OR, RR or HR with their corresponding 95% CIs), and adjusted variables in the design or data analysis.

Assessment of methodological quality

The methodological quality of included studies was assessed based on the Newcastle-Ottawa Scale (NOS) for quality of nonrandomized studies in meta-analyses (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). A ''star'' system of the NOS (range 0 to 9 stars) has been developed for the assessment: each study can be awarded a maximum of one star for each numbered item within the selection and exposure categories, while a maximum of two stars can be given for the comparability category. In this study, a study awarded 6 or more stars was considered as a high-quality study.

Statistical Analysis

Adjusted data (adjusted OR, RR or HR with 95% CI) were applied to compute pooled ORs with its 95% CI. The significance of the pooled ORs was determined by a Z test and two-sided P values <0.05 were considered significant. The chi-square-based Q statistical test was used for heterogeneity analysis (Cochran, 1950). P values <0.05 indicated significant heterogeneity among studies in this study. An I^2 test was used to detect heterogeneity across studies. Negative values of I^2 are set at zero, so that I^2 exists between 0% (no observed heterogeneity) and 100% (maximal heterogeneity) (Higgins and Thompson, 2002). In this study, if P value of Q statistical test <0.05 or I^2>50% suggested significant heterogeneity among studies. The DerSimonian and Laird method for a random-effects analysis was used when heterogeneity was significant (DerSimonian and Laird, 1986); otherwise, the Woolf method (inverse variance method) for a fixed-effects analysis was used (Woolf, 1955). Stratified analyses of each study by methodological quality of study, study design, region, histology of lung cancer, smoking status and case number were conducted to identify the relationship between OC use and lung cancer risk. Sensitive analyses were performed to evaluate the stability and reliability. Visual inspection of Begg's funnel plot and Egger's test were conducted to evaluate the publication bias in the meta-analysis and P values <0.05 were considered statistically significant (Egger et al., 1997; Stuck et al., 1998). The software Stata version 12.0 (Stata Corporation, College Station, TX, USA) was used for all statistical tests.

Results

A total of 14 articles were finally included in this study on OC use and lung cancer risk (Wu et al., 1988; Wu-Williams et al., 1990; Taioli and Wynder, 1994; Kreuzer et al., 2003; Elliott and Hannaford, 2006; Kabat et al., 2007; Schwartz et al., 2007; Dorjgochoo et al., 2009; Rosenblatt et al., 2009; Seow et al., 2009; Baik et al., 2010; Meinhold et al., 2011; Lo et al., 2013; Pesatori et al., 2013). A flow diagram shows how we selected relevant studies is presented in Figure 1. Of the 741 studies identified from the PubMed and EMBASE databases and 8 studies obtained through the references cited in

Table 1. Characteristics of the Studies Included in the meta-analysis

Author	Year	Country	Study Design	Participants	Cases	Age(years)	Adjusted OR or RR or HR	Matched or adjusted variables
Wu	1988	USA	PCC	732	366	30-75	<=2 year vs. none: 0.90(0.50-1.60); >2 year vs. none: 0.40(0.20-0.80)	Age, race, neighborhood, pack-years of smoking, years since smoking stopped, and depth of inhalation.
Seow	2009	Singapore	CS	35298	298	45-75	<10 year vs. none: 0.73(0.50-1.07); >=10 year vs. none: 1.33(0.70-2.52)	Age, year of interview, dialect group, educational level, body mass index, total vegetable intake, total fruit/juice intake, β-cryptoxanthin, total isothiocyanates, duration of smoking, cigarettes per day, and number of years since quitting
Kreuzer	2003	Germany	PCC	1723	811	<76	0.69(0.51-0.92)	Age, sex, region, log(packyear+1), time since smoking cessation, and education
Elliott	2006	United Kingdom	NCC	648	162	NG	1.00(0.70-1.60)	Age, smoking, social class, and parity except where the variable itself is being examined
Kabat	2007	Canada	CS	89835	750	40-59	0.91(0.78-1.06)	Parity , age at menarche, age at first birth , menopausal status, hormone replacement use, body mass index, education, smoking status, pack-years of smoking, study center, and randomization group
Schwartz	2007	USA	PCC	986	488	18-74	0.83(0.57-1.21)	Age at diagnosis/interview, race, pack-years, family history of lung cancer, current body mass index, personal history of chronic obstructive lung disease, years exposed to passive smoke in the workplace, and education level
Rosenblatt	2009	China	CS	267400	828	NG	0.87(0.69-1.10)	Parity, and age using linear splines unless otherwise noted
Dorjgochoo	2009	China	CS	66661	229	40-70	1.03(0.72-1.47)	Education, age at menarche , number of live births, cumulative breast feeding months, body mass index , exercised regularly in past 5 years, smoking, menopausal status, first-degree family history of cancer, and other contraceptive methods
Baik	2010	USA	CS	107171	1729	38-87	1.1(0.99-1.22)	Age at menopause, age at menarche, parity, type of menopause, PMH use, smoking status, age at start smoking, cigarettes per day, time since quitting, fruit/vegetable intake, body mass index, and environmental smoking exposure
Meinhold	2011	USA	PCC+HCC	1041	430	NG	1.24(0.92-1.69)	age, education, smoking, number of smoking adults in household, and current household income
Pesatori	2013	Italy	PCC	906	407	35-79	0.60(0.39-0.93)	Area, sex, residence, age at study, smoking, ETS, education, and body mass index
Lo	2013	Taiwan	HCC	2386	1190	>=18	1.25(0.98-1.61)	Age, sex, ethnic background, and years of education
Wu-Williams	1990	China	PCC	1924	965	<70	0.80(0.50-1.20)	Age, education, personal smoking, and study area
Taioli	1994	USA	HCC	483	180	NG	0.80(0.50-1.50)	Smoking, age at diagnosis, years of education, and body mass index

CS, cohort study; PCC, population-based case-control study; HCC, hospital-based case-control study; NCC, nested case-control study; NG, Not Given or No limitation

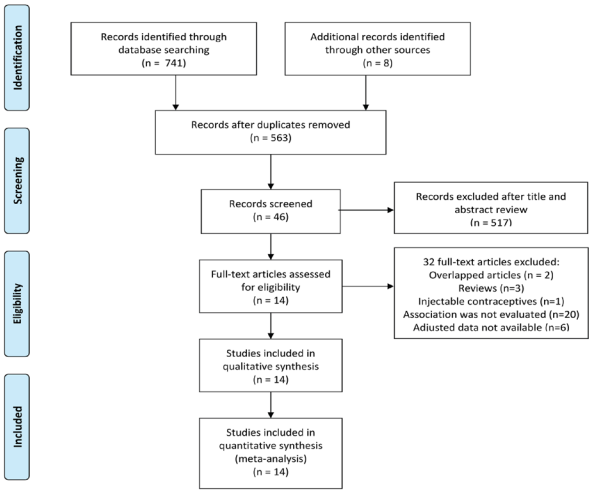

Figure 1. Flow Diagram of the Eligible Study Selection Process

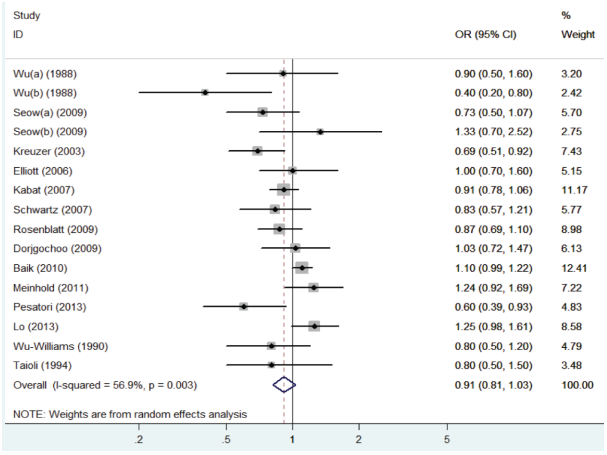

Figure 2. Forest Plot for Association between OC Use and Risk of Lung Cancer

the original articles and review articles, 186 studies were removed because of duplication. After reviewing titles and abstracts, 517 articles were excluded. After reading the full-text of the 46 articles, 32 articles were excluded. Among which, 2 articles were overlapped articles, 3 articles were reviews, 1 article was relevant to injectable contraceptives, 20 articles did not evaluate the association of OC use and lung cancer risk, 6 articles had no adjusted data.

Table 1 showed the characteristics of 14 eligible studies such as the first author's name, year of publication, country, study design, participants, cases, results of studies (adjusted OR, RR or HR with their corresponding 95% CIs) and matched or adjusted variables. The individual studies were published between 1988 and 2013. Five were cohort studies, and the remainders were case-control studies; including 1 nested case-control study, 5 population-based case-control studies, 2 hospital-based case-control studies and 1 study used both population and hospital controls. Of these studies, 5 conducted in Asia, 3 conducted in Europe and 6 conducted in North America. Twelve studies presented results for OC users versus OC never-users, while 2 studies separated the risk estimate according to duration of OC use. Most individual studies were adjusted for a wide range of potential confounders, including age, smoking, and body mass index et al.

The range of quality scores was from 5 to 7; the mean value for the 14 studies assessed was 5.64 stars. High quality studies included 4 case-control studies and 3 cohort studies.

As shown in Figure 2, our overall analysis of 14 studies showed that statistically significant heterogeneity was observed among these studies (P= 0.003), and I^2 was 56.9%. When analysis performed using random effect model, the estimate of the association between OC use and lung cancer risk was not significant (OR=0.91; 95% CI=0.81-1.03), and P value of the test for overall effect was 0.130.

Table 2 shows the associations between OC use and lung cancer risk in subgroup analyses by methodological quality of study, study design, region, histology of lung cancer, smoking status and case number of each study. There was no significant association between OC use and lung cancer risk in both high quality and low quality

Table 2. Stratified Analyses of OC Use on Lung Cancer Risk

Subgroup	N	Model	Heterogeneity		OR (95%CI)	*P*
			I^2 (%)	*P*		
Methodological quality of study						
High quality	7	Random	64.4	0.006	0.92 (0.78-1.09)	0.330
Low quality	7	Fixed	46.9	0.068	0.91 (0.81-1.03)	0.122
Study design						
Case-control study	9	Random	61.8	0.005	0.85 (0.70-1.05)	0.128
Cohort study	5	Fixed	46.9	0.093	1.01 (0.93-1.09)	0.890
Region						
Asia	5	Fixed	43.0	0.119	0.98 (0.86-1.11)	0.726
Europe	3	Fixed	36.4	0.207	0.74 (0.60-0.91)	0.004
North America	6	Random	59.5	0.022	0.95 (0.80-1.12)	0.520
Histology of lung cancer						
Adenocarcinoma	6	Fixed	49.0	0.057	0.90 (0.80-1.01)	0.065
Squamous cell carcinoma	2	Random	80.5	0.023	0.87 (0.46-1.62)	0.656
Small cell lung cancer	2	Random	91.0	0.001	0.78 (0.32-1.90)	0.592
Smoking status						
Smokers	2	Random	87.5	0.005	0.93 (0.74-1.18)	0.233
Non-smokers	5	Fixed	17.3	0.305	1.10 (0.93-1.30)	0.266
Case number						
<500 cases	8	Fixed	45.8	0.055	0.90 (0.78-1.03)	0.118
≥500 cases	6	Random	69.1	0.006	0.95 (0.81-1.11)	0.490

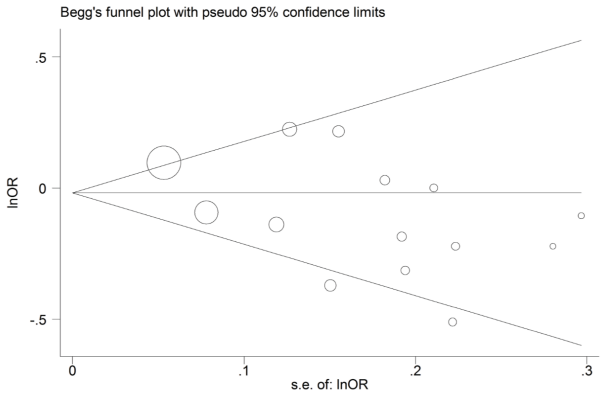

Figure 3. Begg's Funnel Plot for Publication Bias Test

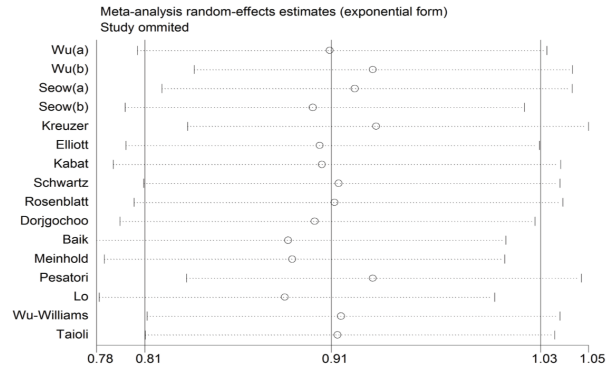

Figure 4. Sensitivity Analysis Via the Deletion of One Study at a Time to Reflect the Influence of the Individual Study on the Pooled ORs

studies. No significant association was found in case-control study and cohort study. There was no significant association in Asia and North America; nevertheless, a significant protective effect was observed in Europe (OR=0.74; 95% CI=0.60-0.91). There was no association between OC use and lung cancer risk regardless of the histology of lung cancer, either squamous cell carcinoma, or small cell cancer; but there was a borderline significant protective effect of the histology of adenocarcinoma (OR=0.90; 95% CI=0.80-1.01). There was no significant association in smokers and non-smokers. Meanwhile, no significant association was observed in studies of more than 500 cases or studies of less than 500 cases.

Table 3. Sensitivity Analysis: ORs, Corresponding 95%CIs and *P* Values after Excluding Each Study

Excluded Study	OR	95%CI	*P* value
Wu	0.935	0.834-1.049	0.252
Seow	0.915	0.808-1.035	0.159
Kreuzer	0.937	0.833-1.053	0.276
Elliott	0.906	0.800-1.026	0.121
Kabat	0.907	0.793-1.038	0.157
Schwartz	0.917	0.809-1.038	0.169
Rosenblatt	0.914	0.804-1.039	0.170
Dorjgochoo	0.903	0.796-1.024	0.112
Baik	0.889	0.784-1.008	0.066
Meinhold	0.891	0.788-1.007	0.066
Pesatori	0.935	0.833-1.050	0.255
Lo	0.887	0.785-1.002	0.054
Wu-Williams	0.918	0.811-1.038	0.171
Taioli	0.916	0.810-1.035	0.159

Begg's funnel plot and Egger's test were used to estimate the publication bias of literature. The shape of the funnel plots seemed approximately symmetrical (Figure 3) and the result of Egger's test did not reveal significant evidence of publican bias, t= -2.05 and *P* = 0.063 for OC users versus OC never-users.

Sensitivity analyses were conducted to assess the influence of individual study on the pooled ORs by omission of each study. As shown in Figure 4, none of the studies appears to be an outlier or has results very different from the rest of the studies. After each study was excluded from the overall meta-analysis, the similar results were obtained (Table 3), which indicated that the result of this meta-analysis was statistically robust.

Discussion

The aim of the present study was to examine the role of OC use in the genesis of lung cancer among women. In this meta-analysis of epidemiological studies, including case-control and cohort studies, we observed that the overall use of OC was not associated with the risk of lung cancer. However, the results have to be viewed with caution because there was significant heterogeneity. To date, some biological evidence has suggested that there is a link between hormonal factors and lung cancer risk. Siegfried et al. hypothesized that oestrogens may possibly influence lung cancer development, either through direct promotion by oestrogen of cell proliferation in the lung, or as a result of the influence of oestrogen on lung carcinogen metabolism or development of lung diseases that predispose to lung cancer (Siegfried, 2001). The effects of estrogen are likely to be adjusted by the estrogen receptors α and β. It is found that ERα mRNA are expressed at low levels in the lung, whereas ERβ has been shown to be expressed in both normal and tumor pulmonary tissue (Kaiser et al., 1996; Delaunay et al., 2000; Omoto et al., 2001). Estrogen in OC was considered to be the likely candidate for mediating growth-promoting effect in lung cancer. However, biological evidence for a link between hormonal factors and lung cancer risk is still limited. In 1980s, the third generation contraceptive estrogen content was dropped to 30 μg, while contraceptive progestin type has also been improved to play the role of antiestrogen. The estrogen in OC, presently, is reduced to 15-20 μg (Qin et al., 2013). Studies included in this meta-analysis were published between 1988 and 2013. Therefore, contraceptive estrogen content was at the lower level. We conclude that the reduction of estrogen in OC might be an important reason result in weaker association between OC use and risk of lung cancer.

When we conducted subgroup meta-analyses according to region, a significant protective effect was observed in Europe, while no significant association was found in Asia and North America. However, we were unable to confirm this result because of insufficient data. Of all 14 studies included in this analysis, only 3 studies reported the association of OC use and lung cancer risk in Europe. Two of them were low quality studies, and both were awarded 5 stars; and the other was award 6 stars.

Siegfried found that estrogens could interact with cigarette smoking on the risk of lung cancer by accelerating the metabolism of smoking-derived carcinogens (Siegfried, 2010). Actions of estrogens that contribute to lung carcinogenesis, especially in the presence of tobacco smoke, may involve both reactive intermediates that damage DNA and steroid hormone receptor signaling that promotes growth. Nevertheless, we did not observe the association in smokers in this study. Only 2 studies reported the association in smokers. The association was also not observed in non-smokers in this study.

According to histologic category, lung cancer is more likely to be adenocarcinoma in women than in men (Lubin and Blot, 1984). This indicates that estrogen may play a different role in various histologic types. In this meta-analysis, no association between OC use and lung cancer risk was observed in both squamous cell carcinoma and small cell cancer. However, there was a borderline significant protective effect of the histology of adenocarcinoma. Therefore, we should pay more attention to studying the association of OC use and adenocarcinoma of lung with larger samples in the future.

There were several limitations in this meta-analysis. First, because all studies did not illustrate style and component (estrogen and progestin) of OC, we could not examine the effects of different types of OC on lung cancer risk. Second, we were unable to perform subgroup analyses by dosage of OC because most of the studies included in this analysis did not report the dosage of OC used. Third, although most included studies adjusted for a wide range of potential confounders, we still could not exclude the possibility that other unmeasured or inadequately measured factors have confounded the true association. Last, common limitations of meta-analyses should be mentioned: pooled results could incorporate the biases of individual studies and embody new sources of bias, mostly because of selection studies and the inevitable heterogeneity among them (LeLorier et al., 1997).

In conclusion, we found that there was no association of overall OC use and lung cancer risk in this meta-analysis of epidemiologic studies, including case-control and cohort studies. Although a significant protective effect of OC use on lung cancer was observed in Europe, interpretation should be cautious because of the potential biases of low-quality studies. More attention should be paid to study the association of OC use and adenocarcinoma of lung because a borderline significant protective effect of the histology of adenocarcinoma was observed. Our findings require further research, such as more well-conducted and large-scale epidemiological studies are needed to affirm the effect of OC use on lung cancer.

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