

Hormone replacement therapy and lung cancer risk in women: a meta-analysis of cohort studies

Hormone replacement therapy and lung cancer risk

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Abstract

Background: Discordant results about the causal relationship between hormone replacement therapy use (HRT) and lung cancer risk in women had been reported. We therefore conducted a meta-analysis of cohort studies to evaluate this association.

Methods: The PubMed and Embase databases were searched. Fixed- or random-effects model was used to pool the study-specific relative risks (RRs) with corresponding 95% confidence intervals (CIs). Sensitivity analysis, publication bias, and subgroup analysis were performed.

Results: A total of 13 cohort studies met the inclusion criteria. Combined results indicated that compared with nonusers, women with HRT use were at a decreased risk (RR: 0.95, 95% CI: 0.91-0.99, $I^2 = 30.8%$, P for heterogeneity = .137). In subgroup analysis by geographic area, smoking status, type of hormones, and histology type of lung cancer, no significant association between HRT use and lung cancer was observed in most subgroups except in those studies which reported risk estimates adjusted for age, body mass index, smoking, and other confounders (RR: 0.95, 95% CI: 0.91-0.99, $I^2 = 33.0%$, P for heterogeneity = .214). Both Begg funnel plot and Egger test ($P = .243$) suggested no evidence for publication bias.

Conclusion: Our meta-analysis suggests ever use of HRT is associated with a decreased risk of lung cancer in women.

Abbreviations: BMI = body mass index, CIs = confidence intervals, HRT = hormone replacement therapy, RRs = relative risks.

Keywords: lung cancer, risk factors, hormone replacement therapy, meta-analysis

1. Introduction

Lung cancer is the most common diagnosed cancer and first leading cause of cancer death.^[1] In 2019, an estimated 228,150 men and women will be diagnosed with lung cancer and 142,670 will die from this disease in the United States.^[1] The etiology of lung cancer is largely unclear. Tobacco smoking is believed to be the established risk factor for lung cancer.^[2,3] Women appear more likely than men to develop adenocarcinoma, especially among never smokers and have better survival than men globally.^[2,3] Moreover, estrogen and progesterone receptor expression in normal and lung tumor cells were confirmed,

estrogens may promote lung tumorigenesis, and progesterone inhibited growth of progesterone receptor-positive non-small-cell lung cancers cells.^[4,5] Based on the experimental evidences and discrepancies on lung cancer pathology, risk factors, and prognosis between men and women, the role of female hormonal factors in lung cancer development had been the subject of speculation for many years. Hormone replacement therapy (HRT) is the most effective treatment for menopausal symptoms in postmenopausal women, as well as younger patients who are into early menopause due to surgery, chemotherapy, or radiotherapy. In recent years, a great number of epidemiological studies have assessed the relationship between HRT use and lung cancer risk, however, mixed results were reported.^[6-22] Some studies found a significant inverse or nonsignificant inverse relation^[6-8,14,15]; some found an increased risk, although the association was not statistically significant.^[17,20,22] In order to delineate the role of HRT use in lung cancer risk, a systematic search of the literature and a meta-analysis of cohort studies were performed.

2. Methods

We reported this meta-analysis in accordance with PRISMA Statement.^[23] Ethical approval is not required, as this study is a meta-analysis of published studies.

2.1. Literature search

Two databases PubMed and Embase databases) were searched (updated to May 9, 2019). Our search terms involved hormone, reproductive factors, menstrual factors, lung cancer, and risk.

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The process of search was shown step by step in Supplemental Table 1. Additional studies were reviewing the reference lists of eligible studies. No language limitation was set.

2.2. Selection criteria and exclusion criteria

We included cohort studies that assessed the association between HRT use and lung cancer risk in women. Adjusted risk estimates with 95% CIs were reported necessarily. If multiple studies pertained to the same subjects, the one with the largest sample sizes or the longest follow-up years was included. Cohort studies with crude risk estimates, case-control studies, conference abstracts, reviews, and letters without original data provided were excluded.

2.3. Data extraction

Two reviewers independently extracted the following information: author, year of publication, country, the period of cohort enrolled, the number of lung cancer cases and participants, adjusted risk estimates and their 95% CIs in maximally multivariable-adjusted models, and confounder for control. Any disagreements were solved by discussion to reach a consensus.

2.4. Statistical analysis

RR was used as a common measure of the association between HRT and lung cancer risk. To compute the summary RR for ever HRT users vs non-users, when one study reported more than one category fell into the range considered for ever HRT use, we first combined the corresponding estimates with fixed-effects model before combined with other studies. The method was widely used in previous meta-analyses.^[24–26] Subgroup analyses were performed according to geographic area, smoking status, confounder, type of hormones, and histologic subtype. Publication bias was estimated by the Begg funnel plot and Egger test at the $P < .10$ level of significance.^[27,28] We conducted a sensitivity analysis by excluding one study at a time to examine whether its effect on the overall results. The Higgins I^2 statistic and Q test were used to assess the heterogeneity.^[29] The value of I^2 ranges from 0% to 100%.^[30] When P for Q test $< .1$, the heterogeneity was considered to be significant. In the presence of significant heterogeneity, the combined risk estimates were computed using random-effects models, otherwise, fixed-effects models were adopted.^[31] All analyses were performed in Stata version 12.0 (StataCorp. College Station, TX).

3. Result

The flowchart of study selection was presented in Figure 1. A total of 432 articles were identified from PubMed and Embase databases. Five cohort studies as potentially available studies were identified through additional search. After excluding the duplicates from two databases and reviewing the titles and abstracts, 67 studies with full-text were assessed. Fifty four studies were further excluded as these studies were reported as case-control studies, conference abstracts, meta-analyses, reviews, notes, comments, or study protocols. Therefore, 13 cohort studies were identified in this meta-analysis.^[6–18]

Table 1 shows the main characteristic of included studies. A total of 11,391 lung cases were diagnosed in 968,440 participants. These studies were performed in USA, China,

Singapore, Canada, Japan, and Italy, and published between 2005 and 2015. The follow-up year ranges from five to thirty. Various confounders, such as age, smoking history, body mass index (BMI), education, ethnicity, dietary factors, oral contraceptive use, personal disease history, reproductive factor, and menstrual factors, were taken into consideration in original studies.

Figure 2 shows the RRs with corresponding 95% CIs for each study and the pooled result. No significant heterogeneity was observed ($I^2 = 30.8\%$, P for heterogeneity = .137). The pooled RR and 95% CI were 0.95 (0.91–0.99). Furthermore, subgroup analyses were performed according to geographic region, smoking status, confounders controlled, type of hormones, and histologic subtype (Table 2). Significant heterogeneity was found in subgroup of small lung cancer ($I^2 = 58.7\%$, P for heterogeneity = .089) and estrogen and progestin combination therapy ($I^2 = 60.0\%$, P for heterogeneity = .058). Subgroup analyses showed that the significant association was only observed in those studies with age, BMI, smoking, and other confounders considered (RR: 0.95, 95% CI: 0.91–0.99, $I^2 = 34.6\%$, P for heterogeneity = 0.131). The pooled RRs and 95% CIs were 0.96 (0.99–1.02), 0.97 (0.72–1.30), 1.04 (0.80–1.35), 1.07 (0.94–1.21), 0.97 (0.89–1.05), 1.08 (0.79–1.47), 0.97 (0.83–1.12), 0.95 (0.91–0.99), 0.92 (0.84–1.01), and 1.01 (0.87–1.06) for North America, Europe, Asia, adenocarcinoma, non-small lung cancer, small lung cancer, never-smoking, ever-smoking, estrogen, and estrogen and progestin combination therapy, respectively.

Sensitivity analyses were performed to assess the influence of a single study on the overall risk estimate by excluding one study in each turn. Sensitivity analyses indicated that our results were not robustness (Table 3). The Begg funnel plot does not show any substantial asymmetry (Fig. 3). The Egger test suggested no evidence of publication bias ($P = .243$).

4. Discussion

In the current meta-analysis of 13 cohort studies, we found that HRT use was associated with a decrease risk of lung cancer in women. Before interpreting our results further, important issues need to be considered.

4.1. Dose-response

Eight of 13 studies evaluated the lung cancer risk with duration of HRT use.^[5–10,15,16] Most of these studies indicated that there was no trend with duration of use. Kabat et al found that the associated trend over levels of duration of HRT use was of borderline statistical significance ($P = .07$). Specifically, women with ten years or more of HRT use were at elevated risk (RR: 1.51, 95% CI: 1.14–1.99). Assessment of a dose-risk relationship in a meta-analysis of epidemiology studies provides evidence for a suspected causal relationship between exposure and disease. However, we cannot perform a dose-response analysis of duration of HRT use according to the method proposed by Greenland et al^[32] and Orsini et al,^[33] as insufficient data (i.e., at least 3 quantitative categories and the number of cases and person-years in each category) was reported in original studies. Therefore, the shape of dose-response relationship is still unclear.

4.2. The role in the carcinogenesis of lung cancer subtypes

Our major analysis indicated that women with HRT use were associated with a decreased lung cancer risk. In subgroup

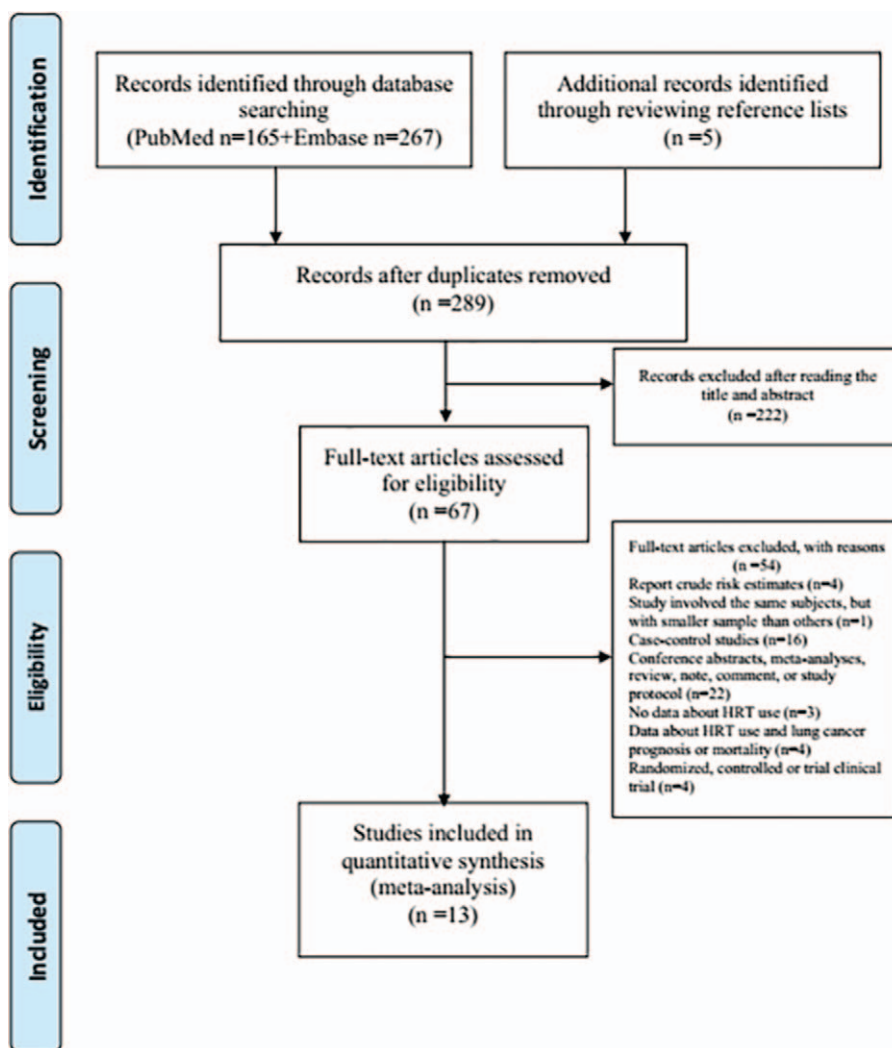


Figure 1. Flow chart for the process of selecting eligible publications.

analysis, a non-significantly increased risk was observed in adenocarcinoma (RR: 1.07, 95% CI: 0.94-1.21) and small cell lung cancer (RR: 1.08, 95% CI: 0.79-1.47), but not in non-small cell lung cancer (RR: 0.97, 95% CI: 0.89-1.05). Lung adenocarcinoma is the predominant histological subtype of lung cancer in women. The discrepancy in lung cancer subtypes associated with HRT is open to discussion.

4.3. The gap between observational studies and randomized controlled trials

Subgroup analysis of four randomized controlled trials in a meta-analysis showed a positive association with borderline significance between HRT use and lung cancer (RR=1.18, 95% CI 0.99-1.42).^[32] However, result from our meta-analysis of cohort studies indicated a decreased risk of lung cancer in HRT users. The significance of the discrepancy is unclear. Compared with cohort studies, randomized controlled trials have several merits, such as blindness, randomness, and standardization. After careful reading those four randomized controlled trials, several unique characteristics should be proposed. First, all randomized

controlled trials were not originally designed to assess the relationship between HRT use and lung cancer incidence. The subjects were carefully selected, and thus it is not representative of the general population. Second, the sample size was relatively small. Third, the follow-up time was relatively short. Therefore, observational studies may better reflect a relatively true real-world study.

4.4. Comparison with other meta-analyses

Several meta-analyses on this issue have been published.^[4,34-39] Two meta-analyses reported HRT use was associated with a decreased risk of female lung cancer,^[34,38] one found an increased lung adenocarcinoma risk in nonsmoking women with HRT use^[35], and three indicated HRT use had no effect on the risk of lung cancer.^[4,35,38] Noticeably, findings from previous meta-analyses were mainly based on retrospective case-control studies.^[4,34-37] Furthermore, a pooling analysis of observational studies and randomized controlled trials may result in methodological error.^[34,35] In the latest meta-analysis by Bae et al,^[38] fourteen cohort studies were included. However, 7 of 14 cohort

Table 1
Characteristics of the included studies of the relationship between lung cancer risk and hormone replacement therapy.

Last author, publication year	Country†	Enrolment period	End time of follow-up	Case/ Cohorts	RR with 95% CI (ever vs never use)	Variables for control
Tan et al, 2015	Singapore	1994–1997	2011.12.31	311/ 28,222	0.88 (0.62-1.25)	Age, BMI, ethnicity, smoking history.
Schwartz et al, 2015	USA	1993–1998	2012.09.17	2,467/160,855	0.96 (0.88-1.05)	Age, BMI, race/ethnicity, smoking history, education, US region, history of emphysema, history of asthma, and family history of cancer.
Brinton et al, 201	USA	1995–1996	2006. 12	3,512/185,017	0.93 (0.87-0.99)	Age, BMI, race/ethnicity, education, emphysema, smoking history, age at menarche, and type of and age at menopause.
Clague et al, 201	USA	1995–1996	2007.12.31	727/ 60,592	0.95 (0.80-1.13)	Age, race, smoking history, type of menopause, and BMI
Baik et al, 2010	USA	1984	2006.06.01	1,729/107,171	0.95 (0.86-1.05)	Age at menopause/menarche, BMI, parity, type of menopause, smoking history, and fruit/vegetable intake.
Slatore et al, 2010	USA	2000–2002	2007.12.31	344/36,588	1.21 (0.97-1.50)	Age, smoking history, personal history of cancer, family history of lung cancer, chronic obstructive pulmonary disease, BMI, age at menopause, hysterectomy type, and nonwhite race/ethnicity
Seow et al, 2009	Singapore	1993–1998	2005.12.31	298/35,298	1.38 (0.76-2.49)	Age, BMI, year of interview, dialect group, education, total vegetable intake, total fruit/juice intake, h-cryptoxanthin, total isothiocyanates, and smoking history.
Smith et al, 2009	USA	1972–1974	2002.12.31	97/2,861	1.13 (0.73-1.74)	Age, BMI, education, marital status, smoking history.
Rodriguez et al, 2008	USA	1992	2003.06.30	659/72,772	0.82 (0.72-0.95)	Age, smoking history, BMI, age at menopause, education, weekly servings of fruit, physical activity, total h-carotene intake, and oral contraceptive use
Corrao et al, 2008	Italy	1998–2000	2005.12.31	124/73,505	0.97 (0.72-1.30)	Age
Weiss et al, 2008	China	1996–2000	2005.12	220/71,314	0.50 (0.16-1.56)	Smoking history
Kabat et al, 2007	Canada	1980–1985	2000.12.31	750/89,835	1.07 (0.90-1.26)	Parity, age at menarche/first birth, menopausal status, oral contraceptive use, BMI, education, smoking history, study center, and randomization group.
Liu et al, 2005	Japan	1990–1994	2002.12.31	153/44677	1.45 (0.84-2.49)	Age, public health center area, and smoking history.

BMI=body mass index.

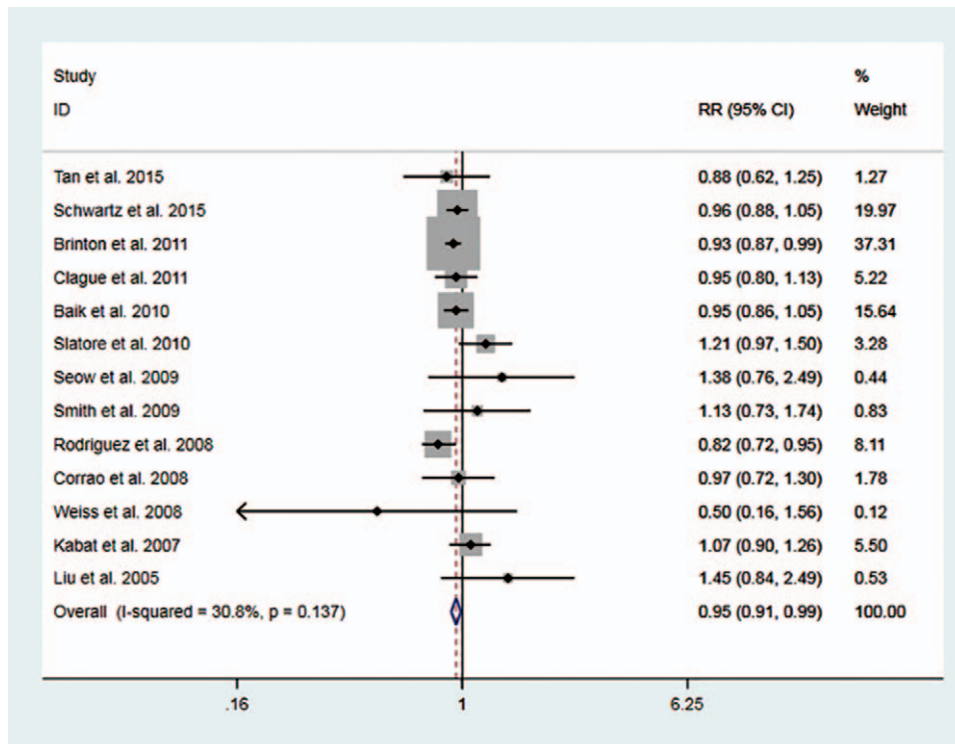


Figure 2. Forest plot for study-specific and pooled RRs and 95% CIs of HRT use and lung cancer risk.

Table 2
Results of subgroup analysis.

Category	Number of included studies	Pooled results		Heterogeneity	
		RR with 95% CI	P	I ²	P
All studies	13	0.95 (0.91-0.99)	.012	30.8%	.137
Geographic area					
North America	8	0.96 (0.99-1.02)	.163	41.9%	.099
Europe	1	0.97 (0.72-1.30)	NA	NA	NA
Asia	4	1.04 (0.80-1.35)	.763	37.1%	.189
Histology					
Adenocarcinoma	5	1.07 (0.94-1.21)	.302	0.0%	.442
Non-small	2	0.97 (0.89-1.05)	.443	31.4%	.227
Small	3	1.08 (0.79-1.47)	.626	58.7%	.089
Smoking status					
Never-smoking	8	0.97 (0.83-1.12)	.651	12.0%	.337
Ever-smoking	5	0.93 (0.87-1.00)	.064	20.5%	.284
Adjusted for age, smoking, and BMI					
Yes	10	0.95 (0.91-0.99)	.010	34.6%	.131
No	3	1.02 (0.80-1.32)	.852	38%	.199
Type of hormone					
E	4	0.92 (0.84-1.01)	.086	33.0%	.214
E+P	4	1.01 (0.87-1.06)	.935	60.0%	.058

E=estrogen replacement, E + P = estrogen and progestin combination therapy, NA=not available.

Table 3
Results of sensitivity analyses.

Study excluded	Pooled results RR with 95% CI	Heterogeneity I ²	P
Tan et al, 2015	0.95 (0.91–0.99)	0.014	35.90%
Schwartz et al, 2015	0.95 (0.91–0.99)	0.018	36.30%
Brinton et al, 2011	0.96 (0.92–1.01)	0.139	33.90%
Clague et al, 2011	0.91 (0.91–1.03)	0.285	36.50%
Baik et al, 2010	0.97 (0.90–1.04)	0.37	36.50%
Slatore et al, 2010	0.94 (0.91–0.98)	0.004	11.80%
Seow et al, 2009	0.95 (0.91–0.99)	0.01	30.40%
Smith et al, 2009	0.95 (0.91–0.99)	0.01	34.20%
Rodriguez et al, 2008	0.96 (0.92–1.00)	0.073	12.60%
Corrao et al, 2008	0.96 (0.91–1.02)	0.237	36.50%
Weiss et al, 2008	0.95 (0.91–0.99)	0.013	31.70%
Kabat et al, 2007	0.94 (0.91–0.98)	0.005	28.20%
Liu et al, 2005	0.95 (0.91–0.99)	0.009	26.70%

studies provided crude risk estimates. As a meta-analysis of observational studies, the effect of confounding factor and bias (recall and selection bias) are major concerns. To clarify the issue, we performed an updated meta-analysis which only included prospective cohort studies with adjusted risk estimates reported. Thus, a more precise estimation of the relationship between HRT use and lung cancer may be derived.

4.5. Implications for clinical practice

Since HRT use remains the most widely used and effective treatment for postmenopausal symptoms in women, its benefits and harms effect are concern. Previous findings suggested HRT use was associated with an increased risk of breast cancer, endometrial cancer, stroke, and pulmonary embolism, but a decreased risk of colorectal cancer, hip fractures, and diabetes.^[39,40] In our meta-analysis of prospective cohort studies, we found that HRT use was associated with a decreased risk of lung cancer. Based on these findings, we concluded those women with HRT use may be reassured by bearing decreased risk of lung cancer and menopausal replacement therapy has a complex pattern of risks and benefits.

4.6. Limitations

Several limitations should be acknowledged. First, sensitivity analysis showed our results were not robust. Second, subgroup results should be treated with considerable caution, as the small number of included studies was included. Third, residual confounders may confound the true association, although the multiple -adjusted risk estimates were adopted. Finally, potential publication bias is still a threat to the robustness of our findings.

4.7. Conclusion and future directions

In conclusion, evidence from current prospective cohort studies indicated women with ever HRT use was associated with a

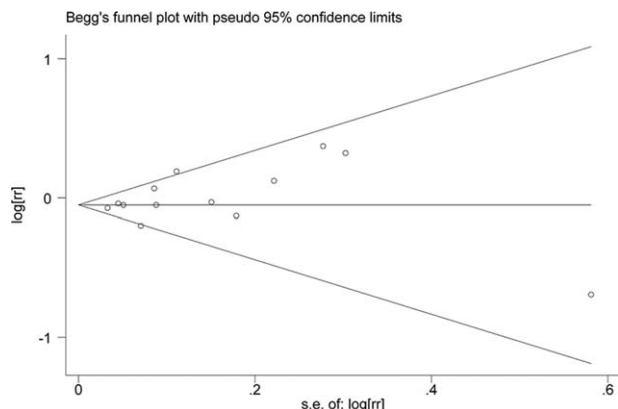


Figure 3. Begg funnel plot.

decreased risk of lung cancer. Further prospective studies with adequate numbers of lung cancer cases, detailed information on type of hormone use, dose of hormones, duration of HRT use, and histologic type, are needed to confirm and extend these findings.

Author contributions

Conceptualization: Baoping Lang, Chao Jin.

Data curation: Baoping Lang, Chao Jin.

Formal analysis: Baoping Lang, Chao Jin.

Writing – original draft: Baoping Lang, Chao Jin.

Writing – review & editing: Baoping Lang, Chao Jin.

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