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Hormone therapy and lung cancer mortality in women: Systematic review and meta-analysis

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ABSTRACT

The mortality of lung cancer presents a significant difference between the sexes. A role of hormone therapy (HT) in lung cancer mortality has been suggested, but the evidence is inconclusive. We sought to elucidate this issue with a meta-analysis. We conducted a systematic literature search in both Pubmed and Embase. Studies that reported the association of HT and mortality of lung cancer cases were included. Pooled hazard ratio (HR) was computed as the effect size to reflect the association between HT and lung cancer mortality. In total, 11 studies were included in the meta-analysis. The pooled HR of HT in relation to lung cancer mortality was 0.97 (95% CI 0.83–1.12, I^2 = 59.2%, p = 0.006) in all studies disregarding study design, and it was 0.80 (95% CI: 0.69–0.92, I^2 = 21.4%, p = 0.278) in prospective cohort studies. Results of this meta-analysis were robust, and there was no indication of significant differences in association in small and large studies. We observed a protective role of HT use in lung cancer mortality in pooled prospective cohorts, but not in pooled retrospective cohorts and post hoc analyses of randomized controlled trials. Future studies that address smoking, type and time of HT, menopausal status, and histology are warranted.

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1. Introduction

Lung cancer presents some distinctive differences in both etiology and prognosis between the sexes. Women are more likely to develop adenocarcinoma than men [1]. The incidence of lung cancer in never smokers is significantly higher in women, and women are more susceptible to cigarette exposure in terms of lung cancer incidence [2]. This kind of gender-related difference also exists in lung cancer mortality, which is reflected by the observation that women with lung cancer present significantly better clinical outcomes than their male counterparts. This prognosis advantage retains after a full consideration of stages and histological subtypes [3]. The incidence and prognosis of lung cancer are thus suspected to be sex hormone related. More relevant studies emerged after the verification of the expression of estrogen and progesterone receptors in lung cancer tissue [4,5].

Hormone therapy (HT) is the primary source of long-term exogenous estrogen and/or progestogen exposure in postmenopausal women. Although many studies have explored the association between HT and lung cancer incidence [6], limited studies explored the possible association between HT use and lung cancer mortality, while existing findings were highly inconsistent [7,8]. The potential prognostic role of HT in lung cancer mortality remains elusive, given a small number of lung cancer cases in most studies that employed different designs and had some unique features in their study populations. We summarized present evidence to elucidate the association between HT use and mortality in female lung cancer patients by conducting a systematic review and meta-analysis.

2. Experimental

2.1. Literature search strategy

We conducted a literature search in Pubmed and Embase. We completed all electronic search of the literature on February 22,

Abbreviations: HT, hormone therapy; HR, hazard ratio; CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio; SMR, standardized mortality ratio; ESR, estrogen receptor; PR, progesterone receptor; NSCLC, non-small cell lung carcinoma.

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2016. The time range of publication search was set between 1985 and 2016. We only included publications written in English. We developed a search strategy which consists of: (1) hormone therapy, hormone replacement therapy, hormone use, menopausal hormone therapy, estrogen or progestogen; (2) lung cancer, lung carcinoma, lung tumor or lung neoplasm; (3) survival, mortality or prognosis. We also checked citation lists of studies identified in the database search process to prevent potential missing.

2.2. Inclusion criteria for relevant studies

Two reviewers independently reviewed all searched studies (Li & Lin) and compared results. Discrepancies were examined by the third reviewer (Tse) followed by a group discussion. We regarded one study eligible only if it fulfilled all the following criteria: (1) participants being histology confirmed female lung cancer cases; (2) cohort study or randomized controlled trial (RCT); (3) exposure of interest defined as a history of exogenous estrogen and/or progestogen; (4) survival analysis according to the use of HT; (5) hazard ratio (HR) and 95% confidence interval (CI) can be obtained (either directly provided or can be estimated indirectly with data or figures). In the case of an overlap of patients in different reports, we only included the one with the most extensive data and/or the longest follow-up period.

2.3. Data extraction and quality assessment

We extracted information from each eligible study, including first author, publication year, study design, country or region of the study, number of lung cancer cases, average age, race proportion, smoking status, the percentage of postmenopausal women, histological type, and stage. We not only extracted HRs with 95% CIs regarding ever use of HT but also extracted HRs of HT use in subgroups (i.e. smoking status, postmenopausal, type of HT, pathological subtypes, HT withdrawal duration) whenever possible. If both univariable and multivariable HRs were reported in a study, we extracted the adjusted one. We extracted HRs for all causes of death after lung cancer diagnosis and lung cancer-specific death. Risk ratio (RR) or standardized mortality ratio (SMR) was considered as an estimation of HR if HR was not reported in a study. We employed the Newcastle-Ottawa Scale (NOS) for the quality assessment of observational studies [9]. For post hoc analyses of RCTs, we conducted the quality assessment with recommendations from the Cochrane Handbook [10]. Two reviewers (Li and Lin) independently assessed all included studies; discrepancies were solved by discussing with the third reviewer (Tse).

2.4. Statistical analysis

We used HR as the effect size to reflect the association between HT use and mortality of lung cancer patients. The rationale for pooling results of observational studies and RCTs in a meta-analysis has been suggested, and this approach is expected to provide more advantages [11]. If a study did not report HR directly, we conducted a well-established sequential procedure to estimate the univariable HR and its 95% CI with a survival figure provided in the study. This method has been widely applied in the meta-analysis of mortality [12,13]. We used the software Engauge Digitizer Version 4.1 to generate estimations of survival data from survival curves; then we inputted data into the Microsoft Excel software macro designed by J.F. Tierney to estimate the HR and its 95% CI [14].

We calculated the pooled HR with the meta-analysis method to evaluate the association between HT use and lung cancer mortality. HR < 1 indicated ever use of HT was associated with lower risk of lung cancer mortality; HR > 1 indicated higher risk of mortality among ever users of HT. Because included studies had noticeable variances, the random-effect model was applied in all meta-analyses [15]. We measured heterogeneities among studies with Q test and I^2 test. If $p < 0.10$ in a Q test, this result suggests the likelihood of a significant heterogeneity among studies. We also conducted subgroup analyses to explore sources of heterogeneity. Some studies directly provided HRs of different types of HT, non-small cell lung cancer (NSCLC), and postmenopausal lung cancer women, these HRs were used in corresponding subgroup analyses rather than HRs of overall HT use. We conducted Begg's test to explore differences of effect sizes in small and large studies. To detect whether certain studies can significantly alter the pooled result, we conducted a sensitivity analysis by deleting one study each time to examine fluctuations of the pooled HR and its 95% CI. All statistical analyses were performed using STATA 12.0 (Stata Corporation, College Station, Texas).

3. Results

The literature screening process is shown in Fig. 1. After screening according to the preset inclusion criteria, 11 studies were eligible and included in the final meta-analysis [7,8,16–24]. We did not encounter significant discrepancies in judging eligibility and extracting data.

3.1. Study characteristics

Characteristics of the 11 studies regarding the association between HT use and lung cancer mortality are shown in Table 1. They were published between 1996 and 2016. Nine of them were conducted in the United States while two studies were carried out in Canada and Sweden. Five studies were prospective cohorts, three were retrospective cohorts, and the remaining three were post hoc analyses of RCTs, which aimed at discovering long-term heath impact of HT. Uniformly, white race was dominant in all included studies except for two studies that did not describe racial proportions. By contrast, the proportion of never smokers varied substantially among studies. While most studies only included postmenopausal women, three studies involved a minor proportion of premenopausal estrogen and/or progestogen users. Nine studies provided results of multivariable Cox proportional hazards regression analysis. We derived an unadjusted HR from survival curves in one study because only *p*-value of multivariable analysis was available.

3.2. Quality assessment

Table 2 shows the quality assessment results for each study according to the Newcastle-Ottawa Scale for cohorts and the Cochrane handbook for RCTs. Included cohort studies, regardless of the design, are of similar quality. All cohorts had relatively good performance on selection. Because most studies presented HRs adjusted for important established prognostic factors including cancer stage and smoking, they had good or acceptable scores in the comparability domain. However, they had weaker performance in the outcome domain; some of them did not provide information on loss of follow-up, and only one publication clearly stated the length of follow-up. All three RCTs were of high quality.

3.3. The association between HT use and lung cancer mortality

Fig. 2 shows the pooled HRs and sub-pooling results by the study design. HRs were inconsistent among studies, with one being positive, one being negative and nine being statistically insignificant. The pooled HR of all included studies was 0.97 (95% CI

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