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Review

Menopausal hormone therapy and risk of lung cancer—Systematic review and meta-analysis

Claudia M. Greiser[a], Eberhard M. Greiser[a,b], Martina Dören[c,*]

[a] Epi.Consult GmbH, Musweiler, Germany
[b] Institute for Public Health and Nursing Research, Faculty of Health Sciences, Bremen University, Bremen, Germany
[c] Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, Clinical Research Centre of Women's Health, Hindenburgdamm 30, D-12200 Berlin, Germany

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ABSTRACT

Objectives: Lung cancer rates increase among women in many regions of the world. To explore whether menopausal hormone therapy (MHT) plays a role.
Methods: We conducted a systematic search of the literature and performed meta-analyses of cohort studies (C), case–control studies (CC), randomized controlled trials (RCTs), and cancer registry studies (CR) to analyse the impact of estrogen therapy (ET), estrogen/progestin therapy (EPT) and any hormone therapy (HT) on lung cancer risks. We explored associations between ever-use of therapies and risks, analysed annual changes of risk, and the impact of therapies on histological subtypes. We calculated summary odds ratios, relative risks, 95% confidence intervals (CI; fixed-effects model), and assessed heterogeneity across studies. Eighteen studies were eligible (9 CC, 4 C, 3 RCT, 2 CR).
Results: We found a significant increase of risk – 76.2% – in non-smoking women with adenocarcinoma (CI 1.072–2.898) reporting ever-use of HT. Estrogen plus progestin therapy does not change the risk; however, the pooled analysis of 2 RCTs points at an increased risk (RR 1.359; CI 1.031–1.791). Our further results should be interpreted with caution as significances were found in analyses only when smoking and non-smoking women, various hormone regimens, or histological subtypes, respectively, were pooled.
Conclusions: Dedicated studies designed to more adequately delineate the role of MHT are necessary to substantiate whether use of MHT is a risk factor for this or other types of lung cancer.

Contents

1. Introduction

Lung cancer is currently the most common cancer in the world and the leading cause of cancer-related death. Lung can-

* Corresponding author. Tel.: +49 30 8445 3227; fax: +49 30 8455 2352.
E-mail address: martina.doeren@charite.de (M. Dören).

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cer incidence rates either decreased or were stable among males except in Japan. In contrast, lung cancer rates increased among women [1], but apparently may no longer be increasing at least in some populations [2], and may have leveled off in women after increasing for decades [3]. Above all, the environmental risk factor cigarette smoking is relatively most relevant, but also exposure to asbestos, radon, air pollution are important in this context, as are behavioural, genetic and dietary factors [4,5]. Squamous cell carcinoma was the most frequent type of lung cancer observed in the past, and small cell carcinoma was the next most frequent. In the late 1970s, the first evidence of a shift toward a predominance of adenocarcinoma was noted [6] and now adenocarcinoma of the lung is the most common histologic type [7].

Whether endogenous and or exogenous estrogens including menopausal hormone therapy (MHT) are relevant to contribute to the understanding of the epidemiology and tumor biology of lung cancer in women and men is unclear [8,9]. It is not known whether women may have a greater risk of lung cancer than men at the same level of smoking. Hypotheses have been based on hormonally related differences in response to carcinogens, but the evidence appears to be both limited and mixed [10]. The significance of estrogen and progesterone receptor expression in normal and tumor cells, adenocarcinoma, squamous, and small cell carcinoma of the lung is unknown [11–13], as these receptors are expressed in many other normal and tumor cells of other organs. However, sex differences in lung cancer outcome have been reported; lung cancer survival in women is decreased compared with men in studies adjusted for smoking and comorbidities [14,15].

According to the evaluation of the International Agency of Research against Cancer (IARC) published 2007 [16], large randomized trials suggest that risk for lung cancer was slightly but not significantly elevated in users of combined estrogen/progestin hormonal therapy. Results of observational studies produced different results, suggesting reduced risk [17–19], increased risk [20], or no change of risk [21,22]. Use of MHT was associated with decreased survival in one study in women with lung cancer [23].

In order to better delineate the impact of MHT on lung cancer risk we conducted a systematic search of the literature and performed meta-analyses of available evidence provided by cohort studies (C), case–control studies (CC), randomized controlled trials (RCTs), and cancer registry studies (CR) to analyse the impact of various menopausal hormone therapies [estrogen replacement therapy (ET), estrogen/progestin therapy (EPT) and hormone therapy (HT), the latter including any hormone regimen, sometimes unspecified or unknown preparations] on lung cancer risks. We explored associations between ever-use of these types of therapy and risks, analysed annual changes of risk, and potentially different impacts of HT on histological subtypes.

2. Materials and methods

2.1. Identification of studies

We performed a computerized search of several databases, including Medline (1 January, 1966–25 July 2008), CANCERLIT, EMBASE, Scopus, the Cochrane Library and the Cochrane Controlled Trials Register. We used the Medical Subject Headings and/or text words 'hormone replacement therapy', 'hormone therapy', '(o)estrogen (replacement) therapy', 'estradiol (replacement) therapy', 'estrogen and progest* (replacement) therapy', 'HRT', 'ERT', 'HT', 'post(-)menopausal estrogens (hormones)', 'reproductive hormones', 'non-contraceptive hormones (estrogens)', 'lung cancer' or 'carcinoma' or 'neoplasm' or 'tumo(u)r', 'bronchial cancer' or 'carcinoma' or 'neoplasm' or 'tumo(u)r', 'case(–)control study', 'cohort study', 'cancer registry' and any of the terms 'randomized, randomized, controlled and clinical' in conjunction with 'trial' or 'study' in multiple combinations where applicable. All studies not conducted in women were a priori excluded. We used snowballing (review of references of identified studies), scrutinized systematic reviews addressing various aspects of HT, checked references of previous systematic searches regarding a related cancer topic [24,25] and of systematic evaluations [16] to potentially identify further studies. Search of editorials, supplements, proceedings, books, abstract books and proceedings of major menopause meetings, respectively, was restricted to the preceding 5 years (2003–July 2008). The titles and abstracts of all potentially relevant publications were examined to determine the relevance of the information; full articles were scrutinized if any potentially relevant information was found in a retrieved abstract. Searches were conducted independently by two reviewers (M.D. and C.M.G.). We did not impose language restrictions.

2.2. Inclusion criteria

We included C, CC, RCT and CR, if these publications provided information upon ever-use of any type of HT, risk by duration of use or increase of risk within a given time interval, respectively, of ET, or EPT or HT as defined (C.M.G., M.D. and E.M.G.). Fully published studies, not abstracts, were included if confidence intervals (CI) or standard errors of risk estimates and dates on conduct of the study were provided or if data provided allowed calculation of confidence intervals. In studies with multiple publications from the same population, we included only data from the most recent publication. In the case of double publication, we included only the data sets of the first publication or the one providing the most extractable data.

2.3. Data extraction, statistical methods and assessment of homogeneity

Data were extracted by two reviewers (C.M.G. and E.M.G.), in case of different raw data sets theses differences were resolved by discussion to reach consensus. A priori objectives were the association between (i) hormone regimens (ET, EPT and HT) and risk of lung cancer, (ii) the magnitude of ever-use (estimate of a total) and annual risk in pre-specified hormone regimen groups (ET, EPT and HT), and (iii) the potential impact of specified hormone regimens on histological subtypes. All statistical analyses were performed independently by one reviewer (E.M.G.). First, to summarize effects of HT on risk of lung cancer irrespective of duration or dosage, point estimates and CI were used in a fixed-effects model applying the general variance-based method [26] (see Ref. [25] for details). Second, slopes for both individual studies and summary slopes were calculated using inverse variance-weighted least squares estimates in order to estimate summary slopes for calculation of increase of risk per year of use [27]. We examined heterogeneity with two methods. We analysed studies by applying the general variance-based method [26], providing for Cochran's Q for individual substrata and for various totals of substrata. Additionally, we calculated the proportion of variance in pooled estimates [28] due to heterogeneity in calculating I^2. In case of a paucity of eligible data sets we refrained from doing so [29]. Attributable risks were calculated according to the formula (odds ratio − 1)/odds ratio.

All analyses were stratified by type of MHT:ET, EPT, and HT as defined. Where possible, analyses were stratified according to histology. When pooling was done in studies which provided risk estimates for several mutually exclusive histological entities, we regarded these risk estimates as being derived from independent datasets, analogous to different independent studies. Therefore we refer to 'datasets' instead of 'studies'. We used SAS version 9.1 (SAS Institute, Cary, NC, USA) for all analyses. Due to the heterogeneity of study types (both randomized trials and epidemiologic stud-