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Antiestrogen use in breast cancer patients reduces the risk of subsequent lung cancer: A population-based study

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ABSTRACT

Background: There is accumulating epidemiological and preclinical evidence that estrogen might be a driver of lung cancer. Breast cancer survivors can offer a unique patient cohort to examine the effect of antiestrogen therapy on lung cancer carcinogenesis because many of these women would have received long-term selective estrogen receptor modulators (SERMs) and/or aromatase inhibitors (AIs) as adjuvant treatment. Our hypothesis is that estrogens play a role in lung cancer development, and that antiestrogen therapy would affect the incidence of subsequent lung cancer among breast cancer survivors.
Methods: Using the Taiwan National Health Insurance (NHI) database, the study included 40,900 survivors of non-metastatic breast cancer after primary surgery, and most antiestrogen users complied well with the medication regimen. We evaluate the effect of antiestrogen therapy on the incidence of subsequent lung cancers.
Results: This population-based study revealed that antiestrogen use in breast cancer patients was associated with a reduced risk of subsequent lung cancer in older patients (≥50 years) (HR 0.73, 95%CI 0.54–0.99) when compared with breast cancer survivors who did not use antiestrogens.
Conclusion: The study supports the hypothesis that antiestrogen therapy modifies lung cancer carcinogenesis in older women. Further well-designed clinical trials to explore the potential of antiestrogens in lung cancer prevention and treatment would be worthwhile.

1. Introduction

Smoking is the main cause of lung cancer in many industrialized countries [1,2], but other factors may act as modulators of lung carcinogenesis, especially in the non-smoking population [3]. Exposure to exogenous estrogen through hormone replacement therapy (HRT) in peri- and postmenopausal women has been shown to increase the risk of lung cancer in a duration-dependent manner [4]. The Women's Health Initiate (WHI) randomized clinical trial included more than 16,000 postmenopausal women who received daily HRT or placebo with a median follow-up of 8 years; this study reported a 60% increased risk of dying from non-small-cell lung cancer (NSCLC) and a trend toward more lung cancer diagnosed in the HRT arm compared to the placebo arm [5]. In the WHI trial, after a median follow-up of 14 years the increased risk of death from lung cancer observed during estrogen plus progestin use was attenuated after discontinuation of combined hormone therapy [6].

In contrast, antiestrogen use in 6655 breast cancer patients in the Geneva Cancer Registry had significantly lower subsequent lung cancer mortality [7]. Another study from the Manitoba Cancer Registry included 2320 women with NSCLC, and antiestrogen use was found to significantly decrease lung cancer mortality in women who received antiestrogens both prior to and after a lung cancer diagnosis [8].

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There is accumulating preclinical data to demonstrate that estrogen is a driver of lung cancer [9]. Estrogen can induce NSCLC cell proliferation *in vitro* [10], in human tumor xenografts [11], and in animal models [12]. Many human lung tumors express estrogen receptors (ERs) and aromatase, implying an important role for estrogen in lung cancer carcinogenesis and prognosis [13]. Therefore the effect of antiestrogen therapy on carcinogenesis and outcome of lung cancer should be explored further.

Breast cancer survivors can offer a unique patient cohort to examine the effect of antiestrogen therapy on lung cancer incidence because many of these women would have received long-term selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) as adjuvant treatment and would have lived long enough for any possible subsequent effects to be detected. Our hypothesis is that estrogen plays a role in lung cancer development, and that antiestrogen therapy could affect the incidence of subsequent lung cancer among breast cancer survivors. Using the Taiwan National Health Insurance (NHI) database [14,15], we aimed to evaluate the effect of antiestrogen therapy on the incidence of subsequent lung cancers in breast cancer patients.

2. Materials and methods

2.1. Study population and study design

The Taiwan National Health Insurance (NHI) Research Database is one of the largest nationwide population databases in the world, covering approximately 23 million residents; it included 99.0% of the Taiwan population by 2004 and 99.5% of the population by 2010 [14–16]. Data for our study were obtained from the Registry for Catastrophic Illness Patient Database (RCIPD), a subset of the Taiwan NHI database, which contains complete medical records that include disease diagnoses, hospital admissions, outpatient visits, and prescription medications for all cancer patients. Taiwan NHI databases have been used extensively for epidemiological researches, and the information on prescription medications, diagnoses and hospitalizations is of reliable quality [15,17]. In this study, between January 1, 1999 and December 31, 2012 women who were diagnosed with breast cancer and registered in the RCIPD were identified by the International Classification of Diseases, 9th Revision (ICD-9) codes of 174.0–174.9. We excluded patients who were younger than 18 years old or male, and those with a history of cancers at non-breast sites. While considering the need for long-term follow-up for the incidence of subsequent lung cancer, we also excluded those with lymph-node or distant metastasis at diagnosis. All patients in the study cohort had undergone primary surgery for breast cancer. The primary therapy was defined as primary surgery with or without chemotherapy. Patients who did not receive primary therapy were excluded. To standardize the adjuvant nature of antiestrogen therapy, those who had used antiestrogens after 1 year of breast cancer diagnosis were also excluded. The defined daily dose (DDD) – which is a WHO-advocated drug potency unit to assume average maintenance dose per day for a drug used in adults – is adopted for comparison of different SERMs and AIs. Cumulative DDD (cDDD) is the sum of dispensed DDD of any antiestrogen. An antiestrogen user was defined as one receiving >180 cDDD antiestrogen after primary therapy. Patients who stopped their antiestrogen therapy after 180 cDDD remained in the group of antiestrogen users. Short-term cases – including those receiving <180 cDDD antiestrogens and whose follow-up period was <6 months – were also excluded. To demonstrate the compliance and consistency of antiestrogen use, adherence was calculated by dividing cDDD by the period of antiestrogen use.

The schema of the study design, exclusion criteria, status of antiestrogen use and follow-up are shown in Appendix A, Fig. A1. All breast cancer patients were followed after completion of primary therapy for breast cancer. Antiestrogen users were followed after they started their antiestrogens, and the control non-users were followed after they had received their last primary therapy. The identification of subsequent lung cancer was based on a new registration of lung cancer in the RCIPD or by the diagnosis of lung cancer during hospitalization using the ICD-9 codes 162.0–162.9. Patients were followed up to the occurrence of lung cancer during the study period, and if no event occurred during follow-up the patient was followed until death or December 31, 2012. Antiestrogens covered by the NHI during the study period for breast cancer adjuvant therapy included three SERMs: tamoxifen, raloxifen and toremifene, and four AIs: letrozole, anastrozole, exemestane and aminoglutethimide. Confounding factors – including age at diagnosis, chemotherapy and radiotherapy – were controlled. This study was approved by the Research Ethics Committee of the Buddhist Tzu-Chi General Hospital, Hualien, Taiwan (IRB101-98).

2.2. Statistical analysis

The hazard ratios (HRs) and accompanying 95% confidence intervals (95%CIs) were based on the Cox proportional hazards model and computed with competing risk analysis by the Fine and Gray method, while adjusting for age at the time of breast cancer diagnosis, radiotherapy and chemotherapy. The consistency and difference of risk of lung cancer were evaluated by conducting subgroup analysis for age. The cumulative incidence of lung cancer was plotted using the Kaplan–Meier method. A two-tailed test at a level of 0.05 was considered statistically significant. Statistical analyses were performed using SAS, version 9.3 (SAS, Inc., Cary, NC, USA).

3. Results

We identified 105,444 eligible breast cancer patients who were registered for the first time in the RCIPD. After the exclusion criteria were applied, 40,900 patients were included in the study; 26,228 (64.1%) of these were antiestrogen users and 14,672 (35.9%) were non-users. Among the users, 25,052 (95.5%) had used tamoxifen, 648 (2.5%) had ever used raloxifen and 6888 (26.3%) had ever used AIs. Only 4.4% of antiestrogen users (n = 1148) had used an AI without tamoxifen (Appendix A, Fig. A1). The demographic characteristics of the groups are shown in Table 1. The period between breast cancer diagnosis and start of follow-up was similar in antiestrogen users (median 124 days) and non-users (median 129 days). A slightly longer duration of follow-up was noted for antiestrogen users (median 4.90 years) than for non-users (4.43 years). The 14-year accumulated mortality rate was 7.1% in antiestrogen users and 9.1% in non-users. A higher proportion of non-user patients (66.4%) had received chemotherapy than antiestrogen users (55.5%). A lower proportion of non-user patients (41.4%) had received radiotherapy than antiestrogen users (45.1%). A vast majority (93%) of subjects in each group had completed their primary therapy and had been followed within 270 days after the diagnosis of breast cancer. High proportions of antiestrogen users (85.2%) had adhered to antiestrogen medication over 50% of the cDDD.

During the 14-year study period, 267 patients were diagnosed with subsequent lung cancer. The incidence per 10^5 person-years of lung cancer were 111.8 and 133.9 in antiestrogen users and non-users, respectively. After adjusting for age, radiotherapy and chemotherapy, antiestrogen users had a significantly lower risk of subsequent lung cancer than non-users (adjusted HR, 0.77; 95%CI,