Breast Cancer in First-degree Relatives and Risk of Lung Cancer: Assessment of the Existence of Gene–Sex Interactions

Masaki Tsuchiya¹, Motoki Iwasaki¹, Tetsuya Otani¹, Jun-ichi Nitadori¹, Koichi Goto², Yutaka Nishiwaki², Yosuke Uchitomi³ and Shoichiro Tsugane¹

¹Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, ²Thoracic Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East and ³Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

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Background: Previous studies have shown the sex differences in lung cancer and the associations between estrogen-related genes and non-small cell lung cancer. In the present study, we assumed the existence of shared candidate genes that are common in lung and breast cancers, and examined whether women with a family history of breast cancer are at increased risk of lung cancer compared with men, especially adenocarcinoma, in a case-only study.

Methods: This case-only study was conducted based on the Lung Cancer Database Project at the National Cancer Center Hospital East. A total of 1566 patients with newly diagnosed primary lung cancer were consecutively recruited between 1999 and 2003. Information on their family history of cancer and smoking habit was obtained from a self-administered questionnaire. To assess an interactions between two factors, odds ratios for interaction (ORis) and 95% confidence intervals (CIs) were calculated by case-only contingency table.

Results: A statistically significant ORi was observed between a family history of breast cancer in first-degree relatives (parent and siblings, not including children) and the sex of a patient (ORi: 2.22, 95% CI: 1.02–4.81). A stratified analysis by histologic subtypes showed a statistically significant ORi only for adenocarcinoma (ORi: 3.27, 95% CI: 1.19–8.98). No other family history of cancer, such as stomach, colon and lung cancer, showed a statistically significant ORi.

Conclusion: This study suggests the possibility of gene–sex interaction in lung cancer.

Key words: lung cancer – breast cancer – shared candidate genes – gene – sex interaction

INTRODUCTION

Lung cancer is the leading cause of cancer mortality for both men and women in the world (1). However, there is a large difference in the distribution of histologic subtypes and incidence rates between men and women. Squamous cell carcinoma is the predominant histological subtype in men while adenocarcinoma is the most common in women. The different proportions between men and women might be largely attributable to a gender difference in smoking habits. However, smoking-caused lung cancer is estimated to comprise only 18% in Japanese women (2). This observation suggests that there is a crucial need to explore other contributing factors in women’s lung cancer.

Estrogen and estrogen-related genes, as well as breast cancer, are speculated to be associated with lung cancer in women, as well as sex differences in lung cancer. It has been shown that both normal lung cells and non-small cell lung cancer (NSCLC) cells express estrogen receptors and show biological responses to estrogen (3). Another study has shown that NSCLC cells respond to estrogens/anti-estrogens by altering endogenous gene expression (4). A large-scale prospective cohort study in Japan has reported an association between reproductive factors, estrogen replacement therapy

For reprints and all correspondence: Motoki Iwasaki, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan. E-mail: miwasak@gan2.res.ncc.go.jp

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and the risk of lung cancer (5). In addition, a recent case-control study in Japan has suggested a positive association between endogenous estrogenic exposure and NSCLC with epidermal growth factor receptor (EGFR) mutation (6).

In women, both lung and breast cancer incidence rates are still increasing. A previous study indicated that a positive family history of early onset lung cancer increased the breast cancer risk among first-degree relatives (7). A maternal history of breast cancer increased the risk of lung cancer in nonsmokers (8). Based on prior evidence, estrogen-related genes might be the most plausible candidates linking breast and lung cancers. However, it is still not clear whether these genetic factors contribute to the sex differences in lung cancer.

Therefore, we hypothesized that the fact that adenocarcinoma is dominant among women due to the biological interaction between being women and having estrogen-related genotype susceptible to the breast cancer. In order to explore whether inherited genes that link lung and breast cancer susceptibilities contribute to the sex differences in lung cancer, we assumed that a family history of breast cancer is an indicator of genetic factors in the present study, though family history may reflect both genetic and shared environmental factors. We examined whether women with a family history of breast cancer are at increased risk of lung cancer compared with men, especially adenocarcinoma in a case-only study.

METHODS

STUDY DESIGN

The data from the Lung Cancer Database Project at the National Cancer Center Hospital East were used in the present study (9). Participants of the database study completed the questionnaires during the waiting period prior to admission and the questionnaires were collected after the admission. The database included details about physical size, life style factors (smoking, diet), and medical information (histological subtypes and family history) obtained from both patients’ medical charts and self-reported questionnaires. Blood and DNA samples were also available for the study. All participants gave their written informed consent before participating in the database study. This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center.

PARTICIPANTS

All participants enrolled in this database study were patients with newly diagnosed primary lung cancer who were admitted to the Thoracic Oncology Division of the National Cancer Center Hospital East, Japan. The following criteria were applied for inclusion: patients were informed of their lung cancer diagnosis; the lung cancer diagnosis was confirmed by histological examination; patients were capable of completing the questionnaires; patients had an absence of cognitive impairment; patients had the ability to provide written informed consent; and no problems were foreseen regarding the patient’s participation. In the present study, data from 1566 patients, collected during 1999—2003, with four major histologic subtypes (squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma) were submitted for analysis.

STATISTICAL ANALYSES

Differences in the characteristics of patients with lung cancer were compared between men and women by the Student’s t-test for continuous variables (age and number of siblings) and the χ² test for categorical variables (histology and smoking situation). Smoking situation was defined by pack-years, which is calculated by the multiplication of the number of packs of cigarettes smoked per day by the number of years smoked (never smokers, pack-years <20, 20—40 and >40).

The case-only study can provide increased statistical efficacy over case-control studies to detect gene–environment interactions (10–12), presenting the interaction parameter as an odds ratio for interaction (ORi). Under the assumption of independence between a family history of breast cancer and a patient’s sex, ORis and their 95% confidence intervals (95% CIs) were calculated to estimate the departure from multiplicativity using multiple logistic regression models. The biases arising from non-independence between two variables can be removed using standard statistical multivariable techniques (13). ORis were adjusted for the potential confounding variables age (<65 or ≥65 years) and smoking situation. Stratified analyses were conducted by histological subtypes to further investigate the heterogeneity of results in different histological subtypes.

All statistical tests were two-sided and a P-value <0.05 was considered statistically significant. Participants with missing information for any of the variables in a regression model were omitted from the analyses. Data analyses were conducted using SAS statistical software (version 9.1 for Windows, SAS Institute, Inc., Cary, NC).

RESULTS

The patients’ characteristics stratified by sex are shown in Table 1. The mean age at diagnosis was 64.9 ± 9.0 years for men and 63.7 ± 9.4 years for women (P = 0.03). There was no significant difference by sex regarding the number of siblings or family history of stomach, colon and lung cancer in first-degree relatives, but a significant difference was identified in the family history of breast cancer. Of the four major histologic subtypes, adenocarcinoma was the most frequent histologic subtype, especially predominant among women. Squamous cell carcinoma was the second most frequent histologic subtype, constituting about 30% of male lung cancer. The proportion of never smokers was approximately 14 times higher in women than in men. Similarly,
smoking dose has also been observed to be higher in male smokers than female smokers.

Table 2 shows the interaction between a family history of breast cancer and the sex of a patient with lung cancer calculated as ORi. The ORi for the female patients who had a parent with breast cancer was significantly high after adjustment for age and smoking situation (ORi: 6.17, 95% CI: 1.36–27.98). However, no significant interaction was observed in the analysis of siblings (ORi: 1.51, 95% CI: 0.61–3.73). The ORi for the female patients who had a family history of breast cancer in first-degree relatives (parent and siblings, not including children) was approximately two times higher (ORi: 2.22, 95% CI: 1.02–4.81). Further adjustment for the number of sisters, educational background, or fruit and vegetable intake did not substantially affect the results (data not shown). In order to confirm site specificity for this interaction, we calculated ORis for family history of stomach, colon and lung cancer in first-degree relatives and the sex of patients, but none of these ORi showed statistical significance: ORi: 0.89, 95% CI: 0.60–1.34 for stomach cancer; ORi: 0.75, 95% CI: 0.44–1.28 for colon cancer; and ORi: 1.29, 95% CI: 0.81–2.04 for lung cancer (data not shown in Table 2).

Table 3 further represents the different ORis in each histologic subtype. After adjustment for possible confounding factors, only adenocarcinoma showed a statistically significant difference for interaction (ORi: 3.27, 95% CI: 1.19–8.98).

**DISCUSSION**

Previous studies revealed the sex differences in lung cancer and associations between estrogen, estrogen-related genes and NSCLC. We now show that female patients who have a family history of breast cancer in first-degree relatives are at a greater risk of lung cancer compared with male patients, especially adenocarcinoma. The results of this study indicate the possible existence of a gene–sex interaction, which may be associated with sex differences in lung cancer.

Accumulated evidences suggest that there are genetic contributions in lung cancer susceptibility, although the environment has predominance over genes (14,15). Although a previous population-based case-control study had already shown the association between a family history of breast cancer and lung cancer risk (8), most inherited genetic factors make a minor contribution to cancer susceptibility. Genetic effects can be substantially modified by interactions with the environment. The main finding of this case-only study is that inherited genes that link lung and breast cancer susceptibilities may be associated with the increased risk in women’s adenocarcinoma.

Estrogen-related genes are most plausible candidate genes that link breast cancer and adenocarcinoma of the lung. Based on the results of this study, we suggest that estrogen-related genes play an important role in sex differences in lung cancer such as histologic distributions and prognosis (16). A recent study has shown that women with estrogen receptor (ER) β-positive tumors had a 73% (P = 0.1) increase in mortality, whereas men with ER β-positive tumors had a 55% (P = 0.04) reduction in mortality.
results and that we confirmed site specificity of the smoking situations seems to be properly adjusted. Given smoking situation. At the least, bias arising from different carcinoma showed a decreased ORi after adjustment for the carcinoma showed an increased ORi while squamous cell to shared smoking habits (19). In the present study, adeno-

<table>
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<th>No. of patients</th>
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<th>ORi (95% CI)†</th>
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<td>0.92 (0.10–8.16)</td>
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</table>

ORi, odds ratio for interaction; CI, confidence interval.
*Adjusted for age.
†Adjusted for age and smoking situation.

compared with those with ER β-negative tumors (17). Combined targeting of the ER and the EGFR in NSCLC shows enhanced antiproliferative effects, suggesting an interaction between the ER and the EGFR pathways (18).

The rapid progress in genome science has enabled us to perform genome-wide association studies. A genome-wide scan of women’s adenocarcinoma of the lung with and without a family history of breast cancer is likely to detect shared susceptible genes between lung and breast cancers, merging new genome research with traditional epidemiological studies. Lung and breast cancers are serious concerns for women today. Identification of shared candidate genes will contribute to an understanding of the genetic association with sex difference in lung cancer, the development of new effective therapeutics treatments, and better targeting of high risk groups, especially women more susceptible to adenocarcinoma of the lung.

Four major limitations must be considered when interpreting the present results. First, this study does not consider the effect of shared environmental factors. Lifestyle factors, such as diet and smoking, are often shared by family members. There remains some possibility that the results of this study may reflect genetic factors, shared environmental factors, or both. However, it has been shown that most familial cases of lung cancer cannot be attributed to shared smoking habits (19). In the present study, adenocarcinoma showed an increased ORi while squamous cell carcinoma showed a decreased ORi after adjustment for the smoking situation. At the least, bias arising from different smoking situations seems to be properly adjusted. Given that further adjustment did not substantially affect the results and that we confirmed site specificity of the observed interaction, our findings are unlikely to be influenced by shared environmental factors.

The second limitation, which is critically important in any case-only study, is the validity of the independence assumption. Women may be more likely than men to recall a family history of breast cancer. While the independence between two variables cannot be verified without control subjects, it may be tenable in this study because only adenocarcinoma shows an increased ORi. If recall bias existed, increased ORis would be observed in all histologic subtypes.

The third limitation is the validity of data on the family history of cancer. An evidence-based analysis showed that patient-reported family cancer histories for first-degree relatives were accurate and valuable for breast and colon cancer risk assessments (20). This might not be directly applicable to our study, however, given that Japanese physicians historically have tended not to disclose cancer diagnoses to their patients (21). If inaccurate reports were collected in the present study, the subsequent misclassification might tend to have caused a null result. The significant ORis, however, were unlikely to have been affected by such misclassification.

We found that women with a family history of breast cancer in first-degree relatives were at increased risk of adenocarcinoma of the lung compared with men. This finding provides an interesting insight into sex differences in lung cancer and may hint at an explanation for sex-related biological differences. It should be interpreted cautiously, however, because of the small number of subjects in the stratified analysis by histologic subtype, which is indeed a fourth limitation. Thus, a full understanding of the relationship between genetic factors and sex differences in lung cancer will require not only further epidemiological confirmation but also more genetic and mechanistic studies.

Allowing for these limitations, this study showed that women with a family history of breast cancer are at an increased risk of adenocarcinoma of the lung compared with men, which might imply a possible gene–sex interaction in lung cancer.

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Conflict of interest statement
None declared.
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