Association of EGFR mutations in second primary lung cancer and HER2 expression in breast cancer survivors

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Background: The incidence of second primary lung cancer (SPLC) is increasing with longer survival rates from breast cancer. Despite of studies to suggest the mutual exclusivity of epidermal growth factor receptor (EGFR) and human epidermal growth receptor 2 (HER2) in several cancers, the effect of HER2 expression in breast cancer on EGFR mutations in SPLC is unclear. Therefore, this study aimed to determine the association between HER2 expression and EGFR mutations.

Methods: We conducted a retrospective cohort study of breast cancer survivors diagnosed with SPLC after breast cancer treatment between 1997 and 2018. We investigated the association between HER2 expression in breast cancer and EGFR mutations in SPLC, specifically focusing on negative correlations by using logistic regression analysis.

Results: EGFR mutations in SPLC were detected in 19 of 38 patients. Analysis for HER2 revealed a statistically significant difference in the proportion of EGFR mutations between patients with SPLC and previous HER2 positive breast cancer (43.5%) and those with SPLC and previous HER2 negative breast cancer (90.0%; P=0.021). The ratio of EGFR mutations decreased with the degree of HER2 expression in patients with previous breast cancer (90.0%: for no HER2 expression, 62.5% for HER2 1+, 0.0% for HER2 2+, and 41.7% for HER2 3+: P=0.018). Multivariate logistic analyses revealed that EGFR mutations in SPLC were significantly associated with age [odds ratio (OR): 1.11, 95% confidence interval (CI): 1.01–0.23, P=0.039] and HER2 positive status (OR: 0.04, 95% CI: 0.01–0.56, P=0.017).

Conclusions: This study suggests that the frequency of EGFR mutations in SPLC may be associated with low HER2 expression in previous breast cancer.

Keywords: Breast cancer; lung cancer; HER2; EGFR; second primary cancer

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Introduction

In Korea, breast cancer, a common cancer affecting women for the past several decades, had the highest incidence in 2017 (1). The survival rates of patients with breast cancer have been increasing with early diagnosis and treatment improvement (2). Improved outcomes have led to an increased population of breast cancer survivors; hence, there has been a growing interest in determining the risk of second primary cancers (3,4). In addition, second primary cancers are the cause of death in more than one-half of breast cancer survivors (5). Numerous factors such as hereditary predisposition, common etiologic exposures, and especially the effects of chemotherapy or radiotherapy for the previous breast cancer may play an important role in the occurrence of second primary cancers (6-8). Lung cancer is the most common second primary cancer among breast cancer survivors (9). Previous studies have shown that approximately 5–10% of breast cancer patients are diagnosed with second primary cancers (5).

The incidence of second primary lung cancer (SPLC) is increasing with longer survival rates from breast cancer; however, only few studies have investigated the association between SPLC and breast cancer. In a large registry-based study, the incidence rate of SPLC was significantly higher in estrogen receptor (ER)-negative breast cancer patients than in ER-positive breast cancer patients (10). Another study reported that the incidence of SPLC was higher in human epidermal receptor 2 (HER2) negative breast cancer survivors than in HER2 positive breast cancer survivors. A recent retrospective study showed that the frequency of previous breast cancer was higher in patients with epidermal growth factor receptor (EGFR)-mutant lung cancer than in those with EGFR wild-type lung cancer (11). The family of EGFR receptors plays an important role in cell proliferation (12). However, interest has been centered on EGFR because EGFR mutations greatly affect the prognosis of lung cancer (13). HER2, another member of the EGFR family, is overexpressed in 15–25% of invasive breast cancers and is associated with reduced survival in invasive breast cancer (14). A few studies investigating the association between EGFR and HER2 in cancers have reported that EGFR and HER2 appear to be mutually exclusive in several cancers (15,16). However, no study has investigated the effect of HER2 expression in breast cancer on EGFR mutations in SPLC.

In this study, we investigated the association between HER2 expression in breast cancer and EGFR mutations in SPLC among breast cancer survivors, specifically focusing on negative correlations between HER2 status and EGFR mutation. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-1235).

Methods

Patients and data collection

This study included patients diagnosed with SPLC following breast cancer at the Korea Cancer Center Hospital (KCCH) between January 1997 and January 2018. Inclusion criteria were a pathological diagnosis of lung cancer and a previous history of primary breast cancer diagnosis in our hospital. Screening for SPLC was performed immediately after the diagnosis of breast cancer and included concurrent diagnosis of breast cancer and lung cancer. Finally, this study included patients with SPLC and previous breast cancer confirmed by pathologists at the KCCH. All pathological types of breast cancer were included, but small-cell lung cancer was excluded. Data of all patients were extracted from the Electronic Medical Record (EMR). Relevant clinical information [i.e., age, sex, current smoking status, pathological type of breast cancer and lung cancer, hormonal status of breast cancer (estrogen receptor and progesterone receptor), mutational status (HER2 expression in breast cancer and EGFR mutation in lung cancer), location of breast cancer, breast cancer treatment history, and initial clinical stage by tumor-node-metastasis (TNM) seventh edition] were extracted from the EMR for analysis. The study was conducted in accordance with the Declaration of Helsinki (revised in 2013). The study was approved by the Institutional Review Board of Korea Cancer Center Hospital (2019-11-001), and individual consent for this retrospective analysis was waived.

Immunohistochemistry and molecular analysis

Samples of pathologically confirmed breast cancer tissues were immunostained with rabbit monoclonal antibody, 4B5, for HER2/neu using an automated staining system (Benchmark XT, Ventana Medical Systems, Tucson Arizona, USA) according to the manufacturer’s recommendations. Staining for HER2 was detected using the OptiView DAB IHC detection kit (Ventana Medical Systems, Tucson Arizona, USA) and scored from 0 to 3 using the scoring...
system reported in the guidelines (Figure 1) (17). Samples with a HER2 score of 1+ to 3+ were defined as HER2 positive. Estrogen and progesterone receptors were evaluated according to the American Society of Clinical Oncology/College of American Pathologists guidelines (18). Genomic DNA from tumor tissue samples were analyzed for EGFR mutations using the PyroMark Q96 ID PCR kit (Qiagen, Valencia, CA, USA) and an ABI 3130 analyzer (Thermo Fisher Scientific, Foster City, CA, USA). The samples were analyzed for point mutations and in-frame deletions in exons 18, 19, 20, and 21, as recommended by the Human Genome Variation Society.

Statistical analysis

Categorical variables are presented as number (percentage), and continuous variables are presented as median [interquartile range (IQR)]. The association between HER2 expression and EGFR mutations was assessed using Fisher's exact test. In addition, the linear-by-linear association test was used to analyze trends in EGFR mutation according to the degree of HER2 expression. Univariate and multivariate logistic regression analyses were performed to identify risk factors associated with EGFR mutations. Covariates with a P value of <0.1 in the univariate analysis were included in the multivariate logistic regression analysis with the stepwise method using the backward selection approach. Considering our small sample size, the adjusted multivariate model was evaluated using Statistical Package for Social Science (SPSS version 24.0 for Windows; SPSS, Chicago, USA).

Results

A total of 38 patients with SPLC and previous breast cancer were identified. Patient characteristics are presented in Table 1. All patients were women, with a median age of 65 years (IQR, 58.0–74.5 years). The majority of patients with previous breast cancer (81.6%) had invasive ductal carcinoma. Thirty-three (86.8%) patients were evaluated for HER2 expression, of which 23 (69.7%) patients were HER2 positive. Nearly all (97.4%) patients underwent surgery for breast cancer treatment, of which approximately half (55.3%) received radiotherapy. A major pathological feature of SPLCs was adenocarcinoma (86.8%). EGFR mutations were confirmed in 19 (50%) patients [3 (15.8%) patients: exon 18; 6 (31.6%) patients: exon 19; and 10 (52.6%) patients: exon 21].

Correlation between the degree of HER2-positive expression in breast cancer and EGFR mutation in lung cancer

HER2 expression data of five patients were not available. The results of HER2 expression analysis in the remaining 33 patients are presented in Figure 2. Eight (24.2%) patients had a HER2 score of 1+, 3 (9.1%) had 2+, and 12 (36.4%) had 3+. EGFR mutation showed a negative association with HER2 expression (90% in HER2 negative vs. 43.5% in HER2 positive, P=0.021). In addition, EGFR mutation tended to decrease with an increase in HER2 expression (P=0.018).
Comparison of EGFR mutation risk in the univariate and multivariate model

The independent effects of covariates on the risk of EGFR mutations are shown in Table 2. In the univariate analysis, HER2 expression (OR: 0.085, 95% CI: 0.01–0.79, P=0.03) and previous hormonal therapy (OR: 7.44, 95% CI: 1.25–44.19, P=0.027) were associated with the risk of EGFR mutations. After adjusting for age, estrogen receptor status, and HER2 expression, HER2 expression was associated with a decreased risk of EGFR mutations (OR: 0.04, 95%
CI: 0.01–0.56, P=0.017) in the multivariate analysis. In addition, the risk of EGFR mutation increased with age (OR 1.11, 95% CI: 1.01–1.23, P=0.039). The logistic regression model was statistically significant ($\chi^2[2] = 12.39; P=0.002$). The final model explained 42.1% (Nagelkerke $R^2$) of the variance in EGFR mutations and correctly classified 75.8% of cases.

**Discussion**

This study suggests that the risk of developing EGFR-mutant SPLCs may be significantly lower in patients with previous HER2 positive breast cancer than in those with HER2 negative breast cancer.

The correlation between HER2 status in breast cancer and EGFR-mutant SPLCs has not been reported previously. However, many previous studies have reported the elevated risk for second primary cancers, such as lung cancer after breast cancer, suggesting that treatments such as radiotherapy might be associated with increased risks (19-21). In addition, most studies on the association between EGFR mutations and HER2 overexpression have
HER2 overexpressing breast cancers have different characteristics compared with HER2 negative breast cancers. HER2 overexpressing breast cancers are more likely to have an aggressive tumor grade, a higher risk of recurrence, and a relatively high incidence of brain metastasis than HER2 negative breast cancers (34). However, no remarkable risk factors for HER2 positive breast cancers have been found. Few studies have reported the etiology of HER2 overexpression. A study conducted in China indicated that parity and breastfeeding were inversely associated with HER2 positive breast cancer (35). In addition, other studies have found that older age at first birth or younger age at menarche might affect HER2 overexpression (36,37).

Several methodological limitations should be considered when interpreting the results of this study. First, this study included a small number of patients and therefore, it is difficult to make statistically significant judgments. Only three patients had a HER2 score of 2+ without EGFR mutations. However, despite the small sample size of the study, a strong association between HER2 expression and EGFR mutation was found consistently in both the trend test and multivariate analysis. Second, individual risk factors for EGFR mutations, rather than HER2 overexpression alone, might skew these results. Particularly, EGFR mutations usually develop among Asian, female, and non-smoker populations (38). Nevertheless, the association we observed is worth considering because our study population was mostly homogeneous in terms of patient characteristics (such as age, ethnicity, sex, and smoking history) and thus, had similar risk factors for EGFR mutations. Finally, detailed data on prognosis were not available. The presence of EGFR mutations in SPLC is expected to affect clinical outcomes. Further studies evaluating the prognosis of lung cancer after breast cancer are warranted.

Conclusions

The results of the current study suggest that EGFR mutations in SPLC are more likely to develop in HER2 negative breast cancer survivors. With advances in breast cancer treatment, the number of breast cancer survivors is increasing. Therefore, further studies investigating whether the higher expression of HER2 in previous breast cancer results in an increased risk of developing SPLC without EGFR mutations.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (revised in 2013). The study was approved by the Institutional Review Board of Korea Cancer Center Hospital (2019-11-001), and individual consent for this retrospective analysis was waived.

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