Non–Small-Cell Lung Cancer After Breast Cancer

A Population-Based Study of Clinicopathologic Characteristics and Survival Outcomes in 3529 Women

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Introduction: Annually, 1.4 million women worldwide are diagnosed with breast cancer (BC) and are at risk for another common malignancy: non–small-cell lung cancer (NSCLC). No large population-based study has examined subsequent survival.

Methods: Women with histologically confirmed NSCLC after BC (BC-NSCLC, $n = 3529$) were identified in SEER-18 registries (1988–2009). Clinicopathologic characteristics and survival outcomes were compared among women with first primary NSCLC (NSCLC-1, $n = 151{,}628$). Cox regression analyses were adjusted for patient, BC, and NSCLC factors.

Results: BC-NSCLC was diagnosed at earlier stages (34% localized, 30% regional, 36% distant) than NSCLC-1 (22%, 28%, and 50%, respectively; $p < 0.0001$). For localized and regional BC-NSCLC, surgical resection rates were higher than NSCLC-1 (72% versus 69% [$p < 0.01$] and 56% versus 46% [$p < 0.0001$]), respectively). Radiotherapy was given less often for BC-NSCLC than NSCLC-1 (localized: 15% versus 18%, $p < 0.004$; regional: 38% versus 49%, $p < 0.0001$). Median overall survival (OS) after localized, regional, and distant BC-NSCLC was 5.1 years, 1.9 years, and 5.8 months, respectively. For NSCLC-1, median OS was 4.6 years, 1.5 years, and 4.6 months, respectively. BC history did not affect OS for localized NSCLC, and OS was modestly greater after regional ($p = 0.016$) and distant ($p < 0.0001$) BC-NSCLC compared with NSCLC-1. BC radiotherapy to the ipsilateral chest did not unfavorably influence OS.

Conclusions: BC survivors are more likely to be diagnosed with earlier stage NSCLC versus first primary NSCLC patients, perhaps reflecting heightened surveillance compared with the general population. In contrast to prior studies of NSCLC in survivors of lymphopoietic malignancies, BC history does not appear to adversely affect OS after NSCLC.

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Breast cancer (BC) is the most common malignancy among US women, with an estimated 232,670 cases expected in 2014.[1] Advances in the detection, treatment, and management of BC over the past few decades have resulted in marked improvements in survival, resulting in a growing number of women at risk for the late effects of cancer and its treatment.[2] As of 2012, women with BC accounted for 22% of cancer survivors in the United States, representing a population of over 2.9 million,[3] which is anticipated to grow further in the next few decades.

BC survivors and other cancer survivors are at risk for developing other malignancies.[4] In fact, second and higher order cancers now comprise the most common incident cancer in the United States, representing 18% (or almost one in five of all new cancers),[5] and propelling the study of second malignant neoplasms (SMN) onto the National Cancer Institute's List of Provocative Questions.[6] Following a diagnosis of BC, lung cancer accounts for the largest number of second non-breast malignancies,[4] and given its lethality, represents the most common non-BC cause of death after cardiac and vascular causes.[7–9]

Although a number of studies have examined the risk of developing lung cancer after BC[10–20] and have analyzed risk factors (reviewed in Lorigan et al.),[21] there are no large investigations of subsequent survival. One study of outcomes in BC survivors with second primary lung cancer included only 6 patients,[22] and another included 35 patients.[23] No large, population-based study has comprehensively examined outcomes among BC survivors with second primary non–small-cell lung cancer (NSCLC), taking into account demographic, clinicopathologic, and other variables. It is important to evaluate these outcomes, given the significantly inferior survival recently reported for patients with lymphopoietic malignancies, including Hodgkin lymphoma (HL) and chronic lymphocytic leukemia (CLL), who develop NSCLC.[24,25] Although the inferior survival[24,25] among these patients may be due in part to inherent immune deficiencies associated with some lymphocytic malignancies,[25,26] to our knowledge a diagnosis of BC

is not associated with immunocompromisation. Moreover, the public health impact of any factor that might lessen the otherwise excellent long-term prognosis for BC survivors[3] would only underscore the need for future research into underlying pathways and efforts at prevention and intervention.[27–30]

METHODS

Patients

All women diagnosed with histologically confirmed NSCLC as a SMN after a first BC (excluding those with distant disease) were identified in population-based registries of the Surveillance, Epidemiology, End Results (SEER) 18 Program (1988–2009). The SEER program registries capture about 28% of the US population. For our study, a minimum latency of 2 months was required, as used in SEER to exclude synchronous primary cancers.[31] The resultant 3529 patients (BC-NSCLC) were grouped by SEER Historic Stage of localized (i.e., confined to lung or bronchial tree with no regional extension or nodal or distant metastases), regional (i.e., ipsilateral regional nodes and/or extension to regional sites), or distant (i.e., metastasis to contralateral thoracic or distant nodes, malignant pericardial or pleural effusions, distant metastases, and/or extension to sites such as heart, abdomen, spine, contralateral lung, skeletal muscle, skin, and brachial plexus) stage NSCLC. This staging is described in detail in historic SEER coding manuals (http://seer.cancer.gov/tools/codingmanuals/historical.html). Because SEER did not record lung cancer stage before 1988, study entry began in 1988. For the NSCLC-1 comparison group, all female patients diagnosed with a first primary NSCLC (n = 151,628) were identified from the same registries during 1988–2009. Eligible NSCLC histologies were squamous cell carcinoma, adenocarcinoma, bronchiolo-alveolar carcinoma, adenosquamous carcinoma, large cell carcinoma, and non–small-cell carcinoma, not otherwise specified (histology codes listed in Table 1).

The SEER Program records sociodemographic parameters for each patient's county of residence, as determined from census data, from which we considered the proportion of adults aged 25 years and older, residing within that county with less than a high-school education, and the cost of living adjusted median income as measures of socioeconomic status.[32,33]

Restriction to Histologically Confirmed NSCLC

In view of the strict criteria that the SEER program applies to define SMN (http://seer.cancer.gov/tools/mphrules/), our study was restricted to histologically confirmed NSCLC. Despite these stringent criteria, a small percentage of BC-NSCLC adenocarcinoma may represent metastatic BC. Although to our knowledge an independent verification of NSCLC adenocarcinoma in the SEER program has not been undertaken, in a recent pathology review of lung cancer in BC survivors in the Swedish Cancer Registry, misclassification of lung metastases as new primaries diminished with calendar-year period to less than 5% for BC diagnosed in 1980.[34] Our study included only BC patients diagnosed in 1988 or later. Thus, in view of the improvements in histologic diagnostic procedures with time, and the rigorous criteria that the SEER program requires to define SMN,[35] we estimate that any effects of residual misclassification are small.

Statistical Analysis

Frequency distributions of variables were compared using Fisher's Exact test, with continuous variables first being transformed into categorical variables (for these analyses only). Overall survival (OS; i.e., all-cause) was estimated using Kaplan-Meier methods, with survival times measured from date of NSCLC diagnosis until date of death or last follow-up (through December 31, 2009). To compare OS between BC-NSCLC and NSCLC-1, both the log-rank and supremum log-rank[36] tests were used; in comparison to the log-rank test, the power of the supremum log-rank test is less sensitive to the presence of nonproportional hazards (e.g., when survival curves cross). Lung cancer cause-specific survival (LC-CSS) time was measured from date of NSCLC diagnosis until date of death or last follow-up (through December 31, 2009); here, only death from lung cancer was designated as an event. The SEER program abstracts data from death certificates to derive a single cause of death. For OS and LC-CSS, Cox regression (controlling for covariates) was also used for survival comparisons. LC-CSS analyses were further complemented by regression analyses of cumulative incidence using the proportional subdistribution hazard regression model of Fine and Gray.[37] For BC-NSCLC, the stage-specific effect of radiotherapy for BC on survival outcomes after developing an ipsilateral NSCLC was assessed by the stratified log-rank test, stratified by year of diagnosis (i.e., 1988–1998 versus 1999–2009). All analyses were conducted using the R statistical software package.[38] All p values were two-sided, with $p < 0.05$ defined as statistically significant, as in prior studies of survival after second malignancies.[24,33]

RESULTS

Patient and Tumor Characteristics

Table 1 outlines demographic and clinicopathologic characteristics at BC diagnosis, grouped by subsequent NSCLC stage. Among the NSCLC stage groups, the distributions of age, BC stage, estrogen receptor (ER) status, grade, and type of BC surgery within each stage were similar. No difference in the proportion of women given radiotherapy initially was evident (p = 0.18, omitting unknown status). Black women were slightly overrepresented among distant BC-NSCLC (p = 0.006). Women with localized (versus more advanced) NSCLC more likely had BC in 2000–2009.

Table 2 outlines clinicopathologic characteristics of BC-NSCLC and NSCLC-1 patients at NSCLC diagnosis. The NSCLC stage distribution of BC-NSCLC (34% localized, 36% distant), differed significantly ($p < 0.00001$) from NSCLC-1 (22% localized, 50% distant). BC-NSCLC was diagnosed in more recent years and at slightly more advanced ages than NSCLC-1, reflecting its SMN nature. The prevalence of lung adenocarcinoma among BC-NSCLC patients with localized or regional disease was slightly greater than for NSCLC-1. Women with either localized or regional BC-NSCLC were considerably more likely to undergo cancer-directed surgery than NSCLC-1 patients, with corresponding percentages of 72% and 69% (p = 0.004), and 56% and 46%, respectively ($p < 0.0001$). At