The Breast 24 (2015) 131–136

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Heterogeneity in hormone-receptor status and survival outcomes among women with synchronous and metachronous bilateral breast cancers

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ARTICLE INFO

Article history:
Received 2 September 2014
Received in revised form
19 November 2014
Accepted 1 December 2014
Available online 18 December 2014

Keywords:
Estrogen receptor
Synchronous breast neoplasms
Metachronous breast neoplasms
Prognosis
Second primary neoplasm
Molecular epidemiology

ABSTRACT

To examine whether discordance in the hormone-receptor status predicts clinical outcomes in patients with bilateral synchronous (SBC) or metachronous breast cancer (MBC), we analyzed data from the Surveillance, Epidemiology, and End Results program (1998–2011) using Cox models. After excluding 10,231 patients with missing data on hormone receptors in at least one tumor, 4403 SBC and 7159 MBC were included in the study. Among SBC cases, patients with estrogen receptor (ER)-discordant tumors had higher mortality risk (multivariable-adjusted hazard ratio [HR] = 1.96, 95% confidence interval [CI] 1.60–2.40) than patients with ER concordant-positive tumors, whereas patients with ER concordant-negative tumors had the highest risk (HR = 2.49, 95% CI 2.03–3.07). Among MBC cases, patients with a positive-to-negative change in ER status (HR = 1.32, 95% CI: 1.08–1.62) or ER concordant-negative tumors (HR = 1.48, 95% CI: 1.19–1.85) had worse survival than patients with ER concordant-positive tumors. In conclusion, discordance in the hormone-receptor status was an independent predictor of survival outcomes.

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Introduction

Hormone receptors are established biomarkers for prognosis and treatment of breast cancer patients [1]. Tumor heterogeneity is becoming important in the management of breast cancer. Using estrogen receptor (ER) as a biomarker, 5–10% of multifocal/multicentric cancers [2,3] and approximately 20% of bilateral breast cancers are discordant [4–8]. The ER status of metastases differs from that of the primary breast cancer in 10–40% of patients [9–11].

The prognostic relevance of change in hormone-receptor status has been evaluated in neoadjuvant setting and in patients with distant relapse. Chen et al. found that the positive-to-negative change in hormone-receptor status after neoadjuvant chemotherapy was an independent predictor of poor survival [12]. Other studies found that cases with discordant receptor status of metastatic disease and primary breast cancer have a worse prognosis than those with ER concordant-positive status [13–15].

A recent review and meta-analysis has suggested that patients with synchronous bilateral breast cancer (SBC) have worse prognosis than patients with single unilateral breast cancer [16]. However, it is unclear whether inconsistent hormone-receptor status predicts worse clinical outcomes among SBC patients. It is also unclear whether the hormone-receptor status of the first cancer is a prognostic factor for the second breast cancer among patients with metachronous breast cancers (MBC). To address these questions, we conducted a large retrospective cohort study of patients with bilateral breast cancers.

Patients and methods

Patient selection

Using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program [17], we conducted a retrospective, population-based cohort study of women with two

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http://dx.doi.org/10.1016/j.breast.2014.12.001
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primary breast cancers. Using a unique identifier assigned to each patient in SEER 18 registry database (1998–2011), we identified 22,976 female patients who had bilateral breast cancers with the first cancer being diagnosed between 1998 and 2005. Of these patients, we excluded those lacking follow-up data ($n = 180$, 0.8%) and those with stage IV first or second cancer ($n = 1003$, 4.4%), and those with unknown ER- or progesterone (PR)-status in one of the two tumors ($n = 10{,}231$, 44.5%). After these exclusions, 11,562 patients remained, including 4403 patients in the SBC cohort and 7159 in the MBC cohort. According to our previous concordance study [8], two tumors were considered synchronous if they were diagnosed within 6 months.

The SEER database contains demographic information including age, race, and marital status. Tumor characteristics reported for each of the two tumors were histology, stage, grade, laterality, ER and PR statuses. Treatment information is available on surgery and radiotherapy, but not on chemotherapy and hormonal therapy. Stage was reported according to the American Joint Committee on Cancer TNM classification system.

Statistical analysis

First, we explored the missing data patterns of ER and PR between the two breast cancers. We compared patients who had complete data on hormone-receptor status in both cancers with patients who were dropped because of missing hormone-receptor status in at least one cancer using Chi-square tests or Wilcoxon rank-sum tests. We also examined factors related to missing ER status among patients who had ER data available only for one tumor, by using signed-ranks tests.

We examined the combined effect of the hormone-receptor statuses of two tumors on overall survival (OS) and breast cancer-specific survival (BCSS). OS was defined as the time interval between the date of the second cancer diagnosis and the date of death or last follow-up. BCSS was defined as the time interval between the date of the second cancer diagnosis and the date of death due to breast cancer or the date of last follow-up. Survival curves were estimated by the Kaplan–Meier method. We used piecewise Cox models to examine the independent effect of hormone receptors. After checking the proportional hazard assumption in classical Cox models, we found that it was violated for hormone receptors. Therefore, we stratified follow-up time into intervals so that the proportional hazards assumption held in each interval. We found that a model stratified at 5 years of follow-up fulfilled this condition and was parsimonious. The period-specific hazard ratio (HR) and 95% confidence interval (CI) were calculated from Cox models.

The SBC and MBC cohorts were analyzed separately. In the SBC cohort, patients were categorized into three groups according to the hormone-receptor status of the two tumors: concordant positive (+/+), concordant negative (−/−), and discordant (+/− and −/+). Other demographic and clinical factors of both cancers as listed above were adjusted for in the multivariable models. Age at diagnosis was modeled as a continuous variable with restricted cubic-spline transformation (5 knots at 42, 55, 64, 73, and 85 years old). In the MBC cohort, patients were categorized into four groups according to the hormone-receptor status of the two tumors: concordant positive (+/+), concordant negative (−/−), negative-to-positive change (−/+), and positive-to-negative change (+/−). We first examined the effect of the ER status of the two cancers. Then, we examined the effect of the PR status and adjusted for ER status in the model. A two-sided P value ≤ 0.05 was considered statistically significant.

As discordance in stage and grade between two cancers may be important for predicting survival outcomes, we explore the appropriate ways to model tumor stage and grade of two cancers in Cox models. Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to gauge model fit while penalizing model complexity; the lower the AIC and BIC values, the better the model fit. Statistical analyses were conducted using Stata 13 software (StataCorp, College Station, TX).

Results

Missing data patterns of hormone receptors

Of the 10,231 patients who were excluded because of missing data in hormone receptors, 7049 (69%) patients had ER and PR statuses only for one cancer, 2533 (25%) patients had no ER and PR data in either cancers, 594 (6%) patients had missing data in PR status but not in ER status, and 55 (0.5%) patients had missing data in ER status but not in PR status. We compared these 10,231 patients with the 11,562 patients who had complete data in ER/PR (included in further analysis) and found that patients with invasive breast cancer or diagnosed in recent years were more likely to have complete ER/PR data (Supplementary Table S1**).** Patients with complete ER/PR data were slightly older than patients with missing ER/PR. Patients with complete ER/PR also had 30% higher risk of dying than patients with missing ER/PR data, but after adjusting for age, stage, year of diagnosis, and type of breast cancer (synchronous or metachronous), the survival difference was attenuated. We also conducted within-patient comparison among women who had missing ER data in only one cancer (Supplementary Table S2). Invasive tumors instead of DCIS were more likely to be tested for ER than the contralateral tumors. When both tumors were invasive, the larger tumors were more likely to be tested.

Characteristics of SBC and MBC patients

Table 1 depicts the clinical characteristics of 4403 SBC and 7159 MBC cases. The average age at diagnosis for SBC patients was 63.1 years (SD = 13.7); for MBC patients, the average age was 59.4 years (SD = 12.9) at first diagnosis and 64.6 years (SD = 13.0) at second diagnosis. Among SBC cases, the two tumors were ER-discordant in 422 (10%) patients. In MBC cohort, the ER negative-to-positive (−/+) change was observed in 1008 (14%) patients and the ER positive-to-negative (+/−) change was observed in 1080 (15%) patients (Table 1). Most of the SBC cases were treated with mastectomy (60%), whereas the predominant surgical treatment of the first breast cancer in MBC patients was lumpectomy (60%).

Outcomes of SBC according to hormone-receptor status

In the SBC cohort, the median follow-up was 6.8 years [interquartile range (IQR) 7.0–10.9 years, range 5.5–13.9 years]. During a total of 32,271 person-years of follow-up, 1568 patients died, including 722 from breast cancer, 205 from other cancers, and 641 from other causes. Patients with concordant-positive (+/+) ER status had better clinical outcomes than patients with concordant-negative (−/−) ER status, whereas patients with discordant ER status had an intermediate prognosis (Supplementary Fig. S1**)**. The separation among the three groups was more pronounced during the earlier years of follow-up and for BCSS. In the multivariable analysis, we stratified the analysis before and after 5 years of follow-up, because the proportional hazard assumption was violated if constant hazard ratio was assumed for the entire duration of follow-up (Table 2). We found that ER-discordant cases had approximately 2-fold higher all-cause mortality (HR = 1.96, 95% CI: 1.60–2.40; $p < 0.001$) than ER concordant-positive cases and lower all-cause mortality (HR = 0.78, 95% CI: 0.61–1.01; $p = 0.06$) than ER concordant-negative cases in the first 5 years. Similarly ER-

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