Published in final edited form as:

Breast. 2015 April ; 24(2): 131–136. doi:10.1016/j.breast.2014.12.001.

Heterogeneity in Hormone-Receptor Status and Survival Outcomes among Women with Synchronous and Metachronous Bilateral Breast Cancers

Zora Baretta[1], **Olufunmilayo I. Olopade**[2], and **Dezheng Huo**[3]

[1]Department of Oncology 2, Istituto Oncologico Veneto IOV – IRCCS, Padova, Italy.

[2]Center for Clinical Cancer Genetics & Global Health, Department of Medicine, University of Chicago, Chicago, Illinois, USA.

[3]Department of Public Health Sciences, University of Chicago, Chicago, Illinois, USA.

Abstract

To examine whether discordance in the hormone-receptor status predicts clinical outcomes in patients with bilateral synchronous (SBC) and metachronous breast cancer (MBC), we analyzed data from the Surveillance, Epidemiology, and End Results program (1998−2011) using Cox models. After excluding 10231 patients with missing data in 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.

Keywords

Estrogen Receptor; Synchronous Breast Neoplasms; Metachronous Breast Neoplasms; Prognosis; Second Primary Neoplasm; Molecular Epidemiology

Correspondence and reprint requests: Dr. Dezheng Huo, Department of Public Health Sciences, University of Chicago 5841 S. Maryland Avenue, MC 2000, Chicago, IL 60637 Phone: 1-773-834-0843, Fax: 1-773-702-1979 dhuo@health.bsd.uchicago.edu.

CONFLICT OF INTEREST

The authors declare that they have no financial and personal interest that could inappropriately influence the conduct and interpretation of the work presented in this manuscript.The contents of this manuscript have not been copyrighted or published previously, and this manuscript is not under consideration elsewhere.

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 primary breast cancers. Using a unique identifier assigned to each patient in SEER 18 registry database (1998-2011), we identified 22976 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*=10231, 44.5%). After these exclusions, 11562 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 gouge 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 10231 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 10231 patients with the 11562 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 32271 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 Figure 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-discordant cases had 2.8-fold higher risk of dying from breast cancer (HR=2.79, 95% CI: 2.14-3.64; p<0.001) than ER concordant-positive cases in the first 5 years, but had similar risk of dying from breast cancer (HR=0.85, 95% CI: 0.62-1.16; p=0.30) compared with ER concordant-negative cases. By contrast, there was no statistically significant difference among the three groups in either OS or BCSS after 5 years.

When we examined the outcomes according to PR status, we found that there were significant differences among PR-discordant, concordant-negative, and concordant-positive

cases in the univariate analysis (**Supplementary Figure S1**) and in the multivariable analysis (**Table 3**, Model 1). In particular, PR discordant patients had higher all-cause mortality (HR=1.42, 95% CI: 1.19-1.69; p=0.0001) and breast cancer-specific mortality (HR=1.75, 95% CI: 1.36-2.24; p<0.0001) than PR concordant-positive patients in the first 5 years, while PR discordant patients had lower all-cause mortality (HR=0.80, 95% CI: 0.65-0.99; p=0.04) and breast cancer-specific mortality (HR=0.73, 95% CI: 0.55-0.95; p=0.02) than PR concordant-negative patients. However, PR status was no longer significantly associated with OS or BCSS after adjusting for ER status (**Table 3**, Model 2).

Outcomes of MBC according to hormone-receptor status

In the MBC cohort, the median follow-up time from the diagnosis of the second cancer was 3.8 years (IQR 1.8−5.9 years, range 0.1−13.1 years). During a total of 27527 person-years of follow-up, 1462 patients died, including 835 from breast cancer, 149 from other cancers, and 478 from other causes. Kaplan-Meier analysis showed that patients with concordant-negative (−/−) ER status had the worst OS and BCSS, followed by patients with a positive-to-negative change (+/−) in ER status, whereas patients with concordant positive (+/+) or negative-to-positive change (−/+) had the best clinical outcomes (**Supplementary Figure S2**). These differences were attenuated in the multivariable analysis which adjusted for several prognostic factors including tumor stage and grade from both cancers (**Table 4**). In the first 5 years, the ER negative-to-positive (−/+) group (HR=0.75 for OS and HR=0.66 for BCSS) had lower risk of dying compared to the ER concordant-positive (+/+) group, whereas the ER positive-to-negative (+/−) group (HR=1.32 for OS and HR=1.44 for BCSS) and the ER concordant-negative (−/−) group (HR=1.48 for OS and HR=1.45 for BCSS) had a higher mortality risk compared to the ER concordant-positive (+/+) group. After 5 years, ER (−/−) patients had a lower all-cause mortality compared to patients with ER (+/+) breast cancers.

The results for the four PR groups were similar with those observed for the ER groups (**Supplementary Figure S2** and **Table 5**). After adjusting for ER status, the association between PR status and OS and BCSS in the first 5 years was no longer statistically significant (**Table 5**, Model 2).

Prognostic effects of tumor stage and grade of two cancers

In patients with SBC, the common practice of staging is to consider the higher stage of two cancers. As shown in **Supplementary Table S3**, the model that included both stages (model A) and the model with higher stage (model B) had similar predictive values on BCSS, but model B is less complicated, suggesting that the practice of using higher stage is justified. Similarly, the model with higher histologic grade (model D) fit the data as well as the model with both grades (model C). Based on these results, higher stage and grade were adjusted for in the analysis of hormone receptors in the SBC cohort. Of note, among SBC patients in which the two tumors were at different stage, the odds of the higher stage tumor being ER negative versus the lower stage tumor was only 1.15:1.

In the MBC cohort, tumor stage of previous cancer was associated with BCSS after accounting for tumor stage of current cancer (**Supplementary Table S4**, Model B).

Although the model with higher stage (model C) fit the data well, it was not as good as model B according to Chi-square statistic and Akaike information criterion. Similarly, histologic grade of previous cancer was an independent prognostic factor after adjusting for histologic grade of current cancer. Based on these results, stage and grade of both tumors were adjusted for in the analysis of hormone receptors in the MBC cohort.

DISCUSSION

In this study, we evaluated the prognostic impact of heterogeneity in hormone-receptor status in two cohorts of bilateral breast cancer patients. In both cohorts of patients, we found that heterogeneity in hormone-receptor status could be used to predict the overall survival and breast cancer-specific survival. The prognostic value of the ER status was predominant over that of the PR status. We also found that the effect of the hormone-receptor status varied with respect to the follow-up time.

In patients with SBC, we found that ER-discordant patients have a higher mortality risk than ER concordant-positive patients and a lower mortality risk than ER concordant-negative patients during the first 5 years. By contrast, our study justified the common practice of using the higher stage and grade of the two tumors. These findings support the need to evaluate hormone-receptor expression in all breast cancer lesions, regardless of tumor size or stage. Moreover, heterogeneity in the hormone-receptor status could change the therapeutic management of patients with SBC; both hormone therapy and chemotherapy may be considered for SBC patients with discordant ER status. A recent study focusing on multifocal/multicentric breast cancer has already showed that heterogeneity of molecular markers leads to change in adjuvant treatment in 12% of cases.[3] Notably, almost half of SBC patients in our study had missing data in ER or PR in at least one of the two cancers. Usually larger or higher stage tumor was being tested for hormone receptors, but the smaller/lower stage tumor could also be ER negative, so it is possible that some of these patients may not receive optimal therapies.

In patients with MBC, we found that a change in ER status occurred in one-quarter of the patients, and the ER status of the first cancer could affect clinical outcome of the second breast cancer. We also found that stage and grade of the first breast cancer independently predicted clinical outcome of the second breast cancer. However, after adjusting for tumor stage and grade of both the first and second cancer, the predictive value of ER status of the first cancer was attenuated. In another word, ER status of previous cancer did not provide additional prognostic information if we already know grade and stage of first cancer. On the other hand, ER status of previous cancer may still important to guide therapy after diagnosis of contralateral breast cancer as the lag time between two cancers was about 5 years and a recent clinical trial demonstrated that continuation of tamoxifen for 10 years reduced breast cancer mortality compared to tamoxifen treatment for 5 years.[18]

We found that the combined hormone-receptor status of the two cancers had differential effects on clinical outcomes over time. A statistically significant difference between discordant and concordant-positive (+/+) cases was found only during the first 5 years after diagnosis in SBC cases; in the MBC cohort, +/− and −/− cases had worse prognosis than +/+

cases during the first 5 years. This observed non-proportional hazard ratio is consistent with previous studies in patients with single breast cancer, which showed that the risk of relapse or death is more frequent in patients with ER-negative breast cancers during the first 5−7 years after diagnosis, and in patients with ER-positive breast cancers thereafter.[19,20] The effects of PR status overlapped with those of ER status. In multivariable analyses that adjusted for ER status, the prognostic value of PR status disappeared or weakened. This result is not surprising, because PR is an ER-regulated gene and is considered as a surrogate marker for functional ER.[21]

Although not a primary focus of the study, we observed that many bilateral breast cancer patients died from other cancers, such as lung cancer, colon cancer, ovarian cancer, non-Hodgkin lymphoma, and pancreatic cancer. Previous study reported that bilateral breast cancer patients had an increased risk of non-breast third cancer, which is possibly due to genetic factors and treatment of breast cancer.[22]

The strengths of our study include the relatively large sample size, the population-based registry data, and the specific information concerning the cause of death. However, there were some limitations. First, hormone-receptor assays were not standardized across clinics in SEER, although a study showed that ER measurement is reliable for SEER registries.[23] The methods for measuring hormone receptors and cut-off for calling positivity changed over time.[24] Second, data on chemotherapy and endocrine therapy were not available in SEER database, so we were not able to examine ER/PR as predictive biomarkers in addition to prognostic markers. Chemotherapy, endocrine therapy, and supportive care also evolved in the past 2 decades, with effective agents such as taxanes and trastuzumab being introduced in the late 1990s. In order to define a cohort that is relatively homogeneous in treatment and hormone-receptor testing, we focused the analysis to patients with first cancers diagnosed in 1998-2005. Last, only 32% (n=2,256) of patients with MBC were followed up beyond year 5, so the statistical power for survival analysis in >5 years is limited, which may be one reason for the observed non-significant results. However, the non-significant results in >5 years are consistent from data in patients with single breast cancer.[19,20]

This study shows that heterogeneity in hormone-receptor status is an important prognostic marker for patients with bilateral breast cancers. For patients with SBC, our results justified the evaluation of hormone-receptor expression in both cancers to better define treatment and prognosis of these patients. For patients with MBC, tumor characteristics of previous cancer including stage, grade, and hormone receptors are important to predict survival outcomes of the current cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

This work was supported in part by the American Cancer Society MRSG-13-063-01 (to D.H.) and the National Cancer Institute in the National Institutes of Health (P50 CA125183 to O.I.O. and D.H.). OIO is an American

Cancer Society Clinical Research Professor. Dr. Zora Baretta took part of Global Health Fellowship Program at The University of Chicago. The funding agencies had no involvement in the study design, analysis and interpretation of data, and the writing of the manuscript.

REFERENCES

1. Goldhirsch A, Ingle JN, Gelber RD, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol. 2009; 20:1319–29. [PubMed: 19535820]
2. Choi Y, Kim EJ, Seol H, et al. The hormone receptor, human epidermal growth factor receptor 2, and molecular subtype status of individual tumor foci in multifocal/multicentric invasive ductal carcinoma of breast. Hum Pathol. 2012; 43:48–55. [PubMed: 21733550]
3. Buggi F, Folli S, Curcio A, et al. Multicentric/multifocal breast cancer with a single histotype: is the biological characterization of all individual foci justified? Ann Oncol. 2012; 23:2042–6. [PubMed: 22219015]
4. Intra M, Rotmensz N, Viale G, et al. Clinicopathologic characteristics of 143 patients with synchronous bilateral invasive breast carcinomas treated in a single institution. Cancer. 2004; 101:905–12. [PubMed: 15329896]
5. Bu-Ali H, Solh M, Kapur A, et al. Receptor characteristics of the second tumor in synchronous versus metachronous breast cancer. Am Surg. 2008; 74:702–5. discussion 706. [PubMed: 18705570]
6. Stark A, Lu M, Mackowiak P, et al. Concordance of the hormone receptors and correlation of HER-2/neu overexpression of the metachronous cancers of contralateral breasts. Breast J. 2005; 11:183–7. [PubMed: 15871703]
7. Brown M, Bauer K, Pare M. Tumor marker phenotype concordance in second primary breast cancer, California, 1999-2004. Breast Cancer Res Treat. 2010; 120:217–27. [PubMed: 19629680]
8. Huo D, Melkonian S, Rathouz PJ, et al. Concordance in histological and biological parameters between first and second primary breast cancers. Cancer. 2011; 117:907–15. [PubMed: 20945326]
9. Curigliano G, Bagnardi V, Viale G, et al. Should liver metastases of breast cancer be biopsied to improve treatment choice? Ann Oncol. 2011; 22:2227–33. [PubMed: 21343379]
10. Idirisinghe PK, Thike AA, Cheok PY, et al. Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. Am J Clin Pathol. 2010; 133:416–29. [PubMed: 20154280]
11. Guarneri V, Giovannelli S, Ficarra G, et al. Comparison of HER-2 and hormone receptor expression in primary breast cancers and asynchronous paired metastases: impact on patient management. Oncologist. 2008; 13:838–44. [PubMed: 18650259]
12. Chen S, Chen CM, Yu KD, et al. Prognostic value of a positive-to-negative change in hormone receptor status after neoadjuvant chemotherapy in patients with hormone receptor-positive breast cancer. Ann Surg Oncol. 2012; 19:3002–11. [PubMed: 22437200]
13. Liedtke C, Broglio K, Moulder S, et al. Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. Ann Oncol. 2009; 20:1953–8. [PubMed: 19596702]
14. Spataro V, Price K, Goldhirsch A, et al. Sequential estrogen receptor determinations from primary breast cancer and at relapse: prognostic and therapeutic relevance. Ann Oncol. 1992; 3:733–40. [PubMed: 1450062]
15. Lower EE, Glass EL, Bradley DA, et al. Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Res Treat. 2005; 90:65–70. [PubMed: 15770528]
16. Holm M, Tjonneland A, Balslev E, et al. Prognosis of synchronous bilateral breast cancer: a review and meta-analysis of observational studies. Breast Cancer Res Treat. 2014; 146:461–75. [PubMed: 25007962]
17. Surveillance, Epidemiology, and End Results (SEER) Program. Research Data (1973-2011), based on the November 2013 submission. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch; 2014. (www.seer.cancer.gov)

18. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013; 381:805–16. [PubMed: 23219286]
19. Anderson WF, Chen BE, Jatoi I, et al. Effects of estrogen receptor expression and histopathology on annual hazard rates of death from breast cancer. Breast Cancer Res Treat. 2006; 100:121–6. [PubMed: 16685588]
20. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007; 13:4429–34. [PubMed: 17671126]
21. Cui X, Schiff R, Arpino G, et al. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. J Clin Oncol. 2005; 23:7721–35. [PubMed: 16234531]
22. Kwast AB, Liu L, Roukema JA, et al. Increased risks of third primary cancers of non-breast origin among women with bilateral breast cancer. Br J Cancer. 2012; 107:549–55. [PubMed: 22713658]
23. Ma H, Wang Y, Sullivan-Halley J, et al. Breast cancer receptor status: do results from a centralized pathology laboratory agree with SEER registry reports? Cancer Epidemiol Biomarkers Prev. 2009; 18:2214–20. [PubMed: 19661080]
24. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010; 28:2784–95. [PubMed: 20404251]

Table 1

Characteristics of 11562 Bilateral Breast Cancer Patients, SEER 1998-2011

Characteristics	SBC cohort (*n*=4403)	MBC cohort (*n*=7159)	
		First cancer	Second cancer
Year of diagnosis	1998-2005	1998-2005	1998-2011
Age at diagnosis, mean±SD	63.1±13.7	59.4±12.9	64.6±13.0
Months between two cancers, median (IQR) range	0 (0-1) 0-6	60 (33-87) 7-164	
Race/ethnicity, *n* (%)			
White	3571 (82)	5390 (76)	
Black	317 (7)	751 (11)	
Asian	233 (5)	478 (7)	
Latino	257 (6)	515 (7)	
Others/unknown	25	25	
Marital status, *n* (%)			
Single	563 (13)	834 (12)	
Married	2300 (54)	3800 (56)	
Divorced/ separated	498 (12)	829 (12)	
Widowed	891 (21)	1326 (20)	
Unknown	151	370	
Estrogen receptor, *n* (%)			
+/+	3611 (82)	4137 (58)	
−/−	370 (8)	934 (13)	
Discordant	422 (10)		
+/−		1080 (15)	
−/+		1008 (14)	
Progesterone receptor, *n* (%)			
+/+	2930 (67)	2835 (40)	
−/−	657 (15)	1441 (20)	
Discordant	816 (19)		
+/−		1741 (24)	
−/+		1142 (16)	
Histology of two tumors combination, *n* (%)			
Ductal/ductal	2769 (63)		
Ductal/lobular	612 (14)		
Ductal/other	615 (14)		
Lobular/lobular	202 (5)		
Lobular/other	72 (2)		
Other/other	133 (3)		

Characteristics	SBC cohort (*n*=4403)	MBC cohort (*n*=7159)	
		First cancer	Second cancer
Histology, *n* (%)			
Ductal		5819 (81)	5759 (80)
Lobular		515 (7)	648 (9)
Other		825 (12)	752 (11)
Grade, *n* (%)			
Well differentiated	599 (14)	1331 (20)	1318 (20)
Moderately differentiated	1978 (47)	2663 (41)	2607 (39)
Poorly or non-differentiated	1632 (39)	2577 (39)	2676 (41)
Unknown	194	588	558
AJCC stage, *n* (%)			
0	148 (3)	580 (8)	1220 (18)
1	1434 (33)	3467 (49)	3458 (50)
2A	1208 (28)	1552 (22)	1143 (17)
2B	660 (15)	649 (9)	399 (6)
3A	466 (11)	410 (6)	306 (4)
3B	182 (4)	149 (2)	148 (2)
3	254 (6)	206 (3)	213 (3)
Unknown	51	146	272
Tumor size in cm, median (IQR)	2.1 (1.4-3.3)	1.5 (1.0-2.5)	1.3 (0.8-2.1)
No. of positive nodes			
0	2373 (55)	5090 (73)	5378 (79)
1-3	1217 (28)	1291 (18)	902 (13)
4-9	438 (10)	389 (6)	313 (5)
≥ 10	265 (6)	226 (3)	214 (3)
Unknown	110	163	352
Surgery			
No	90 (2)	83 (1)	296 (4)
Lumpectomy	1283 (29)	4300 (60)	3297 (46)
Mastectomy	2425 (55)	2743 (38)	2993 (42)
Bilateral mastectomy	605 (14)	33 (0.5)	573 (8)
Radiotherapy			
No	2680 (63)	2849 (41)	4398 (64)
Yes	1593 (37)	4046 (59)	2499 (36)
Unknown	130	264	262

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; MBC, metachronous breast cancer; SBC, synchronous breast cancer; SD, standard deviation

Table 2

Prognostic Effects of Estrogen-Receptor Status in Women with Synchronous Breast Cancers, SEER 1998-2005

Estrogen-receptor status	Overall Survival					
	No. of patients	No. of patients at year 5	No. of events	Rate[a]	HR (95% CI)[b]	
					≤ 5 years	> 5 years
+/+	3611	2963	668	4.0	1.0 (ref)	1.0 (ref)
Discordant	422	293	133	7.5	1.96 (1.60-2.40)	0.98 (0.72-1.35)
−/−	370	229	142	9.6	2.49 (2.03-3.07)	0.84 (0.58-1.20)
P value					<0.0001	0.62

Estrogen-receptor status	Breast Cancer-Specific Survival					
	No. of patients	No. of patients at year 5	No. of events	Rate[a]	HR (95% CI)[b]	
					≤ 5 years	> 5 years
+/+	3611	2963	491	1.8	1.0 (ref)	1.0 (ref)
Discordant	422	293	103	3.7	2.79 (2.14-3.64)	1.01 (0.62-1.65)
−/−	370	229	128	5.4	3.29 (2.54-4.26)	1.03 (0.65-1.64)
P value					<0.0001	0.99

Abbreviations: HR, hazard ratio; CI, confidence interval

P value is from the omnibus test of comparing three groups in Cox model

[a] Death rate per 100 person-years

[b] Adjusted in a piecewise Cox model for age at diagnosis, race/ethnicity, marital status, AJCC stage, grade, histology of both cancers, surgery type, radiotherapy, and time interval between the two cancer

Table 3

Prognostic Effects of Progesterone-Receptor Status in Women with Synchronous Breast Cancers, SEER 1998-2005

Progesterone-receptor status	Overall Survival							
	No. of patients	No. of patients at year 5	No. of events	Rate[a]	Model 1, HR (95% CI)[b]		Model 2, HR (95% CI)[c]	
					≤ 5 years	> 5 years	≤ 5 years	> 5 years
+/+	2930	2415	966	4.4	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Discordant	816	613	316	5.6	1.42 (1.19-1.69)	0.95 (0.76-1.20)	1.11 (0.90-1.37)	0.97 (0.75-1.24)
−/−	657	456	286	6.4	1.77 (1.48-2.12)	0.93 (0.72-1.20)	1.08 (0.84-1.38)	1.04 (0.77-1.40)
P value					<0.0001	0.81	0.58	0.92

Progesterone-receptor status	Breast Cancer-Specific Survival							
	No. of patients	No. of patients at year 5	No. of events	Rate[a]	Model 1, HR (95% CI)[b]		Model 2, HR (95% CI)[c]	
					≤ 5 years	> 5 years	≤ 5 years	> 5 years
+/+	2930	2415	390	1.8	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Discordant	816	613	155	2.7	1.75 (1.36-2.24)	1.00 (0.70-1.44)	1.15 (0.85-1.56)	1.04 (0.69-1.55)
−/−	657	456	177	3.9	2.41 (1.89-3.06)	1.09 (0.76-1.57)	1.22 (0.86-1.72)	1.20 (0.76-1.89)
P value					<0.0001	0.89	0.47	0.74

Abbreviations: HR, hazard ratio; CI, confidence interval

P value is from the omnibus test of comparing three groups in Cox model

[a] Death rate per 100 person-years

[b] Adjusted in a piecewise Cox model for age at diagnosis, race/ethnicity, marital status, AJCC stage, grade, histology of both cancers, surgery type, radiotherapy, and time interval between the two cancers

[c] Adjusted for estrogen-receptor status of both cancers and all variables in Model 1

Table 4

Prognostic Effects of Estrogen-Receptor Status in Women with Metachronous Breast Cancers, SEER 1998-2011

Estrogen-receptor status	Overall Survival					
	No. of patients	No. of patients at year 5	No. of events	Rate[a]	HR (95% CI)[b]	
					≤ 5 years	> 5 years
+/+	4137	1353	756	4.6	1.0 (ref)	1.0 (ref)
−/+	1008	304	158	4.3	0.75 (0.58-0.96)	0.67 (0.41-1.09)
+/−	1080	317	253	6.1	1.32 (1.08-1.62)	0.70 (0.43-1.12)
−/−	934	282	295	8.6	1.49 (1.19-1.85)	0.52 (0.31-0.88)
P value					<0.0001	0.04

Estrogen-receptor status	Breast Cancer-Specific Survival					
	No. of patients	No. of patients at year 5	No. of events	Rate[a]	HR (95% CI)[b]	
					≤ 5 years	> 5 years
+/+	4137	1353	350	2.2	1.0 (ref)	1.0 (ref)
−/+	1008	304	82	2.2	0.66 (0.46-0.94)	0.74 (0.36-1.53)
+/−	1080	317	162	3.9	1.44 (1.11-1.87)	0.54 (0.25-1.16)
−/−	934	282	241	7.0	1.45 (1.11-1.90)	0.58 (0.30-1.13)
P value					<0.0001	0.23

Abbreviations: HR, hazard ratio; CI, confidence interval

P value is from the omnibus test of comparing three groups in Cox model

[a] Death rate per 100 person-years

[b] Adjusted in a piecewise Cox model for age at diagnosis, race/ethnicity, marital status, AJCC stage of both cancers, grade of both cancers, histology of both cancers, surgery type of both cancers, radiotherapy of both cancers, and time interval between the two cancers

Table 5

Prognostic Effects of Progesterone-Receptor Status in Women with Metachronous Breast Cancers, SEER 1998-2011

Progesterone-receptor status	Overall Survival							
	No. of patients	No. of patients at year 5	No. of events	Rate[a]	Model 1, HR (95% CI)[b]		Model 2, HR (95% CI)[c]	
					≤ 5 years	> 5 years	≤ 5 years	> 5 years
+/+	2835	952	486	4.3	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
−/+	1142	336	202	4.8	0.88 (0.69-1.12)	0.97 (0.63-1.48)	1.04 (0.77-1.40)	1.56 (0.90-2.72)
+/−	1741	542	369	5.4	1.33 (1.10-1.60)	0.70 (0.47-1.04)	1.24 (1.00-1.54)	0.77 (0.49-1.21)
−/−	1441	426	405	7.6	1.44 (1.18-1.77)	0.59 (0.37-0.92)	1.24 (0.94-1.65)	0.94 (0.50-1.77)
P value					<0.0001	0.06	0.21	0.19

Progesterone-receptor status	Breast Cancer-Specific Survival							
	No. of patients	No. of patients at year 5	No. of events	Rate[a]	Model 1, HR (95% CI)[b]		Model 2, HR (95% CI)[c]	
					≤ 5 years	> 5 years	≤ 5 years	> 5 years
+/+	2835	952	203	1.8	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
−/+	1142	336	100	2.4	0.95 (0.67-1.35)	1.05 (0.54-2.02)	1.32 (0.86-2.01)	1.52 (0.61-3.75)
+/−	1741	542	222	3.3	1.56 (1.19-2.04)	0.66 (0.35-1.23)	1.44 (1.06-1.96)	0.82 (0.40-1.69)
−/−	1441	426	310	5.9	1.59 (1.21-2.10)	0.53 (0.27-1.02)	1.47 (1.01-2.14)	0.62 (0.21-1.84)
P value					<0.0002	0.17	0.11	0.45

Abbreviations: HR, hazard ratio; CI, confidence interval

P value is from the omnibus test of comparing four groups in the Cox model

[a] Death rate per 100 person-years

[b] Adjusted in a piecewise Cox model for age at diagnosis, race/ethnicity, marital status, AJCC stage of both cancers, histology of both cancers, surgery type of both cancers, radiotherapy of both cancers, and time interval between the two cancers

[c] Adjusted for estrogen-receptor status of the two cancers and all variables in Model 1