Published in final edited form as:

J Clin Oncol. 2007 October 01; 25(28): 4438–4444. doi:10.1200/JCO.2007.10.6815.

Relationship Between Epidemiologic Risk Factors and Breast Cancer Recurrence

Abenaa M. Brewster, Kim-Anh Do, Patricia A. Thompson, Karin M. Hahn, Aysegul A. Sahin, Yumei Cao, Maureen M. Stewart, James L. Murray, Gabriel N. Hortobagyi, and Melissa L. Bondy

Departments of Clinical Cancer Prevention, Biostatistics, Breast Medical Oncology, Pathology, and Epidemiology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; and Department of Pathology, Arizona Cancer Center, The University of Arizona, Tucson, AZ.

Abstract

Purpose—Early-stage breast cancers are biologically heterogeneous and vary in clinical behavior, supporting the role of factors other than tumor size and lymph node involvement as outcome determinants. We evaluated the effect of epidemiologic breast cancer risk factors on recurrence in women with early-stage disease.

Patients and Methods—Medical records from 2,327 women with early-stage breast cancer, treated at the M.D. Anderson Cancer Center between 1985 and 2000, were used to derive information on epidemiologic, clinical, and histological factors. Cox proportional hazards models were used to estimate the hazard ratios of 5-year risk of breast cancer recurrence adjusted for treatment and stage. Statistical tests were two-sided.

Results—None of the breast cancer risk factors were associated with recurrence, adjusting for tumor characteristics and treatment. A significant interaction between hormone replacement therapy (HRT) use and tumor hormone receptor status on risk of recurrence ($P = .0003$) was observed. Among ever-users of HRT, recurrence risk was two-fold lower for estrogen receptor (ER)-positive and progesterone receptor (PR)-positive tumors compared with ER- and PR-negative tumors; whereas, among never-users of HRT, there was no statistically significant association between recurrence risk and receptor status.

Conclusion—HRT users who develop receptor-positive early-stage disease have better outcomes than those who develop receptor-negative disease. Among never-users of HRT, the expected

AUTHOR CONTRIBUTIONS

Conception and design: Abenaa M. Brewster, Kim-Anh Do, Patricia A. Thompson, Karin M. Hahn, Melissa L. Bondy

Financial support: Melissa L. Bondy

Provision of study materials or patients: Melissa L. Bondy

Collection and assembly of data: Abenaa M. Brewster, Karin M. Hahn, Maureen M. Stewart, James L. Murray, Melissa L. Bondy

Data analysis and interpretation: Abenaa M. Brewster, Kim-Anh Do, Patricia A. Thompson, Aysegul A. Sahin, Yumei Cao, Gabriel N. Hortobagyi, Melissa L. Bondy

Manuscript writing: Abenaa M. Brewster, Kim-Anh Do, Patricia A. Thompson, Melissa L. Bondy

Final approval of manuscript: Abenaa M. Brewster, Kim-Anh Do, Patricia A. Thompson, Karin M. Hahn, Aysegul A. Sahin, Yumei Cao, Maureen M. Stewart, James L. Murray, Gabriel N. Hortobagyi, Melissa L. Bondy

Address reprint requests to Abenaa M. Brewster, MD, MHS, Department of Clinical Cancer Prevention, Unit 1360, PO Box 301439, Houston, TX 77030; abrewster@mdanderson.org.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

beneficial effect of ER- or PR-positive tumors on recurrence risk was absent. These data lend support to the notion that the biology of hormone receptor-positive disease in HRT users differs from that in nonusers.

INTRODUCTION

Breast cancer is the most common malignancy among women in the United States and is the second leading cause of cancer death.¹ The majority of women are diagnosed with early-stage disease and have a 5-year relative survival rate of 83% to 92%.² Despite the excellent overall 5-year survival rate associated with early-stage disease, many of these women will experience a recurrence with risk greatest during the initial years after diagnosis.³ Differences in recurrence rates among women with early-stage disease support the role of factors other than tumor size and lymph node involvement as important determinants of clinical outcomes. Less is known about the effect of epidemiologic characteristics such as reproductive factors and prior hormone use on recurrence risk and overall disease-free survival.

Inconsistent epidemiologic evidence supports a role for environmental and lifestyle factors acting to influence the hormone receptor type of breast cancers that arise in women.⁴⁻⁷ For example, in a recent meta-analysis by Ma et al,⁸ parity and age at first birth were identified as associated with risk for estrogen receptor (ER) -positive/progesterone receptor (PR) -positive tumors, whereas these same exposures were not associated with risk for ER-negative/PR-negative tumors. What remains unclear is whether these risk factors continue to influence the biology of the disease after diagnosis and treatment in a clinically significant manner. It is plausible that epidemiologic risk factors that influence the development of breast cancers also act to affect clinical outcomes. Few epidemiologic studies have evaluated the relationship between environmental and lifestyle factors and breast cancer prognosis, and the results of these limited studies are largely inconsistent.⁹⁻¹⁹ In general, these studies have been limited by small numbers and by the inclusion of patients with more advanced disease in whom clinical features such as lymph node involvement and large tumor size overwhelm the more modest effects of lifestyle or environmental exposures that may affect outcome in earlier, less advanced disease.

To eliminate the confounding effects of advanced disease in assessing the association between host epidemiologic risk factors on disease recurrence, we evaluated 5-year recurrence risk among a large cohort of patients diagnosed with early-stage breast cancer and treated at a single institution. Given our sample size, an a priori hypothesis-driven interaction between hormone replacement therapy (HRT) use and tumor hormone receptor status was explored with the intent to increase our understanding of the joint effects of epidemiologic and clinical risk factors on the risk of breast cancer recurrence.

PATIENTS AND METHODS

Patients were from the Early Stage Breast Cancer Repository (ESBCR), which is a retrospective cohort study of 2,409 women diagnosed with American Joint Committee on Cancer pathologic stage I or II breast cancer²⁰ who registered at The University of Texas

M.D. Anderson Cancer Center (MDACC) between January 1, 1985 and December 31, 2000. Patients were eligible for inclusion in the ESBCR if they were female, were residents of the state of Texas, had surgical treatment for their breast cancer at MDACC with tissue available, and had complete assessment medical records. These criteria were established to ensure long-term disease follow-up. Because of the small percentage of patients from other ethnic groups, we included only whites, African Americans, and Hispanics in the analyses. The final study population consisted of 2,327 breast cancer patients.

The clinical and epidemiologic information for the ESBCR was obtained from manual abstraction of the patient medical records. A manual of instructions was developed, which included operational definitions of all terms and provided comprehensive instructions for coding all variables. The majority of the medical record abstractors had a medical degree and were well trained in reviewing medical records. The study coordinator reviewed each completed abstraction form and compared it with the source documents for data quality. The epidemiologic data were obtained in part from breast cancer risk assessment forms that were included as part of the medical record as early as the 1980s. These forms contained information on reproductive history, tobacco and alcohol use, hormone and oral contraceptive (OCP) use, family history of breast and other cancers, and personal medical history. Clinical information, including pathologic stage, nuclear grade, ER and PR status, and primary treatment including surgery, radiation therapy, chemotherapy, and/or endocrine therapy, was also abstracted from the medical charts. Follow-up information was obtained by direct review of the medical records. However, for patients who did not return to the clinic during their 5 years of active follow-up, we matched our patient records with the MDACC Tumor Registry, which mails annual follow-up letters to each patient registered at MDACC known to be alive to determine their clinical status.

The histologic type of all tumors was defined according to the WHO classification system.²¹ Nuclear grade was defined according to the Black's nuclear grading system with modification of numbers; 1 represents well-differentiated tumors, and 3 represents poorly differentiated tumors.²² ER and PR status of the tumor was obtained from the surgical pathology reports. Immunohistochemistry was used to determine ER and PR status after 1993. The study was approved by the Institutional Review Board of MDACC.

Statistical Methods

The primary end point of the study was time to first breast cancer recurrence. This was defined as the occurrence of local lymph node or breast recurrence; metastasis to contralateral breast, chest wall, or other sites; and second primary breast cancer. Time to event was calculated from the date of earliest treatment (date of definitive surgical procedure or start of neoadjuvant chemotherapy) to the date of first breast cancer recurrence. Patients who were not known to have an event at the date of last contact or who were cancer free 5 years after the date of initial treatment of their breast cancer were censored. The associations between individual epidemiologic risk factors, tumor characteristics, and treatment variables and time to recurrence were initially assessed using univariate Cox proportional hazards regression models. The data were consistent with the assumptions of the Cox proportional hazards regression model from the examination of Kaplan-Meier survival curves and log-

minus-log survival plots. In addition, Martingale residual plots were used to check the functional forms of each continuous covariate.^{23,24}

The epidemiologic variables included in the univariate analysis, assessed at the time of diagnosis, were year of diagnosis, age in years, race, menopausal status (premenopausal/perimenopausal or postmenopausal), age at menarche in years, number of pregnancies, age at first birth in years, first-degree relative with history of breast cancer, OCP use, alcohol consumption, smoking status, and body mass index using WHO classification.²⁵ All types of HRT use (estrogen alone or estrogen and progesterone combination) were included in the analysis, and patients were categorized as never-users or ever-users. The tumor characteristics included tumor size, lymph node involvement, nuclear grade, and hormone receptor status. Treatment variables included chemotherapy, endocrine treatment, surgery type, and adjuvant radiation. The first step at building a multivariate model for time to breast recurrence did not use any interaction terms. A multivariate proportional hazards model was built using the variables that had prognostic potential suggested by the univariate analysis ($P < .1$). A stepwise search strategy was used, and a threshold level of 0.1 for the likelihood ratio test was used as a cutoff to determine whether a variable could be entered into, or removed from, the regression model. As a result of epidemiologic and clinical considerations in model building, year of diagnosis and race were always retained in the main effects and final multivariate model. HRT use is a variable of primary interest and, thus, was also included. The year of diagnosis was retained to adjust for differences in treatment practices and differences in the method of assessment of ER and PR status that occurred during the 15-year period of the study cohort. A single a priori hypothesis-driven interaction between HRT use and tumor hormone receptor status was explored within the context of the final multivariate model containing the interaction term and the main effects terms. Associations were quantified using hazard ratios (HRs) and their 95% CIs. We used SAS version 9.1 (SAS Institute, Cary, NC) to perform all of our analyses.

RESULTS

Patient and Tumor Characteristics

The epidemiologic and clinical characteristics of the study population are listed in Tables 1 and 2. The majority of women were white (79%), and the mean age at diagnosis was 55 years (standard deviation, 12.7 years). Data missing on the core epidemiologic variables did not exceed 20%, with exceptions of 27% missing data for age at first birth and 21% missing data for OCP use (Table 1). Approximately 44% of patients were treated with chemotherapy, and the majority received an anthracycline-based regimen (62%) or an anthracycline/taxane-based regimen (32%). Forty-three percent of patients received endocrine therapy, and 97% of those patients were treated with tamoxifen (Table 2). The overall 5-year recurrence-free survival rate for the population was 85%. During the 5 years of follow-up, 332 patients (14%) developed a recurrence event, 123 patients (5%) died without a recurrence, and 142 patients (6%) were lost to follow-up. Among patients who had a recurrence, 27% were local, 57% were distant metastatic disease, and 16% were second primary breast cancers (data not shown).

Univariate Model of Clinical and Epidemiologic Variables and Risk of Breast Cancer Recurrence

The results of the univariate analysis for the epidemiologic factors associated with breast cancer recurrence are listed in Table 1. Year of diagnosis before 1995 ($P < .01$) and premenopausal status ($P < .01$) were associated with an increased risk of recurrence, whereas use of HRT ($P < .01$) was associated with a decreased risk of breast cancer recurrence. When African American patients were compared with whites, there was an increased risk of recurrence that was statistically significant (HR = 1.46; 95% CI, 1.06 to 2.02).

Larger tumor size, lymph node involvement, high nuclear grade, and ER-negative/PR-negative status were all statistically significantly associated with an increased risk of recurrence (Table 2). Receipt of chemotherapy was associated with an increased risk of recurrence and with high-risk tumor characteristics such as tumor size more than 2 cm ($\chi^2 P < .0001$) and lymph node involvement ($\chi^2 P < .0001$). Endocrine therapy was associated with a decreased risk of recurrence ($P < .01$).

Final Multivariate Hazard Proportional Model of Clinical and Epidemiologic Variables and Risk of Breast Cancer Recurrence

The epidemiologic variables that had prognostic potential suggested by the univariate analyses ($P < .1$) and that were used in the multivariate analysis were year of diagnosis, menopausal status, race, age at menarche, family history of breast cancer, OCP use, and HRT use. Because menopausal status was highly correlated with age at diagnosis (Spearman's rank correlation estimate = 0.8), we included only menopausal status. Age at menarche, family history of breast cancer, and OCP use were found not to be significant in the multivariate model. All of the tumor and clinical characteristics listed in Table 2 were initially included in the multivariate analysis. Nuclear grade, surgery type, and receipt of radiation were found not to be significant.

The final multivariate model, including an interaction term between HRT use and ER/PR tumor status (Table 3), shows only those factors that met the variable selection threshold ($P < .1$) and important epidemiologic factors such as year of diagnosis and race. Tumor size (> 2 v ≤ 2 cm) and lymph node involvement (one v zero nodes) were statistically significant poor prognostic factors. Patients who did not receive endocrine therapy had a statistically significant increased risk of recurrence. A statistically significant interaction was observed between HRT use and hormone receptor status on recurrence ($P = .0003$) adjusted for all the important main effects. To further investigate this finding, we stratified HRT use into categories of estrogen alone (never v ever) and estrogen and progesterone combination (never v ever) in the final multivariate model. There remained a statistically significant interaction between HRT use and hormone receptor status ($P = .003$; data not shown). Because of the small number of events in the stratified HRT categories, results were reported using all of the types of HRT categories (estrogen alone and estrogen and progesterone combination). HRT ever-users with an ER-negative/PR-negative tumor had a two-fold statistically significant increased risk of developing a recurrence compared with HRT ever-

users with an ER-positive/PR-positive tumor. Among HRT never-users, there was no trend towards a difference in recurrence by ER and PR status.

DISCUSSION

In this cohort of women who were all treated at the same center for their early-stage breast cancer, we found no association between many known epidemiologic breast cancer risk factors and breast cancer recurrence independently or after adjusting for clinical and histopathologic characteristics of the presenting lesion. We observed a significant interaction between HRT use before diagnosis and hormone receptor status of the tumor on the risk of recurrence. HRT ever-users with ER-positive/PR-positive tumors had a lower risk of recurrence compared with ever-users presenting with an ER-negative/PR-negative tumor. Unique to this analysis, we did not observe the expected beneficial effect of ER- or PR-positive hormone receptor status on risk of recurrence among never-users of HRT.

Reproductive factors including recent childbirth,^{11,13,17} early age at first birth,¹² decreased parity,¹⁸ and recent OCP use¹⁵ have been associated with an increased risk of breast cancer recurrence or death; however, the results between these case-case studies have been inconsistent. Prior investigations have been limited by lack of standardization of care and incomplete data on treatment, tumor characteristics, and disease stage, which are all strong predictors of breast cancer outcome. In our study, nonreproductive risk factors such as African American race and obesity, which are commonly thought to influence breast cancer outcomes, were not associated with an increased risk of recurrence.^{19,26} The lack of an association maybe related to the small sample size of African American women and the short-term end point of recurrence.

Several epidemiologic studies^{27,28} but not others^{29,30} have shown that HRT use is associated with a greater risk of developing ER-positive/PR-positive or ER/PR mixed status tumors than ER-negative/PR-negative tumors. The Women's Health Initiative randomized trial showed that HRT use was associated with an increased risk of breast cancer with more unfavorable tumor characteristics including advanced stage, but there was no association by hormone receptor status.³¹ The impact of HRT on breast tumor characteristics and on prognosis is not well understood. In our study, HRT ever-users had a higher frequency of ER-positive/PR-positive tumors (59%) and ER/PR mixed status tumors (23%) compared with ER-negative/PR-negative tumors (18%). Among never-users, 54% had ER-positive/PR-positive tumors, 25% had ER/PR mixed status tumors, and 21% had ER-negative/PR-negative tumors ($P < .01$). The ER-positive/PR-positive tumors that developed among HRT ever-users were associated with a decrease in the risk of recurrence compared with the ER-negative/PR-negative tumors. A plausible interpretation of these results is that HRT use before the diagnosis of early-stage breast cancer promotes the development of a less aggressive phenotype of hormone receptor-positive disease, which is associated with a more favorable prognosis and better response to endocrine therapies. Earlier epidemiologic studies have shown HRT use to be associated with improved breast cancer survival.^{32,33} Interestingly, differences in tumor gene expression profiles have been found in ER-positive tumors of HRT users compared with nonusers, suggesting that HRT use alters intrinsic tumor biology.³⁴ Our finding that there was no differential risk of recurrence by ER and PR

status for never-users of HRT is novel and somewhat unexpected. Our data lend support to the hypothesis that tumors that develop in the setting of HRT use are biologically distinct and also raise concerns regarding a higher progression risk among never-users with hormone receptor-positive tumors.

This study has several limitations that should be considered when interpreting and generalizing the findings. First, we did not include information on HRT duration or dose because of the large amount of missing or imprecise data for the breast cancer patients. Because this information was not systematically recorded, the contribution of long- or short-term HRT use as an effect modifier of hormone receptor status on risk of recurrence is not known. Second, we chose to evaluate the risk of recurrence during the first 5 years after initiation of treatment to ensure ascertainment of recurrence events. In this hospital-based cohort, the majority of women were observed for 5 years after their diagnosis in accordance with guidelines for the follow-up of women with a history of breast cancer.³⁵ Given the observational nature of the study, intervals between clinical evaluations for recurrence or a new primary breast cancer were likely not uniform among the patients. We would anticipate that any bias resulting from variability in the time intervals between clinical assessments for recurrence would be nondifferential by epidemiologic risk factors at diagnosis and would result in an attenuation of the observed associations. Third, histopathologic features, ER and PR status, and clinical and epidemiologic variables were recorded retrospectively from the original medical record. However, there was minimal missing information on ER and PR status (15%), systemic treatment received (< 5%), and the epidemiologic variables, which can be attributed to the mechanisms that were instituted at MDACC in the early 1980s to include breast cancer risk factors in the medical record. Finally, the ESBCR cohort represents a select group of women with early-stage disease treated exclusively at a single institution, limiting generalizability of the findings to all patients. Seventy-five percent of these patients with early-stage breast cancer received either chemotherapy or endocrine treatment, and the resulting 13% 5-year risk of breast cancer recurrence may not be typical of the general oncology population. The results of this study will need to be confirmed in a population-based cohort, preferably with the end point of breast cancer survival.

In conclusion, our finding of a differential risk of breast cancer recurrence among HRT ever-users according to tumor hormone receptor status is an intriguing result that has not previously been reported. The study results suggest that, although HRT is associated with an increased risk of breast cancer, HRT users who develop a hormone receptor-positive breast cancer may have a better outcome than HRT users who develop ER-negative/PR-negative disease. The observational nature of this study does not permit conclusions to be made regarding the efficacy of chemotherapy or endocrine treatment among HRT users. A more comprehensive understanding is needed of the mechanisms through which host epidemiologic factors act as effect modifiers of prognostic clinical features to affect tumor development and progression.

Acknowledgments

Supported by Grants No. R01 CA089608 (M.L.B.), R03CA123553 (A.M.B.), and Breast SPOR P50 CA116199 (G.N.H.) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al.: Cancer statistics, 2006. *CA Cancer J Clin* 56:106–130, 2006 [PubMed: 16514137]
2. National Cancer Institute: SEER Cancer Statistics Review, 1975-2002 http://seer.cancer.gov/csr/1975_2002/
3. Early Breast Cancer Trialists' Collaborative Group: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 365:1687–1717, 2005 [PubMed: 15894097]
4. Potter JD, Cerhan JR, Sellers TA, et al.: Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: How many kinds of breast cancer are there? *Cancer Epidemiol Biomarkers Prev* 4:319–326, 1995 [PubMed: 7655325]
5. Colditz GA, Rosner BA, Chen WY, et al.: Risk factors for breast cancer according to estrogen and progesterone receptor status. *J Natl Cancer Inst* 96:218–228, 2004 [PubMed: 14759989]
6. Cotterchio M, Kreiger N, Theis B, et al.: Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. *Cancer Epidemiol Biomarkers Prev* 12: 1053–1060, 2003 [PubMed: 14578142]
7. Huang WY, Newman B, Millikan RC, et al.: Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. *Am J Epidemiol* 151:703–714, 2000 [PubMed: 10752798]
8. Ma H, Bernstein L, Pike MC, et al.: Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: A metaanalysis of epidemiological studies. *Breast Cancer Res* 8:R43, 2006 [PubMed: 16859501]
9. Thalib L, Wedren S, Granath F, et al.: Breast cancer prognosis in relation to family history of breast and ovarian cancer. *Br J Cancer* 90:1378–1381, 2004 [PubMed: 15054458]
10. Malone KE, Daling JR, Weiss NS, et al.: Family history and survival of young women with invasive breast carcinoma. *Cancer* 78:1417–1425, 1996 [PubMed: 8839546]
11. Daling JR, Malone KE, Doody DR, et al.: The relation of reproductive factors to mortality from breast cancer. *Cancer Epidemiol Biomarkers Prev* 11:235–241, 2002 [PubMed: 11895871]
12. Kroman N, Wohlfahrt J, Andersen KW, et al.: Parity, age at first childbirth and the prognosis of primary breast cancer. *Br J Cancer* 78:1529–1533, 1998 [PubMed: 9836489]
13. Thalib L, Doi SA, Hall P: Multiple births and breast cancer prognosis: A population based study. *Eur J Epidemiol* 20:613–617, 2005 [PubMed: 16119435]
14. Rosenberg L, Thalib L, Adami HO, et al.: Childbirth and breast cancer prognosis. *Int J Cancer* 111:772–776, 2004 [PubMed: 15252849]
15. Reeves GK, Patterson J, Vessey MP, et al.: Hormonal and other factors in relation to survival among breast cancer patients. *Int J Cancer* 89:293–299, 2000 [PubMed: 10861507]
16. Holmberg L, Lund E, Bergstrom R, et al.: Oral contraceptives and prognosis in breast cancer: Effects of duration, latency, recency, age at first use and relation to parity and body mass index in young women with breast cancer. *Eur J Cancer* 30A:351–354, 1994 [PubMed: 8204358]
17. Whiteman MK, Hillis SD, Curtis KM, et al.: Reproductive history and mortality after breast cancer diagnosis. *Obstet Gynecol* 104:146–154, 2004 [PubMed: 15229014]
18. Korzenowski S, Dyba T: Reproductive history and prognosis in patients with operable breast cancer. *Cancer* 74:1591–1594, 1994 [PubMed: 8062190]
19. Chlebowski RT, Aiello E, McTiernan A: Weight loss in breast cancer patient management. *J Clin Oncol* 20:1128–1143, 2002 [PubMed: 11844838]
20. Beahrs O, Hensen D, Hutter R (eds): American Joint Committee on Cancer. Manual for Staging of Cancer. Philadelphia, PA, JB Lippincott, 1992, p 149
21. World Health Organization: The World Health Organization histological typing of breast tumors-second edition. *Am J Clin Pathol* 78:806–816, 1982 [PubMed: 7148748]
22. Black MM, Speer FD: Nuclear structure in cancer tissues. *Surg Gynecol Obstet* 105:97–102, 1957 [PubMed: 13442910]

23. Collett D: *Modelling Survival Data in Medical Research* (ed 2). Bristol, United Kingdom, Chapman & Hall, 2003
24. Cox DR: Regression models and life tables. *J R Stat Soc B* 34:187–220, 1972
25. World Health Organization: *Measuring obesity: Classification and description of anthropometric data Report on a WHO Consultation on the Epidemiology of Obesity*. Warsaw, Poland, WHO Regional Office for Europe, 1989
26. Woodward WA, Huang EH, McNeese MD, et al.: African-American race is associated with a poorer overall survival rate for breast cancer patients treated with mastectomy and doxorubicin-based chemotherapy. *Cancer* 107:2662–2668, 2006 [PubMed: 17061247]
27. Kerlikowske K, Miglioretti DL, Ballard-Barbash R, et al.: Prognostic characteristics of breast cancer among postmenopausal hormone users in a screened population. *J Clin Oncol* 21:4314–4321, 2003 [PubMed: 14645420]
28. Lower EE, Blau R, Gazder P, et al.: The effect of estrogen usage on the subsequent hormone receptor status of primary breast cancer. *Breast Cancer Res Treat* 58:205–211, 1999 [PubMed: 10718482]
29. Holli K, Isola J, Cuzick J: Low biologic aggressiveness in breast cancer in women using hormone replacement therapy. *J Clin Oncol* 16:3115–3120, 1998 [PubMed: 9738583]
30. Stahlberg C, Pedersen AT, Andersen ZJ, et al.: Breast cancer with different prognostic characteristics developing in Danish women using hormone replacement therapy. *Br J Cancer* 91:644–650, 2004 [PubMed: 15238982]
31. Chlebowski RT, Hendrix SL, Langer RD, et al.: Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial. *JAMA* 289:3243–3253, 2003 [PubMed: 12824205]
32. Schairer C, Gail M, Byrne C, et al.: Estrogen replacement therapy and breast cancer survival in a large screening study. *J Natl Cancer Inst* 91:264–270, 1999 [PubMed: 10037105]
33. Nanda K, Bastian LA, Schulz K: Hormone replacement therapy and the risk of death from breast cancer: A systematic review. *Am J Obstet Gynecol* 186:325–334, 2002 [PubMed: 11854659]
34. Hall P, Ploner A, Bjohle J, et al.: Hormone-replacement therapy influences gene expression profiles and is associated with breast-cancer prognosis: A cohort study. *BMC Med* 4:16, 2006 [PubMed: 16813654]
35. Khatcheressian JL, Wolff AC, Smith TJ, et al.: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 24:5091–5097, 2006 [PubMed: 17033037]

Table 1.

Univariate Model of Epidemiologic Risk Factors and Breast Cancer Recurrence

Factor	Patients (N = 2,327)				P
	No.	%	HR	95% CI	
Year of diagnosis					< .01
1995–2000	1,096	47.1	1.00		
1990–1994	656	28.2	1.48	1.13 to 1.94	
1985–1989	575	24.7	1.96	1.51 to 2.55	
Age at diagnosis, years					< .01
> 50	1,401	60.2	1.00		
50	926	39.8	1.65	1.33 to 2.06	
Race					.06
White	1,849	79.4	1.00		
African American	232	10.0	1.46	1.06 to 2.02	
Spanish, Hispanic	246	10.6	1.11	0.78 to 1.58	
Menopause status					< .01
Postmenopausal	1,525	65.5	1.00		
Pre-/perimenopausal	780	33.5	1.59	1.27 to 1.98	
Missing	22	1.0			
Age at menarche, years					.10
13	976	41.9	1.00		
12 < 13	536	23.0	0.77	0.58 to 1.04	
< 12	370	15.9	0.75	0.53 to 1.05	
Missing	445	19.2			
No. of pregnancies					.99
0	232	10.0	1.00		
1	256	11.0	0.89	0.55 to 1.44	
2	570	24.5	0.96	0.64 to 1.43	
3	1,088	46.7	0.94	0.65 to 1.37	
Missing	181	7.8			
Age at first birth, years					.68

Patients (N = 2,327)					
Factor	No.	%	HR	95% CI	P
< 20	411	19.6	1.00		
20–24	609	29.1	1.12	0.80 to 1.57	
25–29	336	16.0	1.12	0.76 to 1.65	
30	171	8.2	0.85	0.51 to 1.44	
Missing	568	27.1			
Family history of breast cancer					.07
No	1,837	78.0	1.00		
Yes	443	19.0	0.76	0.56 to 1.02	
Missing	47	2.0			
OCP use					.09
Never	968	41.6	1.00		
Former	780	33.5	1.02	0.79 to 1.32	
Current	89	3.8	1.70	1.05 to 2.75	
Missing	490	21.1			
HRT use					< .01
Never	1,301	55.9	1.00		
Ever	735	31.6	0.63	0.48 to 0.81	
Missing	291	12.5			
Smoking status					.45
Never	1,333	57.3	1.00		
Former	504	21.7	1.07	0.82 to 1.41	
Current	445	19.1	1.19	0.91 to 1.57	
Missing	45	1.9			
Alcohol consumption					.98
Never/rare	1,816	78.0	1.00		
Moderate	369	15.9	1.03	0.77 to 1.38	
Heavy	80	3.4	0.98	0.54 to 1.80	
Missing	62	2.7			
BMI, kg/m ²					.27
Under/normal weight < 25	980	42.1	1.00		

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Patients (N = 2,327)					
Factor	No.	%	HR	95% CI	P
Overweight: 25-< 30	685	29.4	0.82	0.63 to 1.07	
Obese: 30	606	26.0	0.86	0.65 to 1.12	

Abbreviations: HR, hazard ratio; OCP, oral contraceptive; HRT, hormone replacement therapy; BMI, body mass index.

Table 2.

Univariate Model of Clinical Factors and Risk of Breast Cancer Recurrence

Factor	Patients (N = 2,327)				P
	No.	%	HR	95% CI	
Tumor size, cm					< .01
2	1,603	68.9	1.00		
> 2	667	28.7	2.15	1.72 to 2.68	
Missing	57	2.4			
Lymph node status					< .01
Negative	1,558	66.9	1.00		
Positive	765	32.9	2.01	1.62 to 2.50	
Missing	4	0.2			
ER/PR status					< .01
ER positive/PR positive	1,099	47.2	1.00		
ER positive/PR negative or ER negative/PR positive	424	18.2	1.06	0.77 to 1.47	
ER negative/PR negative	436	18.8	2.02	1.55 to 2.63	
Missing	368	15.8			
Nuclear grade					< .01
Modified Black's grade 1	281	12.1	1.0		
Modified Black's grade 2	1,223	52.6	0.93	0.64 to 1.34	
Modified Black's grade 3	685	29.4	1.50	1.03 to 2.18	
Missing	138	5.9			
Surgery					< .01
Modified mastectomy	1,367	58.8	1.00		
Segmental mastectomy	952	40.9	0.59	0.47 to 0.75	
Missing	8	0.3			
Chemotherapy					< .01
No chemotherapy	1,263	54.3	1.00		
Anthracycline	643	27.6	1.64	1.29 to 2.08	
Anthracycline and taxane	335	14.4	1.08	0.77 to 1.52	

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Patients (N = 2,327)					
Factor	No.	%	HR	95% CI	P
Other	52	2.2	1.54	0.78 to 3.01	< .01
Missing	34	1.5			
Endocrine treatment					
Yes	1,005	43.2	1.00		
No	1,305	56.1	1.91	1.51 to 2.42	
Missing	17	0.7			
Radiation					.15
Yes	1,017	43.7	1.00		
No	1,295	55.6	1.18	0.94 to 1.47	
Missing	15	0.7			

Abbreviations: HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor.

Final Multivariate Model of Clinical and Epidemiologic Factors and Risk of Breast Cancer Recurrence With One A Priori Hypothesis–Driven Interaction Term (n = 1,638)

Table 3.

Factor	No. of Patients	No. of Recurrences	Hazard Ratio	95% CI	P
Two-way interaction					
HRT use					< .01
Never					
ER positive/PR positive	564	80	1.00		
ER negative/PR negative	255	56	1.31	0.91 to 1.90	
ER negative/PR positive or ER positive/PR negative	215	40	1.39	0.95 to 2.05	
Ever					
ER positive/PR positive	358	34	1.00		
ER negative/PR negative	109	27	2.10	1.21 to 3.64	
ER negative/PR positive or ER positive/PR negative	137	4	0.30	0.11 to 0.85	
Variable					
Year of diagnosis					.83
1995–2000	864	98	1.00		
1990–1994	469	78	1.01	0.72 to 1.41	
1985–1989	305	65	1.11	0.76 to 1.61	
Race/ethnicity					.97
White	1,309	187	1.00		
African American	157	28	1.04	0.69 to 1.57	
Spanish, Hispanic	172	26	1.03	0.68 to 1.53	
Menopausal status					.03
Postmenopausal	1,023	121	1.00		
Peri-/premenopausal	615	120	1.43	1.03 to 1.98	
Tumor size, cm					< .01
2	1,169	134	1.00		
> 2	469	107	1.86	1.42 to 2.44	
Lymph node status					< .01
Negative	1,069	118	1.00		

Factor	No. of Patients	No. of Recurrences	Hazard Ratio	95% CI	P
Positive	569	123	2.22	1.66 to 2.97	.11
Chemotherapy					
None	837	102	1.00		
Anthracycline	488	91	0.70	0.49 to 0.99	
Anthracycline and taxane	275	39	0.79	0.51 to 1.24	
Other	38	9	1.26	0.61 to 2.62	< .01
Endocrine treatment					
Yes	799	78	1.00		
No	839	163	1.78	1.27 to 2.50	

Abbreviations: HRT, hormone replacement therapy; ER, estrogen receptor; PR, progesterone receptor