Risk Factors for Estrogen Receptor–Positive Breast Cancer

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Hypothesis: Some risk factors associated with breast cancer may be more predictive of estrogen receptor (ER)–positive than ER-negative tumors.

Design: Survey of patients enrolled in a study of breast cancer risk factors.

Setting: Community population in a northern California county.

Patients: A total of 234 individuals diagnosed as having breast cancer between July 1, 1997, and June 30, 1999, reporting Marin County, California, residence and participating in a questionnaire regarding exposure to breast cancer risk factors.

Main Outcome Measure: Diagnosis of ER-positive vs ER-negative breast cancer.

Results: Comparison between ER-positive and ER-negative cases showed several factors predictive of ER-positive tumors. In a multivariate model, years of hormone therapy use remained the most significant predictor of ER-positive disease.

Conclusions: Patients diagnosed as having ER-positive breast cancer were more likely to have undergone hormone therapy. The excess of ER-positive breast cancers reported in Marin County could, therefore, in part, be related to hormone therapy.

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THE COMPARATIVELY HIGH INcidence of breast cancer in Marin County, a small, affluent county of almost 250 000 inhabitants directly north of San Francisco, has been recognized since the early 1990s.[1,2] In 1997, in response to growing concern, a community organization—the Marin Breast Cancer Watch—joined with researchers from the University of California, San Francisco, and the Division of Research at Kaiser to initiate a large, population-based, case-control study seeking to better understand the breast cancer risk factors that could be unique to Marin County. Their study[3] found that many of the well-established factors, such as family history, age at menarche, and parity, were not different in cases and controls, possibly because of overmatching in this relatively homogeneous population. However, significant differences in alcohol consumption, socioeconomic status during adolescence, and frequency of mammographic screening were identified. This study did not find a difference in exogenous hormone use between cases and controls, and neither did the increased incidence of breast cancer in Marin County seem to be attributable to length of Marin County residence.

Recently, based on data from the Northern California Cancer Registry, it has been shown that the excess breast cancer risk in Marin County seems to be due almost entirely to an increased incidence of estrogen receptor (ER)–positive breast cancers.[4] Furthermore, there has been growing evidence from large, prospective, randomized trials[5-9] linking breast cancer to hormone therapy, substantiating the association that had been suggested by observational studies. Given that up to 70% of women 50 years and older in Marin County report a history of hormone therapy,[3] one biologically plausible explanation for the increased incidence of breast cancer in Marin County could be the effect of exogenous hormone use, particularly on ER-positive tumors. Therefore, this study was undertaken to determine whether there exist specific risk factors for ER-positive vs ER-negative breast cancer, particularly with respect to hormone therapy.

Table 1. Hormone Use History and Tumor ER Status

	ER-Negative Group (n = 26)	ER-Positive Group (n = 208)	Total (N = 234)	*P* Value*
Patient age, mean, y	49.9	56.4	55.6	.002
History of hormone therapy, No. (%)				
Never	20 (77)	88 (42)	**108** (46)	
Combined estrogen and progesterone therapy	5 (19)	77 (37)	**82** (35)	.003
Estrogen only or other	1 (4)	43 (21)	**44** (19)	
Hormone therapy status at diagnosis, No. (%)				
Never	19 (73)	87 (42)	**106** (45)	
Past	2 (8)	25 (12)	**27** (12)	.01
Current	5 (19)	95 (46)	**100** (43)	
Duration of hormone therapy, mean, y	0.9	5.6	5.1	<.001

Abbreviation: ER, estrogen receptor.
*Continuous predictors were compared using the Wilcoxon signed rank test; categorical predictors were compared using χ^2 analysis.

METHODS

PATIENT SELECTION

This study is a secondary data set analysis of an earlier study that evaluated overall risk factors for breast cancer in Marin County. The survey was designed and conducted by community investigators from the Marin Breast Cancer Watch, a community-based organization committed to identifying factors that contribute to an increased breast cancer incidence in Marin County, and epidemiologists from the University of California, San Francisco. A detailed description of the study design and patient selection has been presented previously.[3] Briefly, patients were identified through the Northern California Cancer Center, a participant in the National Cancer Institute Surveillance, Epidemiology, and End Results National Cancer Registry. Inclusion criteria consisted of a breast cancer diagnosis between July 1, 1997, and June 30, 1999, in patients reporting Marin County residence at the time of diagnosis. Of 401 patients with breast cancer identified as eligible for the study, 336 completed an interview. Institutional review board approval was obtained for the secondary analysis; no patients were contacted again for this study.

SURVEY INSTRUMENT

The survey instrument consisted of a 2-hour in-person interview that included questions pertaining to reproductive factors, socioeconomic status, adolescent exposures, and social habits. Of 336 patients, 51 declined the full interview but agreed to participate in a shorter telephone interview. Detailed items regarding residence history, menopausal status, exogenous hormone use, and duration of use were included in the long and short interviews. A more comprehensive description of the questionnaire has been previously reported elsewhere.[3] Tumor characteristics, including ER and progesterone receptor (PR) status, were obtained through the Northern California Cancer Center. Of the 336 patients analyzed in the initial study, 234 had a known ER or PR status recorded in the Northern California Cancer Center. These patients are included in the following analysis.

STATISTICAL ANALYSIS

Continuous predictors were compared between the ER-positive and ER-negative groups using the Wilcoxon signed rank test, imposing no assumptions regarding normal data distribution. Categorical predictors were compared using χ^2 analysis. Univariate logistic analysis was performed for variables established as risk factors for breast cancer and for variables previously described as being predictive of increased breast cancer risk in the overall group.[3] Adjustment for age did not alter the findings of the univariate analysis. Multivariate analysis was performed using forward selection, including all predictors that were significant on univariate analysis at $P<.10$. Because history of exogenous hormone use was almost entirely confined to an older age group, the multivariate analysis was limited to women 50 years or older at diagnosis. Menopausal status, although highly statistically significant on univariate logistic regression, was not included in the final model because it was highly collinear with age. Similarly, history of hormone therapy (ever vs never) was excluded from the model owing to collinearity with duration of hormone therapy. The variables included in the final model were age, duration of hormone use, and frequency of mammographic screening.

RESULTS

HORMONE USE IN THE ER-POSITIVE AND ER-NEGATIVE GROUPS

A total of 234 Marin County residents diagnosed as having primary breast cancer were analyzed for the study: 208 had ER-positive tumors and 26 had ER-negative tumors. Most variables were evenly distributed between the ER-positive and ER-negative groups; however, some marked differences were seen, particularly with respect to age at diagnosis and factors related to exogenous hormone use (**Table 1**). Among women 50 years or older at diagnosis, 56.0% (94/168) were currently undergoing hormone therapy, and 69.0% (116/168) reported a history of hormone therapy. Of these 116 patients, 39 (33.6%) had used exogenous hormones for more than 10 years.

UNIVARIATE ANALYSIS

Univariate logistic analysis of categorical variables showed that menopausal status, history of hormone therapy (ever vs never), and frequency of mammographic screening (<4 vs ≥4 mammograms between January 1, 1990, and De-

cember 31, 1994) were predictive of the development of ER-positive breast cancer (**Table 2**). In patients 50 years or older at diagnosis, combined hormonal therapy and the use of other hormonal preparations trended toward significance ($P=.06$ for both). Many previously reported reproductive and social risk factors for breast cancer were not specific to ER-positive cancer in this cohort, including family history (first-degree family member diagnosed as having breast cancer), history of previous benign breast biopsy findings, parity, history of breastfeeding, socioeconomic status, alcohol use, and body mass index. Factors related to Marin County residence (total years of residence and age at first residence) were not predictive of tumor ER status.

MULTIVARIATE ANALYSIS

The final multivariate model was confined to women 50 years or older at diagnosis because only 16.7% of women younger than 50 years reported a history of hormone therapy. We attempted to minimize confounding between age and hormone therapy by limiting the multivariate analysis to women 50 years or older at the time of breast cancer diagnosis. We used a forward selection strategy, including only variables that were significant to at least $P=.10$ on univariate analysis in this age group. By so doing, we sought to mitigate the collinearity between hormone therapy and age. The final model was evaluated using likelihood ratio testing.

The variables tested in the final model were age, duration of hormone therapy (years), and frequency of mammographic screening. Duration of hormone therapy and frequency of mammography remained statistically significant risk factors for ER-positive breast cancer. The odds of developing ER-positive breast cancer vs ER-negative breast cancer increased almost linearly with duration of use, with an odds ratio of 2.14 (95% confidence interval, 1.11-4.12) per 5 years of hormone therapy. All patients who reported more than 5 years of hormone therapy had ER-positive breast cancer (**Figure**).

COMMENT

Conventional epidemiologic studies of breast cancer risk factors have assessed risk as it relates to an increased incidence of all breast cancer phenotypes. However, it is now recognized that breast cancer represents not one but many diseases with markedly differing biological behaviors and different dependencies on such population demographics as age and race/ethnic status. It is evident that not all types of breast cancer respond in the same manner to a particular agent, as illustrated by the differing responses of ER-positive and ER-negative cancers to adjuvant hormonal therapies. Thus, it is reasonable to suppose that the processes of cancer initiation and promotion may also differ depending on tumor subtype and the population at risk.

The Women's Health Initiative[7] reported the ER status of breast cancers diagnosed in women while undergoing hormone therapy vs placebo therapy and found essentially no difference between the estrogen/progestin and placebo groups at 5 years. However, observational data[10-13] have shown that in large retrospective series involving mostly non-Hispanic white women, there seems to be a significantly increased incidence of ER-positive cancers and lobular cancers, which are almost always ER positive.

One important strength of our study is the survey technique. Data were collected for most participants via 2-hour at-home interviews aided by devices such as memory boards and visualization exercises. This method of data collection aimed to optimize proper coding of certain data elements, such as type and duration of hormone therapy.

Our data support that the propensity to develop ER-positive tumors increases with the duration of hormone therapy, so that there was no difference in ER status between patients reporting 5 years of hormone therapy and those having never used exogenous hormones. However, no patient diagnosed as having breast cancer who reported more than 5 years of hormone therapy had ER-negative disease. History of hormone therapy, which was one of the strongest predictors of ER-positive cancer in the present analysis, had not differed significantly between cases and controls in the previous analysis of overall breast cancer risk.[3] Other factors that had been highly predictive of breast cancer overall, including alcohol consumption, socioeconomic status before age 21 years, and body mass index, were not specifically predictive of tumor ER status. These observations support that distinct tumor subtypes are subject to different inciting factors but that there must also exist some risk factors that are generally permissive of breast cancer development. One plausible explanation could be that some risk factors contribute to ER-positive and ER-negative cancers, promoting tumorigenesis in an estrogen-independent manner. Such factors may act directly on cell cycle or apoptotic pathways such that they may promote indiscriminate cancer progression. The alternative explanation, that some factors are associated with ER-negative cancers, is intriguing but was not seen in the present study.

The prevalence of hormone therapy is highly associated with socioeconomic status, with women of higher socioeconomic status more than 3 times more likely to undergo hormone therapy.[14] In the patient population reported herein, 69.0% of women (n=116) 50 years and older reported hormone use, 33.6% (n=52) of whom had taken hormones for more than 10 years. It is possible that this relationship between higher socioeconomic status and hormone therapy may, in part, explain the increased incidence of breast cancer in more affluent geographic areas, such as Marin County and Geneva, Switzerland.[15] Our study population was probably too small to show a difference in ER-positive cancer risk conferred by combined hormone therapy vs other therapies. However, other researchers[10,11] have reported that unopposed estrogen use may also slightly increase the likelihood of developing ER-positive cancers.

The other factor most predictive of ER-positive cancer was frequency of mammographic screening. Arguably, routine screening could be a surrogate marker for either hormone therapy or age. However, frequency of mammography remained a statistically significant pre-

Table 2. Univariate Analysis of Risk Factors for ER-Positive Tumors

	Women ≥50 y at Diagnosis			Women <50 y at Diagnosis		
	ER Negative, No. (%) (n = 15)	ER Positive, No. (%) (n = 153)*	Univariate OR (95% CI)	ER Negative, No. (%) (n = 11)	ER Positive, No. (%) (n = 55)*	Univariate OR (95% CI)
First-degree relative with breast cancer						
No	11 (73)	123 (81)	1.0	10 (91)	42 (78)	1.0
Yes	4 (27)	28 (19)	0.55 (0.16-1.89)	1 (9)	12 (22)	2.86 (0.33-24.6)
Benign breast biopsy history						
None	11 (73)	98 (64)	1.0	9 (82)	48 (87)	1.0
Needle biopsy only	0	12 (8)	NA	0	2 (4)	NA
Surgical biopsy	4 (27)	42 (28)	1.06 (0.31-3.59)	2 (18)	5 (9)	0.47 (0.08-2.80)
Radiation history†						
No	13 (87)	137 (90)	1.0	11 (100)	49 (91)	1.0
Yes	2 (13)	15 (10)	0.69 (0.14-3.39)	0	5 (9)	NA
Menopausal status†‡						
Premenopausal/perimenopausal	8 (53)	18 (12)	1.0	11 (100)	50 (91)	1.0
Postmenopausal	7 (47)	135 (88)	10.2 (3.10-33.7)§	0	5 (9)	NA
Parity†						
Nulliparous	3 (20)	16 (10)	1.0	2 (18)	14 (25)	1.0
1 birth	0	26 (17)	NA	1 (9)	5 (9)	0.71 (0.05-9.70)
2 births	3 (20)	38 (25)	1.6 (0.24-10.57)	2 (18)	14 (25)	1.00 (0.12-8.13)
≥3 births	9 (60)	73 (48)	1.05 (0.21-5.37)	6 (55)	22 (40)	0.52 (0.09-2.97)
Breastfeeding history†						
Never	7 (47)	68 (44)	1.0	6 (55)	22 (40)	1.0
≤6 mo	3 (20)	35 (23)	1.06 (0.25-4.52)	1 (9)	8 (15)	2.18 (0.23-21.0)
≤12 mo	5 (33)	17 (11)	0.32 (0.09-1.17)	3 (27)	10 (18)	0.91 (0.19-4.39)
>12 mo	0	33 (22)	NA	1 (9)	15 (27)	4.09 (0.45-37.5)
Oral contraceptive use†‡‖						
Never	3 (20)	47 (31)	1.0	1 (9)	11 (20)	1.0
Ever	12 (80)	106 (69)	1.74 (0.46-6.53)	10 (91)	44 (80)	2.5 (0.29-21.7)
Hormone therapy						
Never	9 (60)	42 (28)	1.0	10 (91)	45 (82)	1.0
Ever	6 (40)	110 (72)	3.89 (1.27-11.9)§	1 (9)	10 (18)	2.22 (0.25-19.4)
Highest body mass index after age 21 y‡‖						
<25	8 (53)	95 (62)	1.0	9 (82)	40 (73)	1.0
≥25 and <30	6 (40)	37 (24)	0.45 (0.14-1.43)	2 (18)	11 (20)	1.23 (0.23-6.58)
≥30	1 (7)	21 (14)	1.54 (0.18-13.2)	0	4 (7)	NA
Mammograms, 1990-1994, No.‡						
<4	7 (47)	19 (12)	1.0	11 (100)	45 (82)	1.0
≥4	8 (53)	133 (88)	5.65 (1.75-18.3)§	0	10 (18)	NA
Socioeconomic status before age 21 y‖						
Poor/working	1 (7)	29 (19)	1.0	1 (9)	8 (15)	1.0
Lower middle/middle	8 (53)	80 (53)	0.34 (0.04-2.88)	6 (55)	31 (56)	0.65 (0.07-6.16)
Upper middle/upper	6 (40)	42 (28)	0.24 (0.03-2.11)	4 (36)	16 (29)	0.5 (0.05-5.24)
Age began drinking alcohol‡‖						
Before age 21 y	13 (87)	120 (78)	1.0	10 (91)	47 (85)	1.0
Never or after age 21 y	2 (13)	33 (22)	1.49 (0.32-7.02)	1 (9)	8 (15)	1.70 (0.19-15.2)
Drinks after age 21 y, mean, No.†‡						
<1/wk	5 (33)	40 (27)	1.0	2 (18)	17 (31)	1.0
≥1/wk and <2/d	5 (33)	72 (48)	2.27 (0.57-8.96)	8 (73)	28 (52)	0.41 (0.08-2.17)
2/d	3 (20)	32 (21)	1.32 (0.29-5.95)	1 (9)	7 (13)	0.82 (0.06-10.6)
≥3/d	2 (13)	6 (4)	0.39 (0.06-2.52)	0	2 (4)	NA
Tobacco use history						
Never	9 (60)	56 (37)	1.0	7 (64)	27 (49)	1.0
Ever	6 (40)	97 (63)	2.48 (0.82-7.55)	4 (36)	28 (51)	1.81 (0.48-6.91)
Lifetime living in Marin County						
2 mo to 13 y	3 (20)	19 (13)	1.0	7 (64)	25 (45)	1.0
>13 to ≤24 y	4 (27)	36 (24)	1.29 (0.26-6.43)	2 (18)	19 (35)	2.66 (0.50-14.3)
>24 to ≤32 y	4 (27)	38 (25)	2.11 (0.39-11.5)	0	6 (11)	NA
>32 to ≤60 y	4 (27)	58 (38)	2.38 (0.49-11.6)	2 (18)	5 (9)	0.70 (0.11-4.41)
Age moved to Marin County, y						
1-22	3 (20)	24 (16)	1.0	3 (27)	17 (31)	1.0
23-28	4 (27)	49 (32)	1.53 (0.32-7.39)	1 (9)	14 (26)	2.47 (0.23-26.5)
29-36	2 (13)	42 (27)	2.63 (0.41-16.8)	3 (27)	9 (16)	0.53 (0.08-3.18)
≥37	6 (40)	38 (25)	0.79 (0.18-3.47)	4 (36)	15 (27)	0.66 (0.13-3.45)

Abbreviations: CI, confidence interval; ER, estrogen receptor; NA, not analyzed; OR, odds ratio.
*Not all data points were available for all patients.
†Significant predictor of any breast cancer in women younger than 50 years in a previous analysis.
‡Significant predictor of any breast cancer in women of all ages in a previous analysis.
§Statistically significant.
‖Significant predictor of any breast cancer in women 50 years or older in a previous analysis.

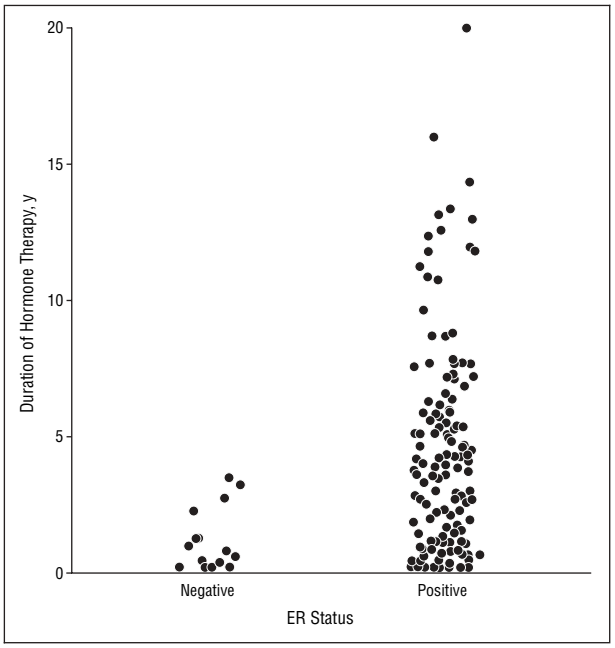

Figure. Effect of hormone use duration on tumor estrogen receptor (ER) status in women 50 years or older at diagnosis (n=167).

dictor of ER-positive cancer even when corrected for duration of hormone therapy and age. Nevertheless, there could exist an interaction between hormone therapy and mammography because only 1 (3%) of 39 women with a history of hormone therapy for more than 10 years had infrequent screening, whereas 12 (23%) of 52 patients with no hormone therapy had infrequent screening. One consequence of hormone therapy could be that the resulting increased breast density, and thus more difficult breast examination, could prompt more frequent evaluation of palpable breast abnormalities. Although hormone therapy has been shown to decrease the sensitivity and specificity of screening mammograms,[16] it is unknown whether this is the basis for more frequent radiologic evaluation. Furthermore, an association between socioeconomic status and frequency of mammographic screening has been shown by other researchers,[14,17] but this relationship is not easily explored in geographic areas that lack socioeconomic diversity, such as Marin County.

In conclusion, in this patient population, duration of hormone therapy was the strongest predictor of ER-positive, vs ER-negative, breast cancer. The previously widespread use of hormones, particularly in affluent populations, may have contributed to the increased risk of ER-positive breast cancer in Marin County and other regions of high socioeconomic status. Future determinants of breast cancer risk should take into account the heterogeneity of breast cancer because tumor proliferation among different subsets of breast cancer seems to be affected by disparate factors.

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REFERENCES

1. Prehn AW, West DW. Evaluating local differences in breast cancer incidence rates: a census-based methodology (United States). *Cancer Causes Control.* 1998; 9:511-517.
2. Clarke CA, Glaser SL, West DW, et al. Breast cancer incidence and mortality trends in an affluent population: Marin County, California, USA, 1990-1999. *Breast Cancer Res.* 2002;4:R13.
3. Wrensch M, Chew T, Farren G, et al. Risk factors for breast cancer in a population with high incidence rates. *Breast Cancer Res.* 2003;5:R88-R102.
4. Benz CC, Clarke C, Moore D III. Geographic excess of estrogen receptor–positive breast cancer. *Cancer Epidemiol Biomarkers Prev.* In press.
5. Delgado RC, Lubian Lopez DM. Prognosis of breast cancers detected in women receiving hormone replacement therapy. *Maturitas.* 2001;38:147-156.
6. Lower EE, Blau R, Gazder P, Stahl DL. The effect of estrogen usage on the subsequent hormone receptor status of primary breast cancer. *Breast Cancer Res Treat.* 1999;58:205-211.
7. 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.* 2003;289:3243-3253.
8. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-333.
9. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA.* 2002;288:58-66.
10. 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.* 2003;21:4314-4321.
11. Li CI, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA.* 2003; 289:3254-3263.
12. Manjer J, Malina J, Berglund G, Bondeson L, Garne JP, Janzon L. Increased incidence of small and well-differentiated breast tumours in post-menopausal women following hormone-replacement therapy. *Int J Cancer.* 2001;92:919-922.
13. Bilimoria MM, Winchester DJ, Sener SF, Motykie G, Sehgal UL, Winchester DP. Estrogen replacement therapy and breast cancer: analysis of age of onset and tumor characteristics. *Ann Surg Oncol.* 1999;6:200-207.
14. Finley C, Gregg EW, Solomon LJ, Gay E. Disparities in hormone replacement therapy use by socioeconomic status in a primary care population. *J Community Health.* 2001;26:39-50.
15. Verkooijen HM, Fioretta G, Vlastos G, et al. Important increase of invasive lobular breast cancer incidence in Geneva, Switzerland. *Int J Cancer.* 2003;104: 778-781.
16. Laya MB, Larson EB, Taplin SH, White E. Effect of estrogen replacement therapy on the specificity and sensitivity of screening mammography. *J Natl Cancer Inst.* 1996;88:643-649.
17. McNagny SE, Wenger NK, Frank E. Personal use of postmenopausal hormone replacement therapy by women physicians in the United States. *Ann Intern Med.* 1997;127:1093-1096.