Sex Hormones, Risk Factors, and Risk of Estrogen Receptor–Positive Breast Cancer in Older Women: A Long-term Prospective Study

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Abstract

Objective: **Antiestrogens reduce the risk of estrogen receptor–positive (ER+) but not ER-negative (ER–) breast cancer. Women at high risk of ER+ cancer would be the most likely to benefit from these treatments, but the best approach to predicting ER+ cancer is uncertain.**
Methods: **We prospectively assessed putative risk factors for breast cancer and archived serum at −190°C from a community-based cohort of 7,676 women ages ≥65 years who had no history of breast cancer. Follow-up for breast cancer over 10.5 years was 99% complete. Using a case-cohort design, we measured baseline levels of estradiol and testosterone in 196 cases of invasive ER+ cancer and 378 randomly selected controls.**
Results: **Women whose testosterone level in highest two quintiles had a 4-fold increased risk of ER+ breast cancer ($P < 0.0001$). High estradiol concentration also indicated an increased risk but was not a significant predictor after adjustment for testosterone. Women with >16 years of education had a 2.1 times increased risk ($P = 0.03$) of ER+ cancer, but no other risk factors were significantly related to an increased risk of ER+ cancer. Women with a family history of breast cancer had a 2.9-fold increased risk of ER– cancer ($P = 0.002$) but no increased risk of ER+ cancer (relative hazard = 1.2, 0.8-1.8).**
Conclusions: **High serum testosterone and advanced education predicted ER+ breast cancer. If confirmed, high testosterone level may be more accurate than family history of breast cancer and other conventional risk factors for identifying older women who are most likely to benefit from antiestrogen chemoprevention.** (Cancer Epidemiol Biomarkers Prev 2005;14(5):1047–51)

Introduction

Antiestrogens, such as tamoxifen, raloxifene, and aromatase inhibitors, reduce the risk of estrogen receptor–positive (ER+) but not ER-negative (ER–) breast cancer (1-4). Current risk factor models, such as the Gail model, were designed to estimate the risk of all breast cancer, regardless of receptor status (5). However, risk factors for breast cancer seems to differ by the receptor status of the cancer (6-10).

Among postmenopausal women, endogenous levels of estradiol and testosterone correlate with overall risk of breast cancer (11-13). However, the relationship between sex hormone concentrations and risk of ER+ breast cancer has not been studied. Furthermore, there has been no prospective study comparing risk factors and sex hormone levels for prediction of breast cancer.

We hypothesized that serum concentrations of estradiol and testosterone would be stronger predictors of ER+ breast cancer than would be risk factors, such as family history of breast cancer. We tested these hypotheses in a large cohort of older postmenopausal women that had been prospectively studied for over 10 years.

Materials and Methods

The Study of Osteoporotic Fractures is a prospective cohort of women ages ≥65 years who were recruited in 1986 to 1987 from four communities in the United States. We did not select women based on risk of breast cancer; only women with bilateral hip replacements or inability to walk independently were excluded. Details about Study of Osteoporotic Fractures have been described elsewhere (11). At the baseline examination in 1986 to 1987, we asked women about their reproductive history, years of education, history of estrogen replacement therapy, history of breast cancer in mothers and sisters, and other potential risk factors for breast cancer (Table 1). Weight (in lightweight clothing without shoes), was measured on a balance beam scale. We report weight instead of body mass index because after age 65, loss of height due to osteoporosis may bias the relationship between body mass index and estrogen-related conditions. Bone mineral density of the distal radius was measured by single photon absorptiometry and bone mineral density of the spine and hip was measured by dual X-ray absorptiometry (Hologic QDR 1000). Serum samples were banked at −190°C. Appropriate consent was obtained from all participants.

Ascertainment and Validation of Breast Cancer and ER Status. Participants were asked annually whether they had a diagnosis of breast cancer since the previous contact. When participants died, we searched death certificates and hospital discharge summaries for the diagnosis of breast cancer. We obtained pathology reports, medical records for all cases and pathology slides, as necessary, to confirm the diagnosis. Classification of ER receptor type was based on pathology reports. One pathologist (B.M.L.) oversaw the process and reviewed and adjudicated all uncertain cases.

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Table 1. Baseline characteristics of the 7,676 subjects

Characteristic	Mean (SD)		*P*
	Invasive ER+ breast cancer (n = 208)	No breast cancer (n = 7,468)	
Age (y)	70.3 (4.3)	71.9 (5.4)	<0.001*
Education (y)	12.9 (2.7)	12.4 (2.8)	0.01*
Weight (kg)	70.9 (12.8)	67.3 (12.6)	<0.001*
Age at menarche (y)	12.9 (1.5)	13.1 (1.5)	0.22
Age at last natural menses (y)	47.7 (5.8)	47.0 (6.3)	0.13
Years of reproductive life (y)	34.7 (6.1)	34.0 (6.5)	0.16
Age at first childbirth (y)	25.4 (5.2)	25.3 (4.9)	0.74
No. live births	2.8 (1.7)	2.7 (1.6)	0.61
No. children breast-fed	1.6 (1.6)	1.6 (1.6)	0.60
Underwent surgical menopause (%)	11.4	9.8	0.46
Past use of estrogen therapy (%)	35.0	31.8	0.33
Family history of breast cancer† (%)	16.2	14.5	0.51
Current smoker (%)	11.1	10.0	0.62
Alcoholic drinks per week	2.4 (4.8)	1.9 (4.1)	0.07
Physical activity (total weekly kcal in past year)	1,711 (1,792)	1,552 (1,627)	0.17
Takes walks for exercise (%)	47.6	49.1	0.66
Distal radius BMD (g/cm^2)	0.38 (0.08)	0.35 (0.08)	<0.001*
Lumbar spine BMD (g/cm^2)	0.88 (0.15)	0.84 (0.16)	0.01*
Total hip BMD (g/cm^2)	0.79 (0.12)	0.75 (0.13)	<0.001*

Abbreviation: BMD, bone mineral density.
*Significant difference at $P < 0.05$ using two-sided t test.
†Having a mother or sister with breast cancer.

Measurement of Sex Hormones. Because estrogen therapy alters sex hormone levels and risk of breast cancer, we excluded women taking estrogen from the study; 196 (94%) of the 208 cases of ER+ invasive breast cancer had blood for measurement of sex hormones. We randomly selected 378 controls who did not develop breast cancer and had blood for sex hormone measurement. The cases included all subjects from our original report. Of 97 cases of breast cancer in that report, 62 were ER+ invasive breast cancer. Four additional cases of ER+ breast cancer developed among the original controls, for a total of 66. The current study added 130 new cases of ER+ breast cancer that were validated up to 2000.

As described previously, serum specimens were collected from all participants at a baseline examination in 1986 to 1988 (11). Specimens were immediately frozen to −20°C for up to 2 weeks and stored in liquid nitrogen at −190°C until assays were done.

For that first report, total estradiol, total testosterone, and sex hormone binding globulin (SHBG) were measured by Coming Nichols Institute (San Juan Capistrano, CA). For the additional cases, Endocrine Sciences Esoterix (Calabassas Hills, CA) measured total estradiol, total testosterone, and SHBG concentrations. In both laboratories, total estradiol was measured by liquid-liquid organic extraction, column chromatography, and RIA. Intra-assay and interassay coefficients of variation ranged from 6% t 14% and 5% to 13% at Coming Nichols and from 3% to 19% and 8% to 15%, respectively at Endocrine Sciences Esoterix. The sensitivity of the assay was 2 pg/mL for both laboratories.

In both laboratories, total testosterone was measured using RIA with chromatographic purification. Intra-assay and interassay coefficients of variation ranged from 4% to 12% and 9% to 11% for the assays done by Coming Nichols and from 3% to 13% and 9% to 14%, respectively for assays done by Endocrine Sciences Esoterix. The sensitivity of the assay was approximately 0.9 ng/d for Coming Nichols and 3 ng/d for Endocrine Sciences Esoterix. All assays were blinded to case or control status.

We used baseline specimens from 30 participants to compare the measurements of sex hormones between the laboratories. Coming Nichols made measurements in 1996 and separate aliquots of baseline samples were split and measured blindly by both laboratories in 2000. The correlations between measurements in baseline samples made by Coming Nichols in 1996 and 2000 were 0.85 for total estradiol and 0.97 for total testosterone. The correlations between measurements made in 2000 by Coming Nichols and Endocrine Science Esoterix were 0.92 for total estradiol and 0.97 for total testosterone. The mean values were also similar for total estradiol and total testosterone. Thus, results of the assays were combined, but all analyses were also adjusted for laboratory.

Results were similar for estradiol and the estradiol/SHBG ratio and for testosterone and the testosterone/SHBG ratio. For simplicity, we present the findings for total estradiol and total testosterone.

Statistical Analysis. We used the whole cohort (n = 7,676), including all 208 cases of invasive ER+ breast cancer, to analyze potential risk factors ER+ breast cancer using proportional hazards models and reported with 95% confidence intervals (95% CI; ref. 14). We included significant ($P < 0.05$) age-adjusted associations in multivariate models. All analyses were done using SAS software (SAS Institute, Inc., Cary, NC).

All analyses involving sex hormone levels included 196 cases of ER+ breast cancer and a random sample of 378 controls that had blood available for these assays (including all of the controls from our previous report who had not developed breast cancer in the interim). The relative hazard for breast cancer was calculated (using the lowest quintile as the reference group) across quintiles of sex steroid hormone levels by using a modification of the proportional hazards model that accounts for the case-cohort sampling design (STATA, Stata Co., College Station, TX). Cut points for quintiles were based on the distribution of hormone levels within the random subset of the cohort.

Because of the small number of cases of ER− breast cancer, our analyses had power to detect only very strong relationships, such as the association between family history and risk of breast cancer.

Results

We validated 272 cases of invasive breast cancer during 10.5 years of 99% complete follow-up (3.4 per 1,000 per year). At the baseline examination, the mean age of participants was over 70 years and 99% of the cohort was Caucasian (Table 1).

25.5 (94%) had blood for hormone measurements and of these, 196 were ER+, 25 were ER−, and ER status was not determined for 34.

Risk Factors. In analyses of the whole cohort, the risk of ER+ breast cancer was significantly increased in women who had >16 years of education (relative hazard, 1.7; 95% CI, 1.1-2.5; $P = 0.01$), increased body weight (relative hazard, 1.2 per 10 kg; 95% CI, 1.1-1.3; $P < 0.001$), and bone density (relative hazard, 1.3 per SD increase in distal radius bone mineral density; 95% CI, 1.1-1.5; $P < 0.001$; Table 2). There were no significant associations between other risk factors and risk of ER+ breast cancer (Table 2). Specifically, family history of breast cancer in a first-degree relative was not significantly associated with an increased risk of ER+ breast cancer (relative hazard, 1.2; 95% CI, 0.8-1.8). In contrast, subjects with a family history had a significantly increased risk of ER− breast cancer (relative hazard, 2.9; 95% CI, 1.1-7.8; $P = 0.03$; $P = 0.09$ for the interaction between ER status and family history).

Sex Hormones, Risk Factors, and ER+ Breast Cancer. In analyses of the cases and controls, levels of testosterone and levels of estradiol were associated with an increased risk of ER+ breast cancer (Table 3). In age-adjusted models, women whose testosterone level was in the highest quintiles (>1,074 and 728-1,074 pmol/L, respectively) had a 5.1-fold (2.5-10.3; $P < 0.001$) and 3.8-fold (1.9-7.8) greater risk of ER+ breast cancer than did women in the lowest quintile (<381 pmol/L). Women in the highest quintile of testosterone had a 2.0% (1.4-2.6) 5-year risk of invasive ER+ breast cancer.

In age-adjusted models, women whose estradiol level was in the highest quintile (>32 pmol/L) had a 2.9-fold greater risk of ER+ breast cancer than women in the lowest quintile (<14 pmol/L). Serum concentrations of estradiol and testosterone were correlated at $r = 0.4$. In models that included both testosterone and estradiol, only testosterone level remained significantly related to the risk of ER+ breast cancer (Table 3). In models that included risk factors and hormone measurements, only testosterone level and advanced education remained significantly associated with risk of ER+ breast cancer (Table 3). The combination of a testosterone in the top two quintiles and at least 16 years of education indicated a 2.8% (1.2-4.4%) 5-year risk of ER+ breast cancer. In contrast, those with a testosterone in the lowest quintile and <16 years of education had a 0.5% (0.2-0.7%) 5-year risk.

Table 2. Age-adjusted associations of risk factors with ER+ invasive breast cancer in the whole cohort

Variable (comparison)	Relative risk (95 % CI)
No. cases*	196
Education > 16 y (≤16 y)	1.7 (1.1-2.5)
Weight (per 10 kg)	1.2 (1.1-1.3)
Distal radius BMD†	1.3 (1.1-1.5)
Family history of breast cancer‡	1.2 (0.8-1.8)
Current smoker (noncurrent)	1.1 (0.7-1.7)
Surgical menopause (natural)	1.2 (0.8-1.9)
Takes walks for exercise (none)	0.8 (0.6-1.1)
Alcoholic drinks/wk (per four drinks)	1.1 (1.0-1.3)
Exercise (kcal/wk; per 1,631 kcal)	1.0 (0.9-1.2)
Age at last natural menses (per 6.3 y)	1.1 (0.9-1.3)
Age at menarche (per 1.5 y)	0.9 (0.8-1.1)
Years of reproductive life (per 6.5 y)	1.1 (0.9-1.3)
Age at first child born (per 5 y)	1.0 (0.9-1.2)
Births (per 1.6 live births)	1.0 (0.8-1.1)
Children breast-fed (per 1.6 children)	1.0 (0.9-1.2)

Abbreviation: BMD, bone mineral density.
*The number of cases in the whole cohort (208) is greater than in the case-cohort analyses because 12 participants did not have sufficient blood for analyses of sex hormone levels in the case-cohort study.
†Per SD increase in BMD.
‡At least one sister or mother with breast cancer.

Discussion

In this large cohort, women who had a high serum testosterone level had a substantially increased risk of ER+ breast cancer. Women with a testosterone concentration in the highest quintile had a 2.0% 5-year risk of invasive ER+ breast cancer. This is higher than the 1.7% risk of all types of breast cancer combined that has been used to identify ''high-risk'' women for consideration of treatment with tamoxifen (15, 16). When the testosterone concentration was known, no other risk factor, except education, was significantly related to the risk of ER+ breast cancer. Estradiol level was also correlated with risk of ER+ breast cancer but this relationship was not statistically significant after adjustment for testosterone concentration.

A pooling of prospective studies found that both total estradiol and testosterone were independently associated with an increased overall risk of breast cancer (13). A smaller recent study found that the relationship between testosterone and overall risk of breast cancer was no longer statistically significant after adjustment for estrone levels (17). However, no prospective study has reported the relationship between sex hormones and risk of ER+ cancer and none has compared the value of sex hormone levels with risk factors for breast cancer.

Testosterone is converted to estradiol by aromatase, which is present in breast and other tissues (17). Thus, serum concentrations of testosterone could reflect the availability of this precursor in breast tissue. In contrast, circulating estradiol results from production of estradiol by a variety of tissues and the rate of estradiol metabolism. One small study (18) observed a modest ($r = 0.3$-0.4) correlation between blood and tumor levels of estradiol or testosterone, whereas a second observed a very high correlation ($r = 0.81$) between testosterone levels in the tumors and blood of postmenopausal women (19). In contrast, one study found little or no significant correlation between estradiol levels in the serum and breast duct fluid (20). Testosterone levels are higher than estradiol levels and easier to measure reproducibly in blood and this could also contribute to a stronger association between testosterone than estradiol level and risk of ER+ breast cancer.

We previously found that postmenopausal women with high concentrations of estradiol had greater reductions in risk of breast cancer with raloxifene than did women with very low concentrations, but that study did not include measurements of testosterone (21). The present study suggests that measurement of testosterone might also be useful for predicting the magnitude of a woman's response to treatments, such as aromatase inhibitors and selective ER modulators that reduce the risk of ER+ breast cancer. Testosterone levels should not yet be used to predict a patient's degree of response to tamoxifen until this possibility has been tested breast cancer chemoprevention trials.

We confirmed the increased risk of breast cancer that has been observed among women in the United States with higher education and higher socioeconomic status, (22, 23) although this has not been found consistently in Europe (14, 24, 25). The reason for this association is not known, although it is possible that highly educated women may be more likely to undergo mammography. We were not able to explore this possibility because we did not assess the rate of mammography in this cohort. Highly educated women may also have a later age at first pregnancy, higher rates of nulliparity, and more use of hormone replacement therapy than other women (26, 27); however, none of these factors explained the association between education and risk of ER+ breast cancer we observed. We considered whether women with higher levels of education have higher endogenous levels of sex hormones; however, there were no significant differences in estradiol or testosterone by levels of education in our cohort (data not shown).

Several (6, 8) but not all studies have found that family history of breast cancer is more strongly related to the risk of

Table 3. Serum sex hormone concentrations and other risk factors for ER+ breast cancer in the nested case-cohort study

Factor	Age-adjusted		Adjusted*	
	Relative risk (95% CI)	*P*	Relative risk (95% CI)	*P*
Weight (per 10 kg)	1.2 (1.1-1.3)	0.002	1.1 (0.9-1.4)	0.26
Education (>16 y)	1.5 (1.0-2.2)	0.05	2.1 (1.1-4.2)	0.03
Distal radius BMD†	1.2 (1.1-1.4)	0.003	1.2 (0.9-1.5)	0.20
Testosterone‡				
Quintile 1 (reference)	1.0		1.0	
Quintile 2	2.6 (1.2-5.4)	0.01	2.4 (1.1-5.5)	0.03
Quintile 3	2.1 (1.0-4.4)	0.06	2.2 (0.9-5.0)	0.07
Quintile 4	3.8 (1.9-7.8)	4.001	4.0 (1.8-8.6)	<0.001
Quintile 5	5.1 (2.5-10.3)	<0.001	3.8 (1.7-8.4)	0.001
Estradiol§				
Quintile 1 (reference)	1.0		1.0	
Quintile 2	0.8 (0.4-1.8)	0.63	0.7 (0.3-1.7)	0.44
Quintile 3	1.4 (0.8-2.5)	0.30	1.2 (0.6-2.2)	0.66
Quintile 4	1.8 (0.9-3.5)	0.08	1.3 (0.6-2.8)	0.45
Quintile 5	2.9 (1.6-5.1)	<0.001	1.8 (0.9-3.6)	0.11

Abbreviation: BMD, bone mineral density.
*Adjusted for weight, education, radius BMD, testosterone, and estradiol. P_{trend} for estradiol = 0.06 and P_{trend} for testosterone < 0.001.
†Per SD increase.
‡Quintiles for testosterone (pmol/L): 1st, <381; 2nd, 381-553; 3rd, 554-727; 4th, 728-1074; 5th, >1,074.
§Quintiles for estradiol (pmol/L): 1st, <14; 2nd, 14-17; 3rd, 18-24; 4th, 25-32; 5th, >32.

ER− than ER+ cancer. Our study supports the view that a family history of breast cancer is more strongly related to the risk of ER− than ER+ breast cancer. Because all women in our study were ages ≥65 years, our result suggests that hereditary influences on the risk of ER− breast cancer continue late into life. Current risk factor models, such as the Gail Model, are based, at least in part, on family history of breast cancer to assess risk. However, our study suggests that family history is not a significant risk factor for ER+ cancer and therefore would not be a reliable way to identify women who would benefit most from SERMS or aromatase inhibitors that only reduce the risk of ER+ breast cancer (1-3). Conventional reproductive risk factors for breast cancer, such as parity and age at menarche, were not significantly related to ER+ breast cancer in this cohort of elderly women. However, large meta-analyses have reported significant associations between alcohol use, parity, breast-feeding, and decreases in overall risk of breast cancer (28-30). Our study may have had too few cases to detect the modest associations observed in these larger analyses. It is also possible that these risk factors are not as strong or as accurately remembered in elderly women.

Case-control studies have usually reported associations between body mass index and risk of ER+ breast cancer and, variably, associations with a few reproductive factors, such as nulliparity and early menarche (28, 29). But these retrospective studies combined ER+ and ER− cancer and also often combined premenopausal and postmenopausal cases. No prospective study has compared the predictive value of multiple potential risk factors and measurements of sex hormones for ER+ breast cancer.

Increased weight and bone density have been associated with an increased risk of breast cancer in postmenopausal women (31-33). We also found significant associations with ER+ breast cancer. However, adjustment for sex hormones attenuated the relationship between weight or bone density and risk of ER+ breast cancer, suggesting that increased weight and bone density are associated with an increased risk of breast cancer at least partly due to their correlations with estradiol levels.

We previously reported that several hormones, including androstenedione, DHBA, and estrone were related to risk of breast cancer; however, only estradiol and testosterone remained statistically significantly related to risk of breast cancer. Therefore, in this analysis, we limited expansion of sex hormone levels to estradiol and testosterone. The previous report did not differentiate ER+ from ER− breast cancer. The associations of estradiol and testosterone with overall breast cancer were similar in this and the previous report.

With an average of 10 years of follow-up after blood was drawn, this study indicates that testosterone and estradiol levels predict a woman's risk of ER+ breast cancer well into the future. The predictive value of these levels may be even stronger for cancer that develops within a few years of measurement. Other strengths of the study include its prospective design and very complete follow-up of participants. Nevertheless, it has several limitations. The participants were Caucasians ages ≥65 years and the results may not apply to non-Whites and younger postmenopausal women. However, about half of breast cancer, however, occurs in women ages ≥65 years (34). We might have underestimated the predictive value of a few risk factors that require distant recall of events, such as age at menamhe. We did not ask about breast biopsies and so we were unable to calculate a Gail risk score. We made only one baseline measurement of sex hormones, but the correlation between single measurements 2 years apart have moderately high correlations for testosterone (r = 0.9) and estradiol (r = 0.7; ref. 35). Thus, our single measurement may have led us to underestimate the true association between serum concentrations of estradiol and testosterone and risk of breast cancer. We did not assess the effects of progesterone receptor type because we had too few cases that were positive for one but negative for the other type of receptor. We did not collect data about a history of breast cancer in second degree relatives so we cannot determine whether family history in these relatives would be associated with the risk of ER+ breast cancer. Finally, this study had too few cases of ER− breast cancer to meaningfully assess the potential relationship between sex hormone levels and risk of ER− cancer.

We conclude that in older postmenopausal women, testosterone concentration and education but not family history or conventional risk factors are strong predictors of risk of ER+ breast cancer. If confirmed, our results suggest that measuring testosterone may be useful for identifying older women who would benefit most from chemoprevention that reduces the risk of ER+ breast cancer.

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Since the acceptance of this article, Misser et al. published findings from the Nurse's Health Study, showing that estradiol, testosterone, androstenedione, and DHEAS were stronger predictors of ER+ than ER− breast cancer. [S.A Misser et al. Endogeneous estrogen, androgen, and progesterone concentrations and breast cancer risk among post menopausal women. JNCI 2004;96:1856-65.]

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