



Report

## Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database

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**Key words:** age-specific rates (or risks), breast cancer model, estrogen receptor $\alpha$ , prognostic factors

### Summary

**Background.** Researchers question whether estrogen receptor $\alpha$ -negative (ERN) and -positive (ERP) represent different stages of one disease or different breast cancer types.

**Objective.** To further examine ER $\alpha$  phenotypes, we stratified incident tumor characteristics in the Surveillance, Epidemiology, and End Results (SEER) Database ( $n = 82,488$ ) by ERN and ERP.

**Methods.** Study variables included black–white race, age-at-diagnosis, and standard incident tumor characteristics. These characteristics were arbitrarily dichotomized into good versus poor prognostic factor groups, for example, good (tumor size  $\leq 2.0$  cm, negative axillary lymph nodes, and good histologic grade) versus poor (tumor size  $> 2.0$  cm, positive nodes, and poor grade). Age frequency density plots were generated from the corresponding age-at-diagnosis frequency histograms. Average annual age-specific incidence rates (or risks) were adjusted to the 1970 United States standard female population.

**Results.** Age frequency density plots demonstrated bimodal premenopausal and postmenopausal breast cancer populations. ERN was correlated with premenopausal disease, black race, and poor prognostic factor groups, whereas ERP was associated with postmenopausal disease, white race, and favorable tumor characteristics. ERN rates increased premenopausally and then flattened to a nearly constant level after 50 years of age. ERP risk rose for most of a woman's lifetime with the greatest risk occurring between 75 and 79 years.

**Conclusions.** ER $\alpha$  exhibited bimodal age frequency distribution with a dichotomous pattern for age-specific rates, racial, and prognostic factor profiles. Menopause had a greater effect on ERN than ERP. Possible implications for breast carcinogenesis and cancer prevention are discussed in the text.

### Introduction

Although ER $\alpha$  is an acknowledged prognostic and predictive factor for established breast cancer [1], its relevance as a risk (or etiologic) factor is less certain. Most researchers believe that breast carcinogenesis is a multistep process [2], extending from a disease that remains local throughout its course to one that is systemic when first detectable [3]. In this one-disease model, breast tumors arise in ERP epithelium that evolves to ERN [4]. An alternate one-disease hypothesis proposes that ERN is the progenitor for ERP [5]. However, other evidence indicates that ER $\alpha$

phenotypes are fixed, exhibiting stability of the nuclear DNA content [6–8] and ER $\alpha$  status [9, 10]. Furthermore, gene expression patterns suggest that ERN and ERP phenotypes might develop from separate stem cells [11, 12].

In a previous population-based survey of white women with node-negative breast cancer, we suggested that joint estrogen receptor $\alpha$  and progesterone receptor $\alpha$  (ERPR) age frequency distribution seemed consistent with two breast cancer types [13]. We subsequently evaluated joint ERPR age frequency distributions for eight racial/ethnic groups, demonstrating that ER $\alpha$  could delineate racial subgroups [14]. In

this analysis, we have expanded our initial frequency-based observations to include average annual age-specific ER $\alpha$  rates, age-adjusted to a standard US female population. Results suggested bimodal breast cancer populations with a complex dichotomous relationship between age-specific rates, ER $\alpha$ , menopausal status, racial, and prognostic factor profiles.

## Material and methods

Breast cancer data were obtained from the National Cancer Institute's (NCI) SEER Cancer Incidence Public-Use CD-ROM 1973–1998, August 2000 submission. This analysis was restricted to Black and White women with infiltrating ductal carcinoma and known ER $\alpha$ . SEER was established in 1973 but did not record ER $\alpha$  until 1990 and had no standard definition or centralized laboratory to determine hormone receptor expression. Depending on the assay utilized, ER $\alpha$  was coded as either present (positive, ERP) or absent (negative, ERN).

SEER's original ASCII 'breast.txt' file ( $n = 385,689$ ) was sequentially filtered for the following:

1. Total breast cancer records that were accrued during the period of ER $\alpha$  collection, that is, 1990–1998 ( $n = 177,819$ );
2. Female sex ( $n = 176,706$ );
3. Black and white race ( $n = 164,766$ );
4. Infiltrating ductal carcinoma of no special type (NST) [15], SEER histologic codes 8010–8011, 8140–8141, and 8500 ( $n = 105,932$ ):
  - (a) ERN ( $n = 20,526$ );
  - (b) ERP ( $n = 61,962$ );
  - (c) Unknown ER $\alpha$  ( $n = 23,444$ ; 22%).

We stratified incident tumor characteristics by ERN versus ERP. Tumor characteristics included age-at-diagnosis, tumor size, axillary nodal status, and histologic grade. Age and tumor size were analyzed as continuous and categorical variables. Cut-off points for age-related categorical variables were chosen to proxy premenopausal (<50 years) and postmenopausal ( $\geq 50$  years) status. Tumor characteristics were arbitrarily dichotomized into favorable (or good) versus poor prognostic factor groups. Good tumor size cut point was  $\leq 2.0$  cm versus  $> 2.0$  cm for the poor group. Axillary node status was coded as negative (good) versus positive (poor). Histopathologic

grading conformed to the *International Classification of Diseases for Oncology – 2<sup>nd</sup> Edition*: Grade I – well differentiated, Grade II – moderately differentiated, Grade III – poorly differentiated, and Grade IV – Undifferentiated [16]. We combined grades I and II versus grades III and IV into good and poor prognostic groups, respectively.

For the calendar period of ER $\alpha$  collection (1990–1998), average annual age-specific breast cancer incidence rates were adjusted to the 1970 US standard female population. Age frequency density plots were constructed with 1-year age increments utilizing a 'smoothing' method of the corresponding age-at-diagnosis frequency histogram [13]. Area under the curve included 100% of the breast cancer records. The vertical axis for each density plot represented smoothed estimates of the density (or proportion, where density  $\times 100 =$  percent) of patients who developed breast cancer at the corresponding age-at-diagnosis on the horizontal axis.

Univariate and multivariate associations were estimated with odds ratios, 95% confidence intervals, and  $p$ -values. Logistic regression was used to derive adjusted odds [17]. Kaplan–Meier [18] product-limit method estimated breast cancer-specific survival. Stratified log rank test compared ERN versus ERP breast cancer survival [19]. Cox [20] proportional hazard model generated unadjusted and adjusted hazard ratios for study variables, expressed as relative risk of death. All  $p$ -values were two-sided.  $p$ -values of  $\leq 0.05$  were considered to be statistically significant.

## Results

ERN versus ERP comprised 24.9% versus 75.1% of known ER $\alpha$  (Table 1). Patients with ERN were significantly younger than were those with ERP, that is, 56.9 versus 63.3 years ( $p < 0.0001$ ). Mean tumor size was significantly larger for ERN versus ERP, that is, 2.5 cm versus 2.0 cm ( $p < 0.0001$ ). Nearly 37% of women <50 years of age had ERN (7324 of 19,797 women), whereas only 21% of women  $\geq 50$  years had ERN (13,202 of 62,691 women). More precisely, ERN% decreased from 36.9 to 21.1% for premenopausal and postmenopausal surrogates, respectively.

ERN% was charted in 5-year age group intervals (Figure 1). Except for ages 20–24 years, ERN% was greater for black than for white women. ERN% for black women rose until 35–39 years of age, compris-

Table 1. Descriptive statistics by estrogen receptor expression (ER), where ER-negative (ERN) is compared to ER-positive (ERP)

ER expression	ERN	ERP	<i>p</i> -value			
Sample size ( <i>n</i> = 82,488)	20,526	61,962				
Row percent (%)	24.9	75.1				
Mean age (yrs)	56.9	63.3	< 0.0001			
Mean tumor size (cm)	2.5	2.0	< 0.0001			
<i>Univariate model</i>						
Variable	Sample size	Column (%)	Sample size	Column (%)	Unadjusted odds ratio	95% CI
<b>Race</b>						
Black	2735	13.3	3818	6.2	2.34	2.22–2.47
White	17791	86.7	58144	93.8	1.00	
<b>Age-at-diagnosis</b>						
< 50 yrs (premenopausal)	7324	35.7	12473	20.1	2.20	2.13–2.28
≥ 50 yrs (postmenopausal)	13202	64.3	49489	79.9	1.00	
<b>Tumor size</b>						
> 2.0 cm (poor)	8502	41.4	17873	28.8	1.86	1.80–1.93
≤ 2.0 cm (good)	10287	50.1	40323	65.1	1.00	
Unknown	1737	8.5	3766	6.1		
<b>Lymph nodes</b>						
Positive (poor)	7040	34.3	17887	28.9	1.28	1.24–1.33
Negative (good)	11680	56.9	38065	61.4	1.00	
Unknown	1806	8.8	6010	9.7		
<b>Histologic grade</b>						
Poor	12577	61.3	17305	27.9	5.02	4.83–5.21
Good	4923	24.0	34000	54.9	1.00	
Unknown	3026	14.7	10657	17.2		
<i>Multivariate model</i>						
Variable	Comparison	Adjusted odds ratio*	95% CI			
Race	Black versus white	1.94	1.82–2.10			
Age-at-diagnosis	< 50 versus ≥ 50 years	1.80	1.72–1.88			
Tumor size	> 2.0 cm versus ≤ 2.0 cm	1.31	1.26–1.37			
Lymph nodes	Positive versus negative	0.86	0.83–0.90			
Histologic grade	Poor versus good	4.48	4.29–4.67			

Key: yrs, years; cm, centimeters; 95% CI, 95% confidence interval.

\*Adjusted odds ratio was derived with logistic regression, the logit estimator compared ERN to ERP.

ing 58% of ERα and then decreased to approximately 20% at ≥85 years. For all ages, ERN% for white women was inversely related to age-at-diagnosis, decreasing from 52% between 20 and 24 years to 15% at ≥85 years.

Univariate descriptive statistics were arranged in contingency tables to demonstrate the odds of ERN

versus ERP for having a given characteristic relative to the reference variable with an assigned value of 1.00 (Table 1). ERN was directly correlated (unadjusted odds ratio > 1.00) with the premenopausal surrogate, black race, and poor tumor characteristics, that is, tumor size > 2.0 cm, positive nodal status, and poor histologic grade. On the other hand, ERP was

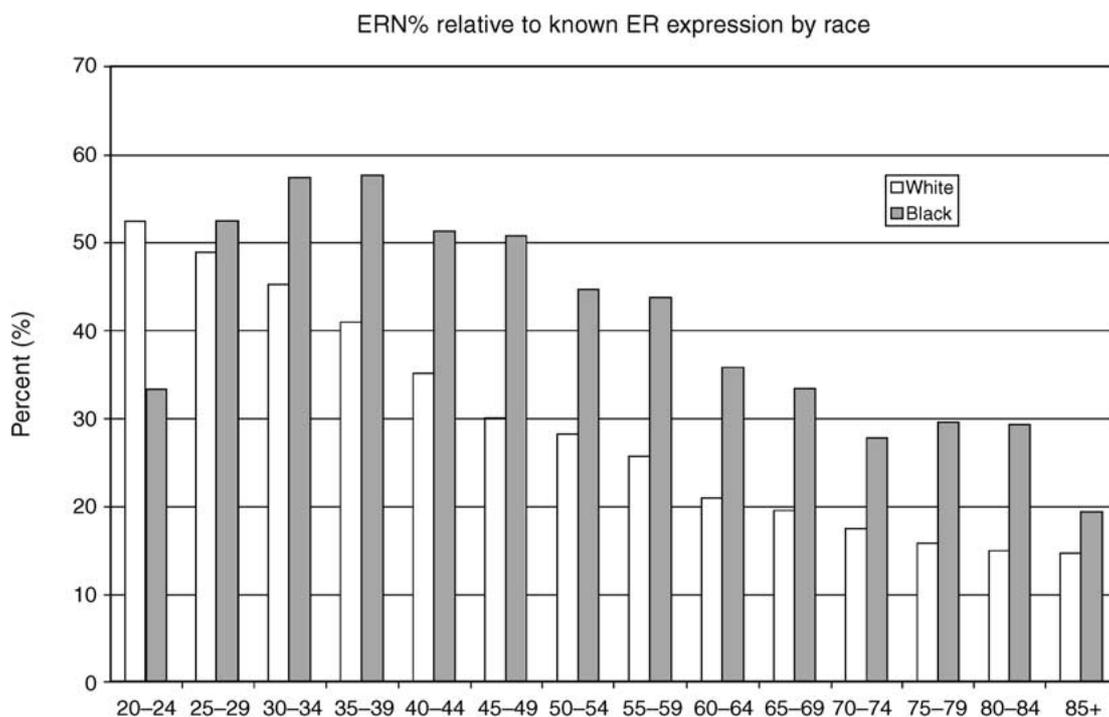


Figure 1. Percent of estrogen receptor $\alpha$ -negative (ERN%) relative to overall estrogen receptor $\alpha$  (ER $\alpha$ ). ERN% was plotted in 5-year age group intervals for black and white race.

correlated with the postmenopausal surrogate, white race, and good prognostic factor groups. All univariate correlations were highly statistically significant ( $p < 0.0001$ ). Unadjusted and adjusted associations were concordant, except for axillary lymph nodes. As previously noted by Clark et al. [21], we did not observe a consistent relationship between ER $\alpha$  and nodal status. ERN was associated with node-positive in the univariate model (odds ratio = 1.28; 95% CI = 1.24–1.33) and negative axillary lymph nodes in the multivariate model (odds ratio = 0.86; 95% CI = 0.83–0.90).

Survival analysis confirmed that ER $\alpha$  was an independent prognostic factor for breast cancer survival. Kaplan–Meier product-limit method demonstrated worse actuarial survival for ERN than for ERP (log rank test,  $p < 0.0001$ ). Cox proportional hazard model showed greater relative risk (RR) of breast cancer death for ERN (RR = 2.63,  $p < 0.0001$ ). ERN remained an independent predictor for cancer-specific mortality after adjusting for menopausal status, race, tumor size, axillary lymph nodes, and histologic grade.

Overall ER $\alpha$  rates displayed two rising trends that were parted by a brief midlife decline (Figure 2a). The

first trend was present from 30 to 50 years of age, after which a second trend with a slower rate continued for most a woman's remaining lifetime with the greatest risk occurring between 75 and 79 years. The brief midlife break in rates has been termed Clemmesen's hook [22], purportedly coinciding with the female climacteric. Age frequency density plots demonstrated bimodal breast cancer population with early and late modes of 50 and 69 years, respectively (Figure 2b). Anderson [23] demonstrated that Clemmesen's menopausal hook in rates corresponded to the sharp dip between the bimodal peaks of the age frequency histogram.

Age-specific rates (Figure 3) and age frequency distribution (Figure 4) were stratified by ER $\alpha$  and race. ERP rates rose continuously until approximately 80 years (Figure 3). For all ages, ERP rates were generally greater than ERN rates. ERP rates for black women were greater than for white women up to 30–34 years of age at which time there was an ethnic cross-over [24, 25]. ERN rates rose during the premenopausal period and then flattened to a constant value after 50 years. Except for ages 20–24 years, ERN rates were greater for blacks than for whites, also see Figure 1.

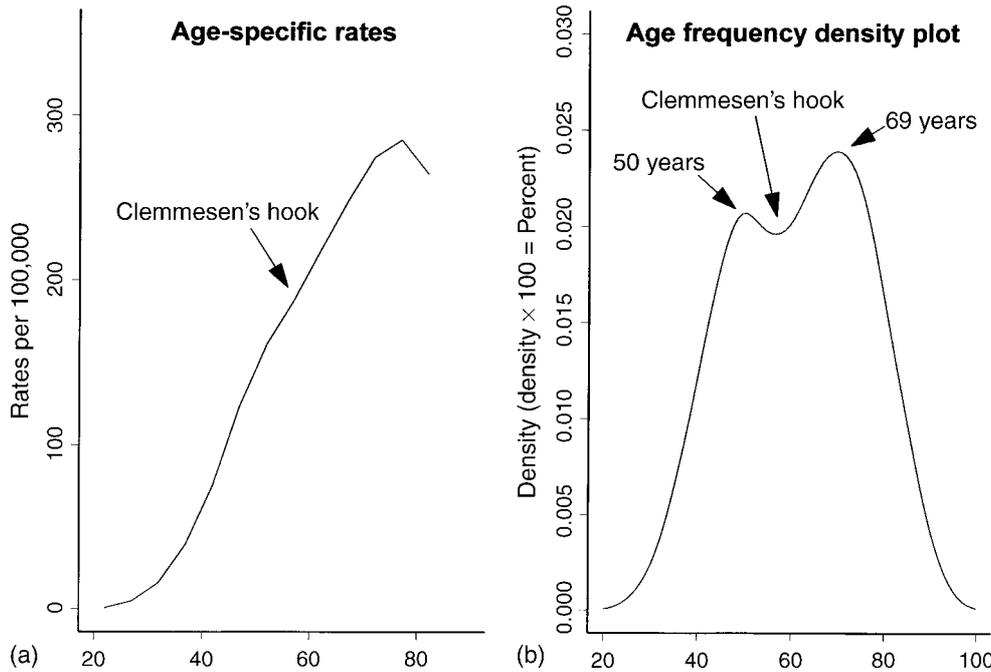


Figure 2. Breast cancer rates and age frequency distribution for known estrogen receptor $\alpha$ . (a) From 1990 to 1998, average annual age-specific rates (rates) were age adjusted to the 1970 United States standard female population. Rates demonstrated two rising trends, which were divided by Clemmesen's menopausal hook. (b) Age frequency density plots were constructed with 1-year age increments utilizing the corresponding age frequency histogram. The vertical axis for each density plot represented estimates of the density, where density multiplied by 100 equaled the percent of total breast cancer records. Area under the curve contained 100% of breast cancer records ( $n = 82,488$ ). The sharp dip between the bimodal peaks corresponded to the mid-life dip in rates, that is, Clemmesen's hook.

Age frequency density plots demonstrated bimodal breast cancer populations for ER $\alpha$  and race (Figure 4). Edwards et al. [26] previously noted that black and white racial groups in the SEER database followed a bimodal age frequency distribution with distinct forms of histologically indistinguishable breast cancer. In this analysis, age frequency distribution for ERP and white race were nearly identical as were the curves for ERN and black race. ERP and white women displayed a predominant postmenopausal breast cancer population, whereas ERN and black women comprised a dominant premenopausal group.

## Discussion

We, as well as many other researchers, have noted a strong correlation between ER $\alpha$ , age-at-onset, racial, and prognostic factor profiles. However, the relationship between ER $\alpha$  rates and menopause is a relatively recent observation. In the Danish Breast Cancer Cooperative Group, Yasui and Potter [27] demonstrated four age-specific risk patterns for joint ER $\alpha$  and

progesterone receptor expression, that is, ER+PR+, ER+PR-, ER-PR+, and ER-PR-. Menopause had a greater impact on joint ER-(ER-PR+ and ER-PR-) than on ER+(ER+PR+ and ER+PR-) phenotypes. Using joint ERPR from the SEER database, Tarone and Chu [5] confirmed this provocative result. We analyzed race, continuous, and dichotomized standard tumor characteristics by ER $\alpha$  to further examine this potentially important observation.

The single most significant risk factor for sporadic epithelial cancer is biologic aging. Nearly 50 years ago, Armitage and Doll [28, 29] noted a linear log-log relationship for cancer incidence and age-at-diagnosis. However, while most epithelial tumors exhibited a single linear trend for age-specific rates, breast cancer displayed not one but two rising trends [30]. In Figure 2a, the first trend from 30 to 50 years was followed by a brief decline, after which a second slower trend increased until approximately 80 years of age. Coined Clemmesen's hook, the brief midlife decline in rates coincided with our menopausal surrogate and the bimodal dip of the age frequency histogram (Figure 2b). When cancer incidence was stratified by

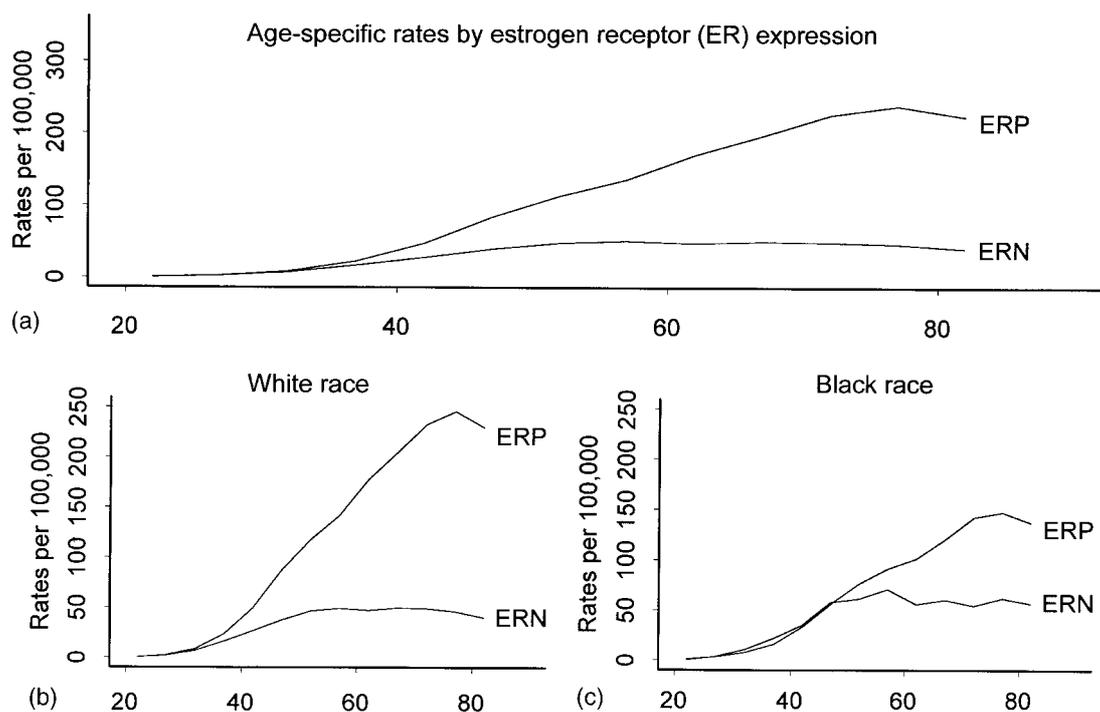


Figure 3. Average annual age-specific rates were stratified by estrogen receptor $\alpha$ -positive (ERP) and -negative (ERN) for total ER $\alpha$ , white and black race. (a) For total ER $\alpha$ , ERP rates rose continuously with the greatest risk occurring between 75 and 79 years. ERN rates increased during the premenopausal period, but then flattened to a constant value after 50–54 years. (b) White race had a greater proportion of ERP and less ERN than did black women. (c) Black race had a smaller amount of ERP and larger component of ERN than did white women.

ER $\alpha$  and race, ERP rates rose continuously (Figure 3). ERN rates increased premenopausally and then flattened to a nearly constant risk near our menopausal surrogate of 50 years.

Peto and Mack [31] noted similar dichotomous age-specific risk for sporadic and familial breast cancer, that is, sporadic rates increased continuously, whereas familial rates increased rapidly to a constant risk prior to menopause. We suspect bifunctional etiologies for dichotomous risks where rising and flat rates result from active and spent etiologic mechanisms, respectively [28, 29]. Similar to most sporadic epithelial cancers, ERP seemingly results from accumulated life long carcinogenic insults, irrespective of menopausal status. On the other hand, ERN – like familial breast cancer – is apparently dependent upon the estrogen-enriched endogenous microenvironment of the premenopausal period.

It might seem counterintuitive for ERN to be dependent while ERP is independent of menopausal status. However, the distinction between tumor initiation and cancer promotion/progression may account for this apparent paradox. It takes 20 years or more

for tumorigenesis to result in clinical epithelial cancer [32]. Initiating carcinogenic events are far upstream and very possibly unrelated to those genetic changes that promote cancer progression [33]. Theoretically, hormone-dependent carcinogenesis could initiate an ERN progenitor with the capacity for autonomous hormone-independent promotion/progression [5, 34]. On the other hand, a hormone-independent genetic alteration could produce a stem cell with an ER $\alpha$  that is hypersensitive to estrogenic promotion/progression [35]. However, regardless of the precise etiologic mechanism, the impact of menopause on ERP and ERN raises practical concerns regarding the timing of cancer prevention.

For example, tamoxifen chemoprevention remains problematic. In the seminal Breast Cancer Prevention Trial (BCPT), tamoxifen prevented the annual rate of ERP by 69% (RR = 0.31; 95% CI = 0.22–0.45) during the treatment period but had no effect upon ERN [36, 37]. However, 60% of the BCPT participants were  $\geq 50$  years of age. Whether tamoxifen given at a younger age would have prevented ERN could not be determined. On the other hand,

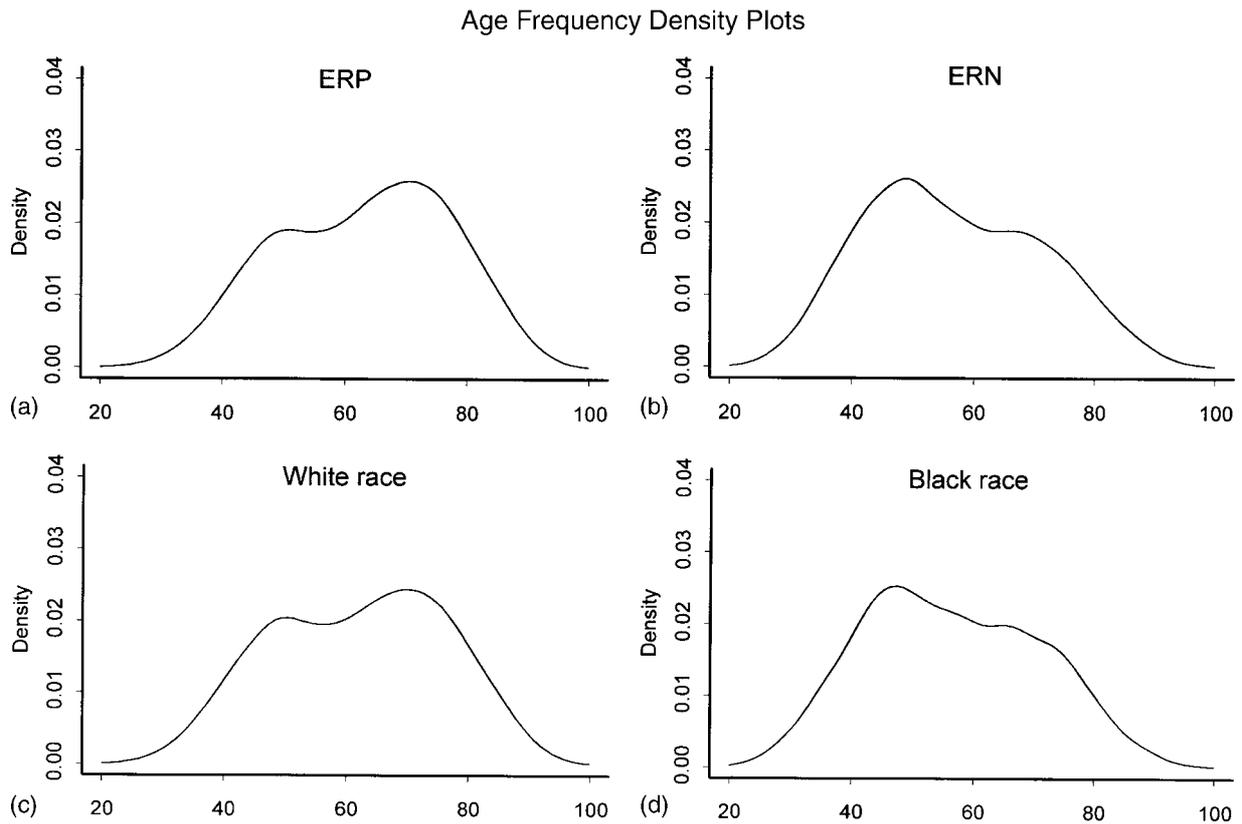


Figure 4. Age frequency density plots stratified by estrogen receptor $\alpha$ -positive (ERP) and -negative (ERN), white and black race. Age frequency distributions were virtually identical for ERP and white women as were the age frequency density plots for ERN and black women. (a) Estrogen receptor $\alpha$ -positive (ERP). (b) Estrogen receptor $\alpha$ -negative (ERN). (c) White race. (d) Black race.

a recent case-control study reported reduced occurrence of contralateral breast cancer in women with BRCA1 by 62% (OR = 0.38; 95% CI = 0.19–0.74) [38]. Limited ER data were available in this study; albeit, it is generally acknowledged that BRCA1 tumors are usually ERN [39, 40]. Unlike the BCPT age frequency distribution, nearly 90% of the case-control participants were < 50 years of age. Possibly, the case-control study prevented early-onset ERN, whereas the BCPT treated late-onset ERP. The BCPT may not have prevented ERN simply because tamoxifen was administered too late in the carcinogenic process. Indeed, experimental evidence suggests that tamoxifen can interfere with both tumor initiation and promotion/progression [41, 42]. Furthermore, if tamoxifen and oophorectomy are nearly equivalent in premenopausal breast cancer treatment [43, 44]; and if premenopausal oophorectomy is effective in preventing BRCA1 tumors [45], then tamoxifen may prevent ERN if administered early in life. This hypo-

thesis would be best tested in a randomized clinical trial.

This analysis has several caveats. (1) Conclusions drawn from bimodal age frequency distribution are potentially flawed by the age distribution of the population at risk. Consequently, we supplemented age frequency density plots with age-specific rates. However, the natural history of breast cancer incidence is now distorted by mammography and it may be difficult to ever determine the true underlying pattern of age-specific rates. Population-based observational studies are also retrospective, and although patterns of age-specific rates may suggest provocative carcinogenic mechanisms, most are untested [46]. Additional prospective studies deserve further attention, that is, risk factor stratification by ER $\alpha$ , gene expression patterns by ER $\alpha$ , etc. A distinction should be made between early and late carcinogenic events. (2) Some researchers have suggested that the SEER population may not be representative of the American breast

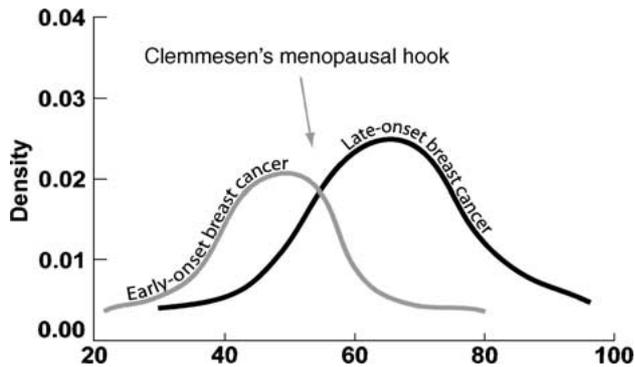


Figure 5. Conceptualized bimodal age frequency distribution for early-onset (premenopausal) and late-onset (postmenopausal) breast cancer, where the two patterns of age-specific risk correspond to two probabilistic normally distributed (bell-shaped) curves.

cancer population-at-large [47]. ER $\alpha$  assays were not carried out in one centralized laboratory and there was a relatively large amount of unknown ER $\alpha$  (22%). Nonetheless, we derived comfort from the fact that SEER's ER $\alpha$  distribution was very similar to other databases, that is, ERN% and ERP% were approximately 20 and 80%, respectively [21].

Notwithstanding the concerns noted, dichotomous age-specific rates suggested a complex relationship between ER $\alpha$  and menopause, which was counterintuitive to a simple multistep model of ERP to ERN tumor promotion/progression. Paradoxically, menopause had a greater impact on ERN than ERP. Bimodal age frequency distribution implied that dichotomous risks were distributed between two breast cancer populations [26, 48–50], conceptualized as early- and late-onset probabilistic bell-shaped curves (Figure 5). First reported in 1930 [51], bimodal female breast cancer populations have been observed in African [52], Asian [53], Italian [54], European and American female cohorts [49] but have not been reported in other female epithelial cancers [22, 23, 55] or in male breast cancer [56, 57].

The similarity between ER $\alpha$ , sporadic, and familial breast cancer rates may provide important etiologic clues. Rising premenopausal and then constant postmenopausal rates imply that ERN and many familial breast cancers are dependent upon premenopausal hormonal interactions, which end abruptly at approximately 50 years. Subsequent constant postmenopausal rates are possibly due to the time delay between premenopausal cancer initiation and postmenopausal tumor promotion/progression. On the other hand, ERP seemingly results from a lifetime of

exposure to sporadic carcinogenic insults, irrespective of menopausal status.

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