

The greater impact of menopause on ER– than ER+ breast cancer incidence: a possible explanation (United States)

Robert E. Tarone^{1,*} & Kenneth C. Chu²

¹*Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892, USA;* ²*Center to Reduce Cancer Health Disparities, National Cancer Institute, Bethesda, MD 20892, USA (*Author for correspondence)*

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Abstract

Objective: Analysis of 3359 Danish breast cancer cases indicated that menopause exerted a greater protective effect on estrogen-receptor negative (ER–) breast cancer than on estrogen-receptor positive (ER+) breast cancer. We examined US age-specific breast cancer rates by hormone receptor status in white and black women and men to investigate this unexpected result.

Methods: Age-specific breast cancer incidence rates from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute were analyzed by joint estrogen receptor and progesterone receptor (ER/PR) status of 101,140 white female and 8870 black female cases and by ER status in 706 white male and black male cases diagnosed from 1992 to 1998. Changes in the rate of increase in rates with age were identified using Poisson regression analyses.

Results: For both white women and black women the age-specific rates of ER– breast cancer cease increasing after 50 years of age, but age-specific rates of ER+ breast cancer continue to increase after 50 years of age. For men the incidence of ER– cancers may increase at a slower rate than incidence of ER+ cancers in older ages. In women the black rates of ER+ cancers are greater than white rates only until age 35, but black rates of ER– cancers are greater than white rates for all ages.

Conclusions: Differences in age-specific breast cancer incidence patterns by hormone receptor status are similar for black women and white women. The incidence pattern for ER– cancers is consistent with a paracrine model for hormone-stimulated growth in normal breast tissue. The continued increase in ER+ cancers after menopause may be explained by both the paracrine growth model and an increase in the proliferation rate of ER+ cells with age.

Introduction

Yasui and Potter showed that the pattern of age-specific breast cancer incidence rates differs by joint estrogen receptor and progesterone receptor (ER/PR) status using estimated incidence rates based on 3359 Danish cases [1]. In log–log regression analyses of incidence rate versus age the rates increased significantly at young ages for all ER/PR groups, but there was heterogeneity in the direction of the incidence curves in older ages. In older women the rates increased significantly, but at a slower rate than in young women, for ER+/PR+ cancers; increased slightly, but not significantly, for ER+/PR– cancers; decreased significantly for ER–/PR+ cancers;

and decreased slightly, but not significantly, for ER–/PR– cancers. The greater protective effect for menopause on receptor-negative cancers, particularly ER– cancers, was unexpected, and suggests a complex relationship between menopause and breast cancer risk [1]. Yasui and Potter suggested that international differences in the age-specific incidence curves might be explained by differences in the distribution of breast cancers by hormone receptor status [1].

Given the potential etiologic significance of the reported differences in age-specific incidence patterns by hormone receptor status, we sought confirmation in both white women and black women using incidence data from the Surveillance, Epidemiology and End

Results (SEER) Program of the National Cancer Institute. ER and PR status are available in the SEER Program, beginning with breast cancers diagnosed in 1990 [2]. We analyzed the 5-year age-specific breast cancer rates by joint ER/PR status for white females and black females to identify changes in the slope of rates plotted against age on a log–log scale. In addition, to adjust age effects for birth cohort and calendar period trends, age–period–cohort analyses were performed for ER+ and ER– cancers for white females. Breast cancer rates for US males were also examined to identify any changes in the rate of increase of breast cancer incidence with age for ER+ and ER– cancers.

Materials and methods

Rates of invasive breast cancer were calculated from population-based data collected by the SEER Program [3]. The percentage of cases with known hormone receptor status increased markedly in the first two years of ER and PR data collection. In addition, two SEER registries were added in 1992. Thus, we analyzed data for white female and black female breast cancer cases diagnosed from 1992 through 1998 among residents of the 11 geographic areas included throughout this time period in SEER: Connecticut; Hawaii; Iowa; New Mexico; Utah; Atlanta, GA; Detroit, MI; Seattle–Puget Sound, WA; San Francisco–Oakland, CA; Los Angeles, CA; and San Jose/Monterey, CA [3].

The ER and PR status were coded by the SEER Program data collectors based on laboratory results as reported in patient medical records [3]. Hence, determinations of hormone receptor status reflect community practice and standards in each SEER area. Immunohistochemical assays would have been the most commonly used tests during the study period, and thus the ER results would largely reflect expression of ER- α [4]. Joint ER/PR status was known for 101,140 white female cases and 8870 black female cases. ER status was available for 105,510 white female cases, 9291 black female cases, and 706 white male and black male cases.

Poisson regression analyses were applied to female rates by hormone receptor status to quantify and compare changes in the slope of the log rate with log age using a method similar to that of Yasui and Potter [1]. In these regression analyses the midpoint of the five-year age group was taken to be the age corresponding to each rate. Changes in slope were evaluated at the midpoint of each age group, and the results were reported for the age group resulting in the smallest deviance. Analyses included 12 five-year age groups from 25 through 84 years of age.

Female breast cancer rates are greatly influenced by birth cohort and calendar period trends [5, 6]; thus cross-sectional patterns of age-specific rates may reflect trends in risk by birth cohort or calendar period [1]. To adjust the age effects for variation by calendar period and birth cohort, age–period–cohort models were fitted by Poisson regression to the female breast cancer incidence data using 1-year age and calendar period intervals [7, 8]. Interpolation was employed to obtain 1-year population estimates from the 5-year age groups available in SEER [8]. One-year age groups from 26 through 83 years of age for the years 1992 through 1998 were used in the age–period–cohort analyses. Changes in the slope of linear trends in age effects were examined using identifiable parameters defined as differences in linear contrasts [8]. Standard errors of the linear contrasts were adjusted for possible over-dispersion when the deviance for the full age–period–cohort model exceeded the number of residual degrees of freedom [9].

Results

The numbers and percentages of SEER breast cancers for females and males by hormone receptor status are reported in Table 1. Joint ER/PR status was available for 74% of white women and 65% of black women, while ER status was available for 77% of white women, 68% of black women, 70% of white men, and 62% of black men. Hormone receptor status was more likely to be unknown for both smallest (<1 cm) and largest (>5 cm) tumors, and more likely to be unknown for cases under 35 or over 70 years of age at diagnosis. The distribution by hormone receptor status for US white women was remarkably similar to that for the Danish women [1], the largest difference being 2.2% fewer US women with ER–/PR+ cancers. Black US women, however, had a significantly different distribution by hormone receptor status ($p < 10^{-6}$ compared to either US white women or Danish women), with fewer ER+/PR+ and more ER–/PR– cancers. Both black men and white men had a much higher percentage of ER+ cancers than women, and ER– cancers were significantly more likely in black men than in white men ($p = 0.0009$).

The log–log plots of age-specific incidence rates by joint ER/PR status for women are shown in Figure 1, and estimates of initial and final slopes are presented in Table 2. The curves for white women and black women have similar shapes for every ER/PR expression combination. For all ER/PR expression categories, rates increase significantly until about 50 years of age, and then the slopes of the curves decrease significantly in older ages. Rates continue to increase significantly in

Table 1. Number and percentage of US breast cancers by hormone receptor status from 1992 to 1998; percentages based on total with known hormone status

(a) Females

Race	Total	Known receptor status	ER+PR+		ER+PR-		ER-PR+		ER-PR-	
			No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
White	137,210	101,140	64,982	64.2	13,167	13.0	3,416	3.4	19,575	19.4
Black	13,634	8,870	4,290	48.4	1,071	12.1	456	5.1	3,053	34.4

(b) Males

	Total	Known receptor status	ER+		ER-	
			No.	Percentage	No.	Percentage
White	900	633	575	90.8	58	9.2
Black	117	73	56	76.7	17	23.3

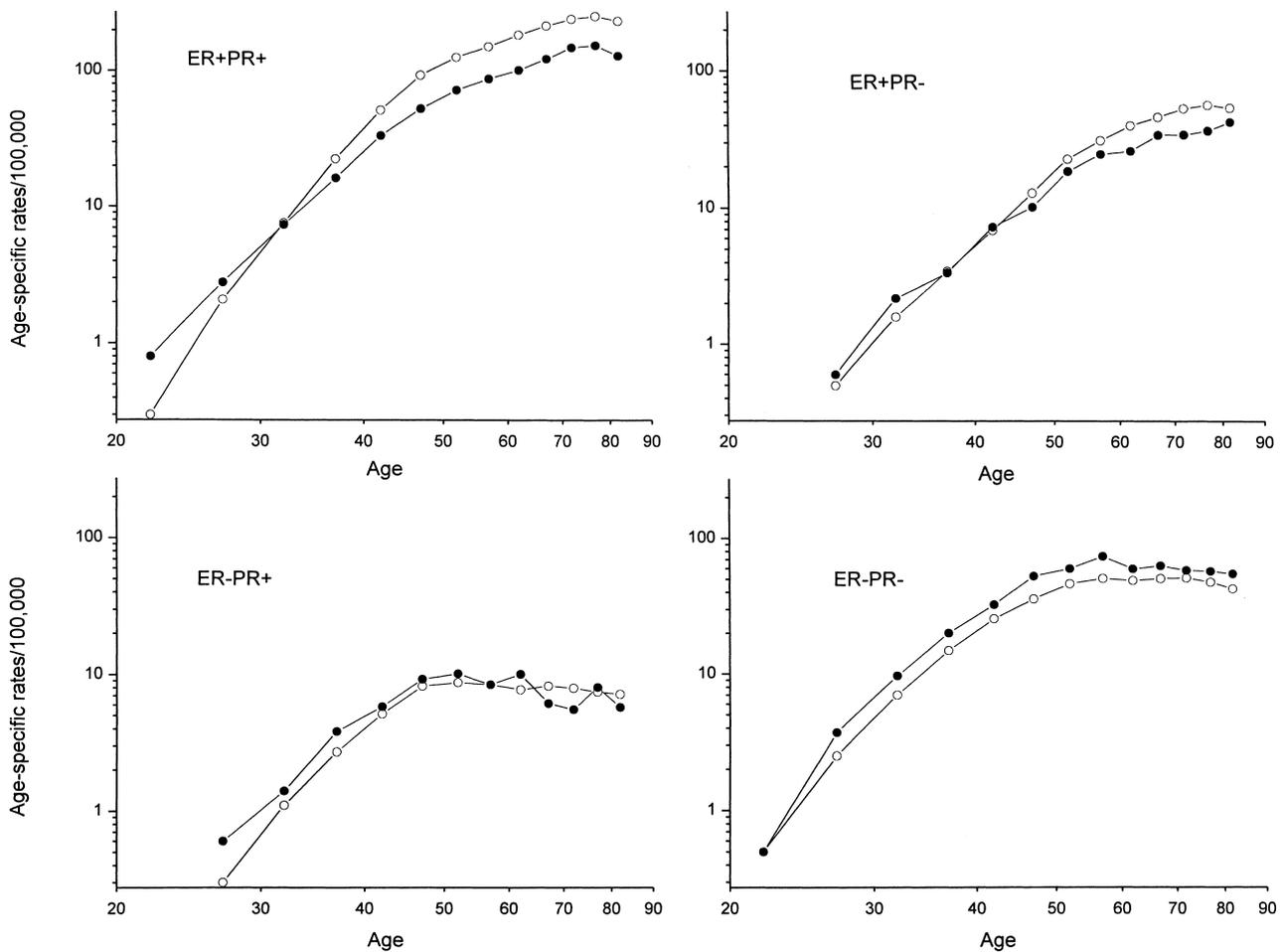


Fig. 1. The 5-year age-specific breast cancer incidence rates for white women (open circle) and black women (closed circle) from 25 through 84 years of age by joint estrogen and progesterone receptor status of breast cancer.

older ages for ER+PR+ and ER+PR- cancers, but rates show no evidence of an increase in older ages for ER-PR- and ER-PR+ cancers.

Figure 2 shows the SEER age-specific rates for ER+ and ER- breast cancers. Rates of ER- cancers are higher for black women at every age. Rates of ER+

Table 2. The fits of log rate–log age linear regression models with one change point to the SEER incidence rates by hormone receptor status

	Age of change	Initial slope ^a	Slope after change	p-Value ^b
<i>White</i>				
ER+PR+	47	6.6	1.8	<0.0001
ER+PR-	57	5.3	1.5	<0.0001
ER-PR+	47	5.3	-0.3	0.01
ER-PR-	52	4.0	-0.2	0.31
ER+	47	6.7	1.9	<0.0001
ER-	47	4.8	0.3	0.14
PR+	47	6.5	1.7	<0.0001
PR-	52	4.4	0.8	<0.0001
<i>Black</i>				
ER+PR+	47	5.4	1.9	<0.0001
ER+PR-	57	4.5	1.3	<0.0001
ER-PR+	47	4.9	-0.9	0.005
ER-PR-	47	4.8	0.1	0.51
ER+	52	4.8	1.6	<0.0001
ER-	47	4.8	0.01	0.94
PR+	47	5.3	1.7	<0.0001
PR-	52	4.1	0.1	0.50

^a Initial slope significantly different from zero with *p*-value < 0.0001.
^b The *p*-values are for the comparison of the final slope to zero.

cancers are initially lower in white women, but are higher in white women over 40 years of age. For both white women and black women there are sharp increases in incidence rates with age before age 50 for both ER+ and ER- breast cancers (Figure 2). For both white women and black women rates do not increase signif-

icantly after age 50 for ER- cancers, while the rates for ER+ cancers continue to increase significantly, although with a significantly smaller slope than for younger women (Table 2). This difference in the shape of the age-specific incidence curve between ER+ and ER- cancers above the age of 50 was observed in all 11 SEER registries, for all stages and grades of cancer, and for both ductal and lobular carcinomas (data not shown).

The age effects from age–period–cohort analyses of ER+ and ER- cancers in white women are shown in Figure 3. The difference in shape between the ER+ and ER- age-specific incidence rate curves shown in Figure 2 is still apparent after adjustment for calendar period or birth cohort trends. For each age-effect curve the rate of increase in risk begins to decrease significantly in the late 30s. The decreases in age effects after age 70 partly reflect the increase in unknown receptor status at oldest ages. The age effects for black women were much more variable than those for white women, particularly for ER- cancers, but also demonstrated that the difference in shape between ER+ and ER- incidence curves is not due to calendar period or birth cohort trends (data not shown).

The age-specific rates for ER+ and ER- breast cancers for males are shown in Figure 4 for ages 40 through 84 (only 24 male breast cancers were diagnosed in men under the age of 40). Although caution is required in comparing these curves because of the small number of ER- cancers, it appears that the curve for ER- cancers may increase at a slower rate than the curve for ER+ cancers in older ages, just as was the case for female cancers.

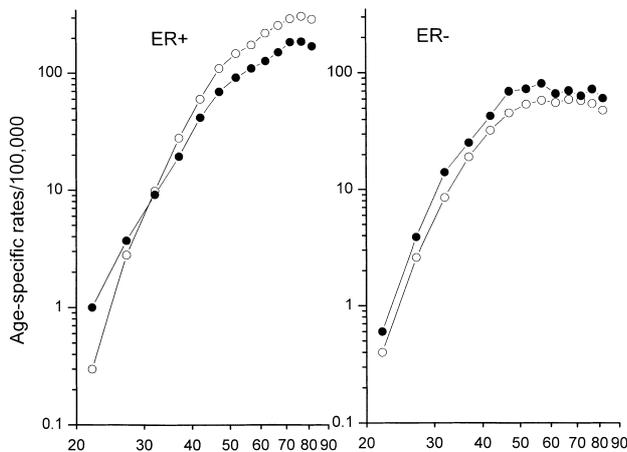


Fig. 2. The 5-year age-specific breast cancer incidence rates for white women (open circle) and black women (closed circle) from 25 through 84 years of age by estrogen receptor status of breast cancer.

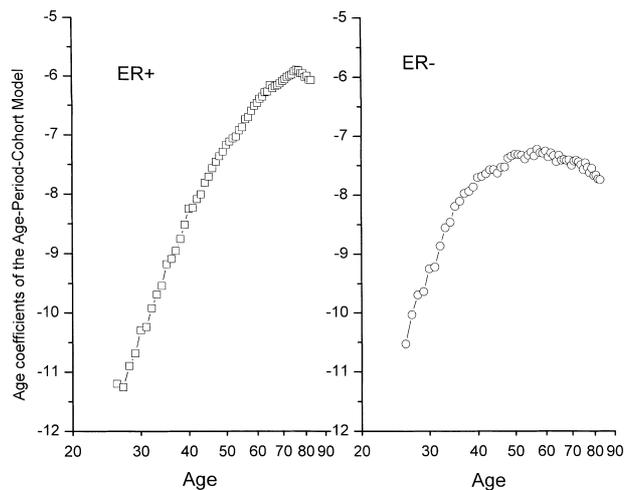


Fig. 3. Estimated age effects for white women from age–period–cohort analyses of 1-year breast cancer incidence rates for ages 26–83 by estrogen receptor status.

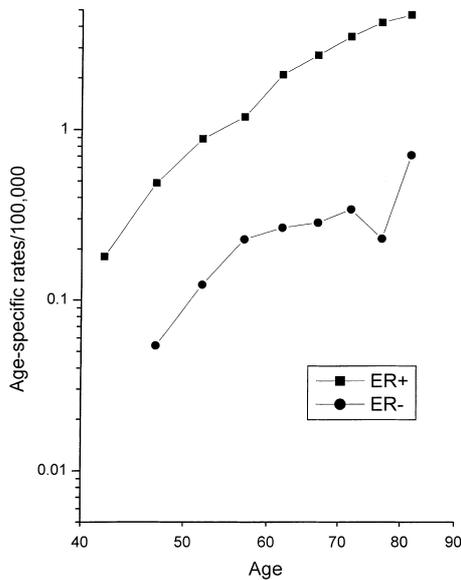


Fig. 4. The 5-year age-specific breast cancer incidence rates for black and white US men from 40 through 84 years of age by estrogen receptor status of breast cancer.

Discussion

The age-specific incidence curves by joint ER/PR expression status for US women are qualitatively similar to those for Danish women [1], but show important quantitative differences. For example, the US incidence rates for ER+/PR- cancers increase significantly after menopause, and the increase in older ages is almost as rapid as that for ER+/PR+ cancers. In addition, the sharp decrease after menopause in rates for ER-/PR+ cancers observed in Danish women was not seen in US women, although slight decreases were observed for both black women and white women (marginally significant for both). Finally, the initial increase in rates of ER-/PR- cancers is almost as rapid as those observed for the other three ER/PR categories. The SEER data confirm, however, that patterns of age-specific rates differ by hormone receptor status [1] and, in particular, corroborate the greater impact of menopause on ER- cancers than on ER+ cancers.

The greater effect of menopause on incidence rates for ER- breast cancer than on ER+ breast cancer in women may appear to be paradoxical [1], but examination of the relationship between ER expression and proliferation in normal breast tissue, suggests a possible explanation. In normal premenopausal breast tissue, less than 10% of cells express ER on average [10–14]. An even smaller percentage of cells in normal breast tissue are proliferating at any time [14–16]. The observation that the population of cells expressing ER and the

population of dividing cells are almost mutually exclusive led to the suggestion that estrogen controls division of ER- stem cells via a paracrine mechanism; ER+ cells act as estrogen sensors, transmitting growth factors to ER- precursor cells [15–18].

It is likely that all breast cancers contain some cells that express ER, but the classification of cancers as ER+ is based on some minimum level of ER expression, with considerable variation among studies in the choice of the threshold level [19]. The percentage of tumor cells expressing ER varies widely, but for most ER+ cancers the percentage lies between 20% and 80% [15, 20]. Thus, in terms of the percentage of cells expressing ER, ER- cancers are much more like normal, premenopausal breast tissue than are ER+ cancers. A recent examination of the expression level of 8102 genes revealed that the overall gene expression patterns of ER- cancers are much more similar to normal breast tissue expression patterns than are those of ER+ cancers [21]. If the proliferation of cells in intermediate lesions in the development of ER- cancers is, as in normal breast tissue, dependent on the estrogen-modulated paracrine growth signal from ER+ cells (either in the developing tumor or in the adjacent normal breast tissue), then the large drop in estrogen levels after menopause may lead to a cessation of growth of ER- intermediate lesions, or even a reduction in the number of intermediate cells [22]. The incidence rate of ER- breast cancers would cease to increase with age after menopause under this model, because of the stable or diminishing pool of intermediate cells. Presumably, the final transformation step in an intermediate cell results in ER- cancer, with hormone-independent, autonomous growth.

The continuing increase with age after menopause in the incidence of ER+ cancers may also be explained, at least in part, by the suggested paracrine model for growth of intermediate lesions. Intermediate lesions with large numbers of ER+ cells may have a growth advantage in the postmenopausal breast [23]. Even in the low-estrogen environment after menopause, there may be sufficient production of growth factors in such lesions to support continued division of ER- cells. In addition, the percentage of proliferating ER+ cells increases somewhat after menopause [11, 14, 24–26], and is higher in proliferative breast lesions than in normal breast tissue [14, 26, 27]. That is, the increase in ER+ cancers with age probably also reflects, to some extent, increased division of ER+ cells. There are, however, almost never more ER+ dividing cells than ER- dividing cells in proliferative lesions in the breast [14, 26, 27], and limited data suggest that this may also be true for most cancers; ER- cells had higher proliferation rates than ER+ cells in ten of 14 ER+ breast

cancers examined [28]. Thus, although increased division of ER+ cells almost certainly contributes to the large number of cancers classified as ER+ (because the classification is based on exceeding a fixed, low threshold value for ER expression), the division of ER- cells appears to be important even in the growth of ER+ cancers.

The observed variation in the percentage of ER+ cells in breast tumors appears to reflect, at least in part, variation in ER expression in normal tissue, as previously suggested based on studies of tumor and normal tissue from breast cancer patients [24]. Indeed, there is a positive association between the level of ER expression in tumor tissue and normal breast tissue from breast cancer patients [25, 29, 30]. The percentage of normal breast cells expressing ER increases after menopause [11, 13, 14, 31, 32], as does the percentage of ER+ breast cancers. The percentage of normal breast cells expressing ER is much lower in Japanese women than Caucasian women [33], consistent with the lower percentage of ER+ cancers in Japanese women [1, 34, 35]. A higher percentage of normal breast cells express ER in men than in women [13], men also have a higher percentage of ER+ cancers (Table 1). ER+ cells are concentrated in the luminal epithelial cells and appear to be absent in myoepithelial and stromal cells in normal breast tissue [10, 12, 13, 36], ER+ cancers have gene expression patterns similar to luminal epithelial cells, while ER- cancers have gene expression patterns similar to myoepithelial cells [21]. All of these associations suggest that the ER status of a cancer may be determined, at least in part, by the local ER expression characteristics of the tissue in which the tumor originates. Thus, consideration of factors related to variation in ER expression in normal breast tissue may shed light on the wide variation of ER expression in breast cancers.

The slope of the age-effect curves from the age-period-cohort analyses decreased in the late 30s for both ER- and ER+ cancers. The decreases are highly significant for both ER+ and ER- cancers. The timing of the decrease may coincide with the onset of lobular involution, which begins well before menopause [37]. It has been suggested that abnormal involution may play a role in breast cancer etiology [38, 39], and there is evidence for ethnic variation in the age of onset of involution [40]. Thus, differences between white and black women in the hormone receptor status of breast cancers may reflect, at least in part, racial differences in the process of involution. The smaller slope for ER- cancers than ER+ cancers in older men was unexpected; the implications of such a difference, if confirmed, are unclear.

Although the distribution of cancers by hormone receptor status in a population will undoubtedly have a profound effect on the shape of the age-specific incidence curve for that population (cf. Figures 1 and 2), it seems unlikely that the decrease in age-specific breast cancer rates with age in older Japanese women is completely explained by the lower percentage of ER+PR+ cancers in Japan [1]. Over half of Japanese cancers are ER+ [34, 35], and our results show that the age-specific rates for both ER+PR+ and ER+PR- cancers increase significantly above 50 years of age. If the patterns of age-specific rates by ER status for Japanese women are similar to those for white women and black women in the US, then the slight decrease in ER- incidence rates in women over the age of 50 would not compensate for the larger increase in ER+ cancers to produce a decrease in rates for all breast cancers in older women.

The main strength of our study is the large population-based sample of breast cancer cases for both white women and black women. A potential weakness is that hormone receptor status was obtained from community laboratories, and thus was obtained using different methods and different threshold levels. The difference between ER+ and ER- cancers in the rate of increase in age-specific rates after menopause was observed in all 11 SEER locations, however, indicating that this difference is robust to laboratory variation. In addition, the distribution of breast cancers in white US women by joint ER/PR status was virtually identical to the distribution in Danish women assayed in a single laboratory [1]. Hormone receptor status was not available for all cases, but there is no reason to think that the absence of hormone receptor information in medical records would depend on hormone receptor status. Hormone receptor status was more likely to be missing in women under 35 or over 70 years of age, but the difference in the shape of the age-specific curves by hormone receptor status is evident even when the youngest and oldest women are excluded from consideration. We could not adjust directly for differences in known breast cancer risk factors, and since some risk factors are known to have very different impact in old women than young women, differences attributed to age could reflect differences in risk factors (*e.g.* different childbearing practices in old and young women). The difference in risk pattern by age for ER+ and ER- cancers was unaffected by adjustment for birth cohort and calendar period, however, suggesting that the difference is primarily age-related.

The wide variation in percentage of cells expressing ER, both among women for normal breast tissue and among cancers, raises questions about the usefulness of

the ER+/ER- dichotomization of tumors in etiologic investigations [1]. The dichotomous classification of cancers as strictly ER+ or strictly ER- based on a low threshold level of ER expression has clinical utility, and can be interpreted as defining a relatively stable phenotype [41]. The dichotomous classification encourages the consideration of ER status as a clonal characteristic; however, it is, in fact, a quantitative characteristic with extreme variation [20]. The quantitative nature of ER expression should be taken into account in analyses of epidemiologic studies.

There are questions about whether breast cancers with different hormonal receptor status have different risk factors [1]. Examination of all studies that have investigated risk factors for breast cancers by ER receptor status show few differences between risk factors for ER+ and ER- cancers [42–51]. The factor which shows the strongest evidence for a possible interaction by ER status is parity. Subgroup analyses are difficult to interpret because of the increased likelihood of false-positive results, but while nulliparity is consistently a risk factor for ER+ breast cancers, the association between nulliparity and risk of ER- breast cancer is less clear. In four studies that could be stratified by both menopausal status and ER status, nulliparity appeared to be protective for ER- cancers in postmenopausal women in three [42, 43, 49], but not the fourth [46]. The possibility that risk factors differ by hormone receptor status, including possibly PR receptor status, deserves further investigation.

References

1. Yasui Y, Potter JD (1999) The shape of age-incidence curves of female breast cancer by hormone-receptor status. *Cancer Causes Control* **10**: 431–437.
2. SEER (2001) *SEER*Stat, ed (4.0). Cancer incidence public-use database, 1973–1998, August 2000 submission*. Bethesda, MD: National Cancer Institute.
3. Fritz A, Ries L (1998) *The SEER Program Code Manual*, 3rd edn. Bethesda, MD: National Cancer Institute, NIH Publication No. 99–2313.
4. Gustafsson J-A, Warner M (2000) Estrogen receptor β in the breast: role in estrogen responsiveness and development of breast cancer. *Steroid Biochem Mol Biol* **74**: 245–248.
5. MacMahon B (1958) Cohort fertility and increasing breast cancer incidence. *Cancer* **11**: 250–254.
6. Stevens RG, Moolgavkar SH, Lee JA (1982) Temporal trends in breast cancer. *Am J Epidemiol* **115**: 759–777.
7. Tarone RE, Chu KC (1992) Implications of birth cohort patterns in population disease rates. *J Natl Cancer Inst* **84**: 1402–1410.
8. Tarone RE, Chu KC (1996) Evaluation of birth cohort patterns in population disease rates. *Am J Epidemiol* **143**: 85–91.
9. McCullagh P, Nelder JA (1989) *Generalized Linear Models*, 2nd edn. London: Chapman & Hall.
10. Petersen OW, Hoyer PE, van Deurs B (1987) Frequency and distribution of estrogen receptor-positive cells in normal, nonlactating human breast tissue. *Cancer Res* **47**: 5748–5751.
11. Jacquemier JD, Hassoun J, Torrente M, Martin P-M (1990) Distribution of estrogen and progesterone receptors in healthy tissue adjacent to breast lesions at various stages – immunohistochemical study of 107 cases. *Breast Cancer Res Treat* **15**: 109–117.
12. Ricketts D, Turnbull L, Ryall G, et al. (1991) Estrogen and progesterone receptors in the normal female breast. *Cancer Res* **51**: 1817–1822.
13. Shoker BS, Jarvis C, Sibson DR, Walker C, Sloane JP (1999) Oestrogen receptor expression in the normal and pre-cancerous breast. *J Pathol* **188**: 237–244.
14. Shoker BS, Jarvis C, Clarke RB, et al. (1999) Estrogen receptor-positive proliferating cells in the normal and precancerous breast. *Am J Pathol* **155**: 1811–1815.
15. Clarke RB, Howell A, Potten CS, Anderson E (1997) Dissociation between steroid receptor expression and cell proliferation in the human breast. *Cancer Res* **57**: 4987–4991.
16. Russo J, Ao X, Grill C, Russo IH (1999) Pattern of distribution of cells positive for estrogen receptor α and progesterone receptor in relation to proliferating cells in the mammary gland. *Breast Cancer Res Treat* **53**: 217–227.
17. Anderson E, Clarke RB, Howell A (1998) Estrogen responsiveness and control of normal human breast proliferation. *J Mammary Gland Biol Neoplasia* **3**: 23–35.
18. Russo J, Russo IH (1999) Cellular basis of breast cancer susceptibility. *Oncol Res* **11**: 169–178.
19. Khan SA (1995) Estrogen and progesterone receptors in benign breast epithelium. *Breast J* **4**: 251–261.
20. Nicholson RI, Bouzubar N, Walker KJ, et al. (1991) Hormone sensitivity in breast cancer: influence of heterogeneity of oestrogen receptor expression and cell proliferation. *Eur J Cancer* **127**: 908–913.
21. Perou CM, Sorlie T, Eisen MB, et al. (2000) Molecular portraits of human breast tumours. *Nature* **406**: 747–752.
22. Moolgavkar SH (1986) Hormones and multistage carcinogenesis. *Cancer Surv* **5**: 635–648.
23. Israel L, Band P (1984) Hormones as cancer growth factors. *Lancet* **2**: 843–844.
24. Walker KJ, McClelland RA, Candlish W, Blamey RW, Nicholson RI (1992) Heterogeneity of oestrogen receptor expression in normal and malignant breast tissue. *Eur J Cancer* **28**: 34–37.
25. Khan SA, Rogers MAM, Khurana KK, Meguid MM, Numann PJ (1997) Estrogen receptor expression in benign breast epithelium and breast cancer risk. *J Natl Cancer Inst* **89**: 37–42.
26. Shoker BS, Jarvis C, Clarke RB, et al. (2000) Abnormal regulation of the oestrogen receptor in benign breast lesions. *J Clin Pathol* **53**: 778–783.
27. Iqbal M, Davies MPA, Shoker BS, Jarvis C, Sibson DR, Sloane JP (2001) Subgroups of non-atypical hyperplasia of breast defined by proliferation of oestrogen receptor-positive cells. *J Pathol* **193**: 333–338.
28. Ballare C, Bravo AI, Laucella S, et al. (1989) DNA synthesis in estrogen receptor-positive human breast cancer takes place preferentially in estrogen receptor-negative cells. *Cancer* **64**: 842–848.
29. Netto GJ, Cheek JH, Nannepaga YZ, et al. (1990) Steroid receptors in benign mastectomy tissue. *Am J Clin Pathol* **94**: 14–17.
30. Khan SA, Rogers MAM, Obando JA, Tamsen A (1994) Estrogen receptor expression of benign breast epithelium and its association with breast cancer. *Cancer Res* **54**: 993–997.

31. Boyd MT, Hildebrandt RH, Bartow SA (1996) Expression of the estrogen gene in developing and adult human breast. *Breast Cancer Res Treat* **37**: 243–251.
32. Bartow SA (1998) Use of the autopsy to study ontogeny and expression of the estrogen receptor gene in human breast. *J Mammary Gland Biol Neoplasia* **3**: 37–48.
33. Lawson JS, Field AS, Champion S, Tran D, Ishikura H, Trichopoulos D (1999) Low oestrogen receptor α expression in normal breast tissue underlies low breast cancer incidence in Japan. *Lancet* **354**: 1787–1788.
34. Nomura Y, Kobayashi S, Takatani O, Sugano H, Matsumoto K, McGuire WL (1977) Estrogen receptor and endocrine responsiveness in Japanese versus American breast cancer patients. *Cancer Res* **37**: 106–110.
35. Nomura Y, Miura S, Koyama H, *et al.* (1992) Relative effect of steroid hormone receptors on the prognosis of patients with operable breast cancer. *Cancer* **69**: 153–164.
36. van Agthoven T, Timmermans M, Foekens JA, Dorssers LCJ, Henzen-Logmans SC (1994) Differential expression of estrogen, progesterone, and epidermal growth factor receptors in normal, benign, and malignant human breast tissues using dual staining immunohistochemistry. *Am J Pathol* **144**: 1238–1246.
37. Cowan DF, Herbert TA (1989) Involution of the breast in women aged 50 to 104 years: a histopathological study of 102 cases. *Surg Pathol* **2**: 323–333.
38. Henson DE, Tarone RE (1993) On the possible role of involution in the natural history of breast cancer. *Cancer* **71**: 2154–2156.
39. Henson D, Tarone RE (1994) Involution and the etiology of breast cancer. *Cancer* **74**: 424–429.
40. Hart BL, Steinbock RT, Mettler FA, Pathak DR, Bartow SA (1989) Age and race related changes in mammographic parenchymal patterns. *Cancer* **63**: 2537–2539.
41. Robertson JFR (1996) Oestrogen receptor: a stable phenotype in breast cancer. *Br J Cancer* **73**: 5–12.
42. Hildreth NG, Kelsey JL, Eisenfeld AJ, LiVolsi VA, Holford TR, Fischer DB (1983) Differences in breast cancer risk factors according to the estrogen receptor level of the tumor. *J Natl Cancer Inst* **70**: 1027–1031.
43. Hislop TG, Coldman AJ, Elwood JM, Skippen DH, Kan L (1986) Relationship between risk factors for breast cancer and hormonal status. *Int J Epidemiol* **15**: 469–476.
44. McTiernan A, Thomas DB, Johnson LK, Roseman D (1986) Risk factors for estrogen receptor-rich and estrogen receptor-poor breast cancers. *J Natl Cancer Inst* **77**: 849–854.
45. Stanford JL, Szklo M, Boring CC, *et al.* (1987) A case-control study of breast cancer stratified by estrogen receptor status. *Am J Epidemiol* **125**: 184–194.
46. Cooper JA, Rohan TE, Cant ELM, Horsfall DJ, Tilley WD (1989) Risk factors for breast cancer by oestrogen receptor status: a population-based case-control study. *Br J Cancer* **59**: 119–125.
47. Kreiger N, King WD, Rosenberg L, Clarke EA, Palmer JR, Shapiro S (1991) Steroid receptor status and the epidemiology of breast cancer. *Ann Epidemiol* **1**: 513–523.
48. Habel LA, Stanford JL (1993) Hormone receptors and breast cancer. *Epidemiol Rev* **15**: 209–219.
49. Potter JD, Cerhan JR, Sellers TA, *et al.* (1995) 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.
50. Yoo KY, Tajima K, Miura S, *et al.* (1997) Breast cancer risk factors according to combined estrogen and progesterone receptor status: a case-control analysis. *Am J Epidemiol* **146**: 307–314.
51. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG (2000) Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. *Am J Epidemiol* **151**: 703–714.