Short Communication

Geographic Excess of Estrogen Receptor-Positive Breast Cancer

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Abstract

**Elevated and more rapidly increasing breast cancer
incidence rates have been described for Marin County,
California (CA), a homogenous, high socioeconomic status
population for which yearly surveillance is facilitated by
its status as a county. The present study evaluates the
histology and hormonal phenotype of the excess breast
cancer cases occurring in white, non-Hispanic women
living in Marin County between 1992 and 2000 and
compares them with patterns occurring in the rest of the
San Francisco Bay Area (SFBA) and other urban parts of
CA. Incidence data for invasive breast cancer histological
subtypes and estrogen receptor (ER) and progesterone
receptor (PR) status were obtained from the 1992–2000
Surveillance, Epidemiology, and End Results program.
Expected numbers for Marin County were computed
based on age-specific rates for five other SFBA counties.
Incidence rates were age-adjusted to the 2000 United
States standard. Marin County breast cancer diagnoses
during 1992–2000 compared with other SFBA and other
urban CA Surveillance, Epidemiology, and End Results
county rates for white, non-Hispanic women consisted of
a disproportionate increase in ER+/PR+ tumors. The
observed absolute excess (*versus* expected) numbers of
Marin County ER+/PR+ lobular and nonlobular
(predominantly ductal) cases were similar; however, the
relative increase appeared greatest for lobular breast
cancer. The progressive increase in breast cancer
incidence rates observed in Marin County over the past
decade is occurring in women with high prevalence of
risk factors predisposing toward excess development of
ER+/PR+ breast cancer.**

Introduction

Worldwide geographic variations in breast cancer incidence
rates have reached 10-fold, with overall rates (age-adjusted to
year 2000 United States female standard population) ranging
from 10 to 20 per 100,000 in many rural Asian populations to
>100 per 100,000 among white non-Hispanics (WNHs) living
in such urban California (CA) regions as Los Angeles and the
San Francisco Bay Area [SFBA (1, 2)]. Among these higher
risk geographic populations, residents of the northernmost and
demographically most homogeneous and affluent SFBA county
of Marin have become the focus of increasing epidemiological
attention over the past decade because of their progressive and
significant increase in breast cancer rates (3–7). Whereas some
of the extreme trends reported for Marin County in the 1990s
may be attributed to inaccurate population extrapolations from
the 1990 United States census, elevated incidence and mortality
rates and time trends for Marin County remain distinctive, and
all studies to date have indicated that (*a*) breast cancer inci-
dence and mortality patterns in Marin County are unlike those
in other urban CA counties and are largely confined to peri- and
postmenopausal women; and (*b*) these patterns are thought to
be largely explained by Marin County's unique demography
and higher prevalence of established socioeconomic and repro-
ductive breast cancer risk factors, rather than by any genetic
predisposition or excess familial risk within the population (4,
6, 7).

Epidemiological and medical concerns are now focused on
defining predisposing factors and biological features of breast
cancers arising in such high-risk geographic populations as
Marin County. In particular, contributions to the distinctive
breast cancer incidence patterns of factors such as health care
access, intensity or differing modalities of mammographic
screening, prevalence of long-term use of combined hormone
replacement therapy, and unknown environmental exposures to
potential breast carcinogens remain uncertain (5). Most nota-
bly, there have not been any studies to date describing the
histological, biological, or hormonal phenotype of breast can-
cers arising in Marin County or, to our knowledge, comparisons
of tumor phenotypes between other geographic regions in the
United States with significantly different breast cancer inci-
dence rates. Specific interest in the histological and hormonal
subtypes of Marin County breast cancers is driven in part by the
recently documented nationwide increase in lobular but not
ductal breast cancer incidence rates (8), the association between
combined hormone replacement therapy and increased lobular
breast cancer rates (9), and observed differences in the age-
specific incidence curves by hormonal phenotype for both
lobular and ductal breast cancers (10–12).

Surrogates of socioeconomic status, such as education and
income, are associated with marked geographic variations in
breast cancer rates but offer few biological clues to effective
breast cancer prevention or intervention strategies and do not
fully account for such established biological risk factors as
ethnicity, reproductive history, use of exogenous hormones, or
alcohol consumption (13). Moreover, the relationship between
reproductive and endocrine risk factors and development of any
specific hormonal phenotype of breast cancer remains contro-
versial (Ref. 14 and references therein). Thus, in an attempt to
better understand the biological features as well as the potential

carcinogenic process(es) underlying the distinctive breast cancer incidence patterns observed in the Marin County female population, we examined histological subtypes and hormonal phenotypes [estrogen receptor (ER)/progesterone receptor (PR) status] of all invasive breast cancers reported for Marin County, SFBA, and selected other urban CA counties over the past decade, with rates calculated using recently available population estimates based on 1990 and 2000 United States census information. It is expected that hormonal phenotyping of Marin breast cancer cases might also lead to better public health planning and community response, including the design of more specific breast cancer prevention strategies.

Materials and Methods

Sources of Data. All cancer incidence and population data were obtained from the Surveillance, Epidemiology, and End Results Program. Study was limited to the interval 1992–2000 because tumor ER/PR status and incidence information from Los Angeles and Monterey county registries are not available from Surveillance, Epidemiology, and End Results for years prior to 1992. All analyses were limited to WNH women diagnosed with invasive breast cancer (International Classification of Diseases—Oncology, 2nd edition, site codes 54.0–54.9). CA registries determine race/ethnic status from medical record review and comparison of patient surnames to standard lists of Hispanic surnames. For the purposes of this report and given the limited number of Marin County cases, all invasive breast cancers were subdivided into two groups: (*a*) lobular cases (International Classification of Diseases—Oncology, 2nd edition, morphology codes 8520 and 8522); and (*b*) nonlobular cases (all other morphology codes, including unknown histology, but primarily consisting of code 8500/ductal histology).

Statistical Methods. Age standardization of rates for each year or aggregated for the 1992–2000 interval were calculated by weighting age-specific rates by the proportions of the United States 2000 census female population in each age group. Expected numbers of cases in Marin County were calculated indirectly by applying age-specific rates for WNH females living in two reference groups, "other SFBA" consisting of five other SFBA counties (Alameda, Contra Costa, San Francisco, San Mateo, and Santa Clara) and selected "other urban CA" consisting of three other Surveillance, Epidemiology, and End Results-participating urban CA counties (Los Angeles, Monterey, and Santa Cruz), to the appropriate Marin County population estimates. A Poisson regression model was fit to the observed known ER/PR case counts and included histological type (lobular *versus* nonlobular), year of diagnosis, age (in 5-year age groups entered as a categorical rather than a continuous variable), and geographic location (Marin, other SFBA, or other urban CA). Cases with unknown ER/PR status were then allocated to an ER/PR category (*i.e.*, ER+/PR+, ER+/PR−, ER−/PR+, or ER−/PR−) according to the proportion of each predicted by the Poisson model. Predicted (expected) Marin County case counts for specific subtypes (*e.g.*, lobular and ER+/PR+) were calculated based on allocated cases and the resulting age-specific rates for the five other SFBA counties as described previously. Allocation in this manner was necessitated by the differing proportions of cases with unknown ER/PR status in different CA counties.

Results and Discussion

Increased Marin County Incidence Rates and Proportion of ER+/PR+ Breast Cancers of All Histological Types. Located north of San Francisco, Marin County is unique among other SFBA, urban CA, and United States counties because of its sociodemography: relatively small and homogeneous populace for an urban county (~250,000 persons, nearly 80% WNH); median home values, per capita income, and resident fraction over age 25 years with college degrees all exceeding twice that of the nation; and elevated rates of breast cancer first apparent more than 10 years ago (3–7). Table 1 shows the aggregate 1992–2000 breast cancer case numbers and updated population-based incidence rates for WNH women living in Marin County, other SFBA, and urban CA counties. Fig. 1*A* compares the age-specific Marin County, other SFBA, and urban CA county rates for all types of breast cancers arising during this 9-year interval and for each 5-year age group. When observed *versus* expected (O/E; based on other SFBA rates) Marin County breast cancer cases are compared for each 5-year age group between 40 and 89 years (data not shown), there is no apparent age-specific trend differing from the 1.07 weighted average in Marin County's relative excess (O/E = 1.07; *P* = 0.006). This lack of an age-specific trend potentially distinguishes the elevated breast cancer risk in this Marin County population from the excess, largely postmenopausal, breast cancer risk recently reported for a demographically similar cohort of 133,479 women in the California Teachers Study group, geographically dispersed across CA (15). Of interest, the excess breast cancer incidence among the California Teachers Study cohort has not yet been reported by histology or hormonal phenotype (15).

Fig. 1*B* shows the corresponding age-specific increase in the proportion of ER+/PR+ breast cancers of all histological types arising in Marin County, as compared with those arising in other SFBA and urban CA WNH women. Aggregated across all age groups for this interval there is a significant excess in O/E ER+/PR+ Marin breast cancer cases (O/E = 1.09; *P* = 0.001). In contrast, no significant geographic differences are observed in either the proportion or observed number of breast cancer cases for the other three hormonal phenotypes: ER+/PR−; ER−/PR+; and ER−/PR− (data not shown).

Increased Relative Risks for ER+/PR+ Lobular and Nonlobular Breast Cancers. United States Surveillance, Epidemiology, and End Results registry data confirm that age-specific incidence curves for ductal and all nonlobular breast cancers have not shifted significantly over the past decade (comprising 70–80% of all breast cancers). In contrast, lobular (including mixed ductal-lobular) breast cancer incidence rates have increased 1.65-fold (now comprising 16% of all breast cancers), and this increase has been highest among WNH women over age 45 years (Ref. 8; data not shown). Relative to ductal breast cancers, lobular breast cancers are more commonly ER+ (10); and ER+ breast cancers are known to account for the progressive increase in United States breast cancer incidence rates after age 45 years, with the higher risk subgroup of ER+/PR− breast cancers showing the greatest proportional increase in incidence rates in aging United States populations

Table 1   Marin, other San Francisco Bay Area (SFBA), and selected other urban California (CA) county breast cancer cases (years 1992–2000), population bases (year 2000, white non-Hispanic females), and year 2000 United States age-standardized incidence rates per 100,000 [95% confidence interval (CI)]

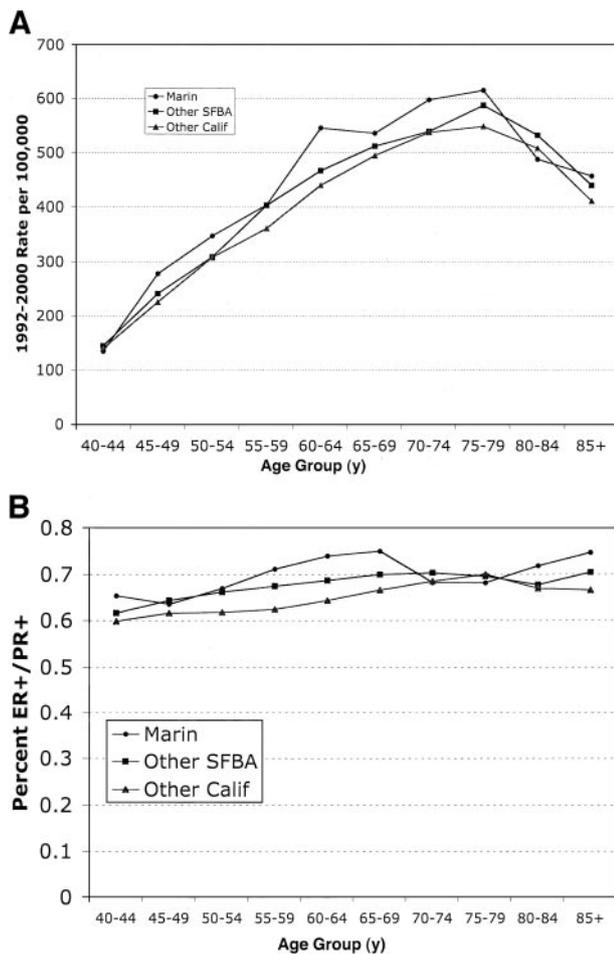|	Cases	Population base	Rate (CI)
Marin	2,017	102,491	171 (163–179)
Other SFBA	23,199	1,343,777	160 (158–163)
Other urban CA	31,335	1,738,512	153 (152–155)

Fig. 1. Age group-specific breast cancer incidence rates are shown for all invasive breast cancers (*A*) and the proportion of ER+/PR+ cases among all histological types with known ER/PR status (*B*) for Marin, other SFBA, and urban CA counties. Rates and cases include only WNH females diagnosed between 1992 and 2000, with age adjustment of county rates to the 2000 United States census.

(11). Given these age- and histology-specific general trends influencing the incidence of different breast cancer hormonal phenotypes, the O/E number of Marin breast cancer cases (1992–2000) was calculated for each of the four hormonal phenotypes dichotomized into lobular and nonlobular histological subgroups, with each subgroup age-standardized and adjusted for unknown ER and PR status cases as described above.

Fig. 2 shows that the statistically significant overall age-standardized excess (O/E) of breast cancer cases in Marin County as compared with the other SFBA counties is due to comparable absolute excesses (O − E) in lobular and nonlobular ER+/PR+ cases. As shown and because lobular breast cancers generally arise much less commonly than ductal cancers, the comparable absolute excess in observed lobular and nonlobular ER+/PR+ cases actually suggests that lobular cancers of this hormonal phenotype have the highest relative risk (O/E = 1.23; *P* = 0.001) and contribution to Marin County's increased breast cancer rates (Fig. 2, *inset*). Nonlobular ER+/PR+ breast cancers also show a significantly increased relative risk (O/E = 1.06; *P* < 0.05) within this geographic population, albeit quantitatively lower than that for lobular ER+/PR+ breast cancers. The smaller number of Marin County cases in

the other subgroups limited statistical ascertainment of significant O/E differences for the other hormonal phenotypes of breast cancer.

Risk Factors Associated with Specific Hormonal Phenotypes of Breast Cancer. Until this past decade, relatively little epidemiological attention had been paid to the histological and hormonal phenotypes associating with well-established breast cancer risk factors. Whereas specific forms of familial and hereditary breast cancers (*e.g.,* BRCA1) are associated with an age-specific incidence of predominantly ER− hormonal phenotype (16), and breast cancer histology and ER/PR hormonal phenotypes both show significantly different ethnic and racial preferences (12, 17), there remains considerable controversy about the association between any of the few human breast carcinogens (*e.g.,* radiation exposure) or well-established menstrual and reproductive breast cancer risk factors (*e.g.,* late menarche and age at first birth, nulliparity, late menopause, lactation history, and so forth) and development of a specific hormonal phenotype of breast cancer (14). Longitudinal studies have shown that, in the absence of exogenous hormonal use and even when controlled for other menstrual and reproductive risk factors, elevated endogenous blood sex steroid levels are strongly associated with postmenopausal breast cancer development and identify women most likely to benefit from the chemoprevention effects of selective ER modulators, strongly implicating increased endogenous sex steroid levels (particularly testosterone and estradiol) with the risk of developing ER+ breast cancer (18–20). However, whereas recent and longer duration use of hormone replacement therapy [especially in the form of estrogen/progestin combinations (CHRTs)] has definitively been associated with an increased incidence of postmenopausal breast cancers (21) and with a preferential increase in lobular cancers (8, 9), studies addressing the hormonal phenotype of CHRT-induced breast cancers have been contradictory to date (22–24).

Additional epidemiological risk factors specific for ER+ or ER+/PR+ breast cancer induction remain poorly described. Several studies, however, have now shown that education level and income directly correlate with breast tumor ER status independent of race/ethnic group, age, and other known breast cancer risk factors (17, 25–28). These socioeconomic correlations with breast tumor ER status raise important biological questions relevant to Marin County and sociodemographically similar populations and concerning unknown environmental and/or lifestyle factors that may selectively promote the induction of ER+ breast cancer.

Recent survey data suggest that there is no significant excess in mammographic screening or hormone replacement therapy/CHRT use by Marin County women over the past decade when compared with other CA women (29, 30). In contrast, this same self-reporting survey indicates that daily per capita alcohol consumption by Marin County female residents is significantly higher than state or nationwide averages (30) and probably also higher than that reported for the sociodemographically similar California Teachers Study cohort with its increased risk for postmenopausal breast cancer (15). In support of these limited data, a population-based case-control study conducted in Marin County between 1997 and 1999 found that despite similar distributions between cases and controls for most established breast cancer risk factors including socioeconomic status, increased alcohol consumption (≥2 drinks/day) was significantly and strongly associated (OR = 2.3) with breast cancer cases (7).

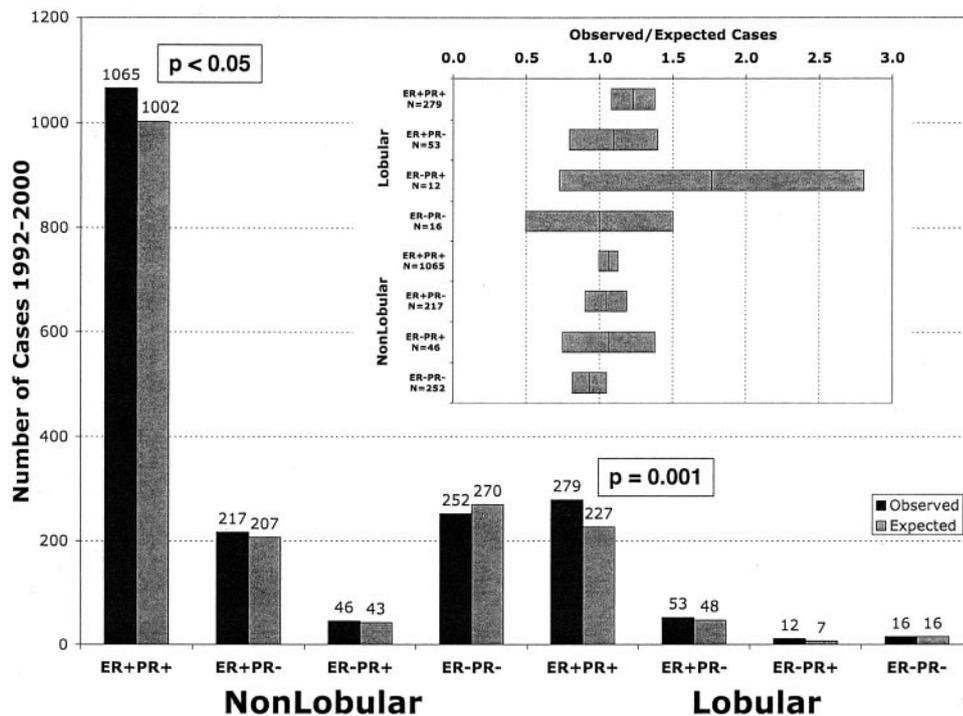Alcohol consumption has been the most consistently pos-

Fig. 2. Observed and expected breast cancer cases arising among Marin WNH females between 1992 and 2000 according to histological type (lobular or nonlobular) and ER/PR status. Observed and expected Marin case counts are shown above vertical bars for each histological and hormonal type of breast cancer. Expected counts are based on rates for other SFBA counties; both the observed and expected counts were corrected for unknown ER/PR cases as described in "Materials and Methods." Significant differences in O/E counts are apparent only for the ER+/PR+ phenotype of nonlobular ($P < 0.05$) and lobular ($P = 0.001$) Marin breast cancers. Inset graph shows relative risks as horizontal O/E bar values ($\pm 95\%$ confidence intervals) for each histological and ER/PR type of Marin breast cancer.

itive and dose-dependent dietary link associated with breast cancer risk in the epidemiological literature over the past two decades (1, 31). In keeping with the Marin case-control findings (7), recent midlife consumption of alcohol appears to confer greater risk than alcoholic consumption earlier in life (1). Breast cancer risk associated with alcohol has been documented across diverse populations and cultures and appears to synergize with other risk factors including CHRT (32). Alcohol has been shown to enhance cellular ER protein levels and specifically stimulate growth of ER+ breast cancer cells in culture (33), although its role in promoting breast cancer development has generally been attributed to its elevating effect on blood sex steroid levels in postmenopausal women (1). Of further relevance to Marin County's excess in breast cancers is additional epidemiological evidence indicating that alcohol selectively promotes development of ER+/PR+ breast cancers (34), although ER− breast cancer-promoting effects by alcohol have also been suggested in conjunction with low folate levels (35). The modifiable nature of this potentially key breast cancer risk factor, by abstinence from alcohol or perhaps dietary folate supplementation in populations at risk, compels more basic research efforts into defining alcohol's cellular and organismal breast cancer-promoting mechanisms. As well, large longitudinal outcome analyses must now be considered to address the broader public health question of risk *versus* benefit from moderate alcohol consumption in women such as those living in Marin County because the competing ill effects of alcohol on breast cancer morbidity and mortality may be outweighed by its potential protective effects against more prevalent and life-threatening cardiovascular diseases in these populations (1).

Acknowledgments

References

1. Willett, W. C., Rockhill, B., Hankinson, S. E., Hunter, D. J., and Colditz, G. A. Epidemiology and nongenetic causes of breast cancer. *In:* J. R. Harris, M. E. Lippman, M. Morrow., and C. K. Osborne (eds.), Diseases of the Breast, pp. 175–220. Philadelphia: Lippincott Williams & Wilkins, 2000.

2. Lacey, J. V., Jr., Devesa, S. S., and Brinton, L. A. Recent trends in breast cancer incidence and mortality. Environ. Mol. Mutagen., *39:* 82–88, 2002.

3. West, D. W., and Davis, T. E. Breast cancer incidence among women in the San Francisco and Monterey Bay areas. Greater Bay Area Cancer Registry Report, *3:* 1–4, 1991.

4. Prehn, A. W., and West, D. W. Evaluating local differences in breast cancer incidence rates: a census-based methodology (United States). Cancer Causes Control, *9:* 511–517, 1998.

5. Prehn, A. W., Clarke, C., Topol, B., Glaser, S., and West, D. Increase in breast cancer incidence in middle-aged women during the 1990s. Ann. Epidemiol., *12:* 476–481, 2002.

6. Clarke, C. A., Glaser, S. L., West, D. W., Ereman, R. R., Erdmann, C. A., Barlow, J. M., and Wrensch, M. R. Breast cancer incidence and mortality trends in an affluent population: Marin County, California, USA, 1990–1999. Breast Cancer Res., *4:* R13, 2002.

7. Wrensch, M., Chew, T., Farren, G., Barlow, J., Belli, F., Clarke, C., Erdmann, C. A., Lee, M., Moghadassi, M., Peskin-Mentzer, R., Quesenberry, C. P., Souders-Mason, V., Spence, L., Suzuki, M., and Gould, M. Risk factors for breast cancer in a population with high incidence rates. Breast Cancer Res., *5:* R88–R102, 2003.

8. Li, C. I., Anderson, B. O., Daling, J. R., and Moe, R. E. Trends in incidence rates of invasive lobular and ductal breast carcinoma. J. Am. Med. Assoc., *289:* 1421–1424, 2003.

9. Li, C. I., Weiss, N. S., Stanford, J. L., and Daling, J. R. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer (Phila.), *88:* 2570–2577, 2000.

10. Stierer, M., Rosen, H., Weber, R., Hanak, H., Spona, J., and Tuchler, H. Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer: correlation of histopathology and prognostic factors. Ann. Surg., *218:* 13–21, 1993.

11. Quong, J., Eppenberger-Castori, S., Moore, D., II, Scott, G. K., Birrir, M. J., Kueng, W., Eppenberger, U., and Benz, C. C. Age-dependent changes in breast cancer hormone receptors and oxidant stress markers. Breast Cancer Res. Treat., *76:* 221–236, 2002.

12. Chu, K. C., and Anderson, W. F. Rates for breast cancer characteristics by estrogen and progesterone receptor status in the major racial/ethnic groups. Breast Cancer Res. Treat., *74:* 199–211, 2002.

13. Gordon, N. H. Socioeconomic factors and breast cancer in black and white Americans. Cancer Metastasis Rev., *22:* 55–65, 2003.

14. Britton, J. A., Gammon, M. D., Schoenberg, J. B., Stanford, J. L., Coates, R. J., Swanson, C. A., Potischman, N., Malone, K. E., Brogan, D. J., Daling, J. R., and Brinton, L. A. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20–44 years of age. Am. J. Epidemiol., *156:* 507–516, 2002.

15. Bernstein, L., Allen, M., Anton-Culver, H., Deapen, D., Horn-Ross, P. L., Peel, D., Pinder, R., Reynolds, P., Sullivan-Halley, J., West, D., Wright, W., Ziogas, A., and Ross, R. K. High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). Cancer Causes Control, *13:* 625–635, 2002.

16. Loman, N., Johannsson, O., Bendahl, P. O., Borg, A., Ferno, M., and Olsson, H. Steroid receptors in hereditary breast carcinomas associated with BRCA1 or BRCA2 mutations or unknown susceptibility genes. Cancer (Phila.), *83:* 310–319, 1998.

17. Li, C. I., Malone, K. E., and Daling, J. R. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. Cancer Epidemiol. Biomark. Prev., *11:* 601–607, 2002.

18. Cauley, J. A., Lucas, F. L., Kuller, L. H., Stone, K., Browner, W., and Cummings, S. R. Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Study of osteoporotic fractures research group. Ann. Intern. Med., *130:* 270–277, 1999.

19. The Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J. Natl. Cancer Inst. (Bethesda), *94:* 606–616, 2002.

20. Lippman, M. E., Krueger, K. A., Eckert, S., Sashegyi, A., Walls, E. L., Jamal, S., Cauley, J. A., and Cummings, S. R. Indicators of lifetime estrogen exposure: effect on breast cancer incidence and interaction with raloxifene therapy in the Multiple Outcomes of Raloxifene Evaluation study participants. J. Clin. Oncol., *19:* 3111–3116, 2001.

21. Beral, V., Banks, E., and Reeves, G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. Lancet, *360:* 942–944, 2002.

22. Cobleigh, M. A., Norlock, F. E., Oleske, D. M., and Starr, A. Hormone replacement therapy and high S phase in breast cancer. J. Am. Med. Assoc., *281:* 1528–1530, 1999.

23. Chlebowski, R. T., Hendrix, S. L., Langer, R. D., Stefanick, M. L., Gass, M., Lane, D., Rodabough, R. J., Gilligan, M. A., Cyr, M. G., Thomson, C. A., Khandekar, J., Petrovitch, H., McTiernan, A., and Women's Health Initiative Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. J. Am. Med. Assoc., *289:* 3243–3253, 2003.

24. Li, C. I., Malone, K. E., Porter, P. L., Weiss, N. S., Tang, M-T., Cushing-Haugen, K. L., and Daling, J. R. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. J. Am. Med. Assoc., *289:* 3254–3263, 2003.

25. Miller, B. A., Hankey, B. F., and Thomas, T. L. Impact of sociodemographic factors, hormone receptor status, and tumor grade on ethnic differences in tumor stage and size for breast cancer in US women. Am. J. Epidemiol., *155:* 534–545, 2002.

26. Brawley, O. W. Disaggregating the effects of race and poverty on breast cancer outcomes. J. Natl. Cancer Inst. (Bethesda), *94:* 471–473, 2002.

27. Gordon, N. H. Association of education and income with estrogen receptor status in primary breast cancer. Am. J. Epidemiol., *142:* 796–803, 1995.

28. Thomson, C. S., Hole, D. J., Twelves, C. J., Brewster, D. H., and Black, R. J., on behalf of the Scottish Cancer Therapy Network. Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival. J. Epidemiol. Commun. Health, *55:* 308–315, 2001.

29. California Department of Health Services, Office of Women's Health. Data Points: Results from the 1997 Women's Health Survey: Menopause Related Symptoms and Use of Medical Care to Treat Them. Issue 1, Number 23, 1999.

30. County of Marin, Department of Health and Human Services. Marin Community Health Survey: Breast Cancer Risk Factors in Marin County Women, 2001. Vol. 1, Issue 1, May 2003.

31. Singletary, K. W., and Gapstur, S. M. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. J. Am. Med. Assoc., *286:* 2143–2151, 2001.

32. Chen, W. Y., Colditz, G. A., Rosner, B., Hankinson, S. E., Hunter, D. J., Manson, J. E., Stampfer, M. J., Willett, W. C., and Speizer, F. E. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. Ann. Intern. Med., *137:* 798–804, 2002.

33. Singletary, K. W., Frey, R. S., and Yan, W. Effect of ethanol on proliferation and estrogen receptor-α expression in human breast cancer cells. Cancer Lett., *165:* 131–137, 2001.

34. Enger, S. M., Ross, R. K., Paganini-Hill, A., Longnecker, M. P., and Bernstein, L. Alcohol consumption and breast cancer oestrogen and progesterone receptor status. Br. J. Cancer, *79:* 1308–1314, 1999.

35. Sellers, T. A., Vierkant, R. A., Cerhan, J. R., Gapstur, S. M., Vachon, C. M., Olson, J. E., Pankratz, V. S., Kushi, L. H., and Folsom, A. R. Interaction of dietary folate intake, alcohol, and risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. Cancer Epidemiol. Biomark. Prev., *11:* 1104–1107, 2002.

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