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 incidence 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 reproductive 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 notably, there have not been any studies to date describing the histological, biological, or hormonal phenotype of breast cancers 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 incidence 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 controversial (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 population 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. 1A 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).

Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases</th>
<th>Population base</th>
<th>Rate (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marin</td>
<td>2,017</td>
<td>102,491</td>
<td>171 (163–179)</td>
</tr>
<tr>
<td>Other SFBA</td>
<td>23,199</td>
<td>1,343,777</td>
<td>160 (158–163)</td>
</tr>
<tr>
<td>Other urban CA</td>
<td>31,335</td>
<td>1,738,512</td>
<td>153 (152–155)</td>
</tr>
</tbody>
</table>
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-
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).

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References
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