Risk of a Second Breast Cancer Associated with Hormone-Receptor and HER2/neu Status of the First Breast Cancer

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Abstract

Objectives: Hormone-receptor (HR) and HER2/neu-receptor (HER2) status of breast tumors are important indicators for targeted therapies. We examine the association of receptor status and risk for a second breast cancer.

Methods: We analyzed data on 106,331 women in the California Cancer Registry whose first cancer is locoregional invasive breast disease, diagnosed from 1999 through 2005, yielding 1,613 second primary breast cancers. Standardized incidence ratios (SIR) with 95% confidence intervals (CIs) were used to evaluate risk of second tumors, accounting for age at first diagnosis, duration at risk, and race/ethnicity.

Results: Among non-Hispanic whites, HR-positive first tumors signal a reduction in risk for second breast cancers (SIR = 0.83, 95% CI: 0.77–0.89) whereas HR-negative status signals elevated risk (SIR = 1.48, 95% CI: 1.29–1.70). Asian/Pacific Islanders, African Americans, and Hispanics are at elevated risk of second breast cancers regardless of HR status of the first tumor. Hispanics with HR-negative first tumors are at greater risk than those with HR-positive disease (HR : SIR = 3.76, 95% CI: 2.97–4.71; HR : SIR = 1.86, 95% CI: 1.56–2.20). HER2 status does not differentiate risk for second tumors in any group examined.

Conclusions: HR status of a first breast cancer is a marker for risk of a second breast cancer. HER2 status does not seem to be a marker of risk for a second breast cancer. Risk differences across race/ethnic groups by HR status suggest heterogeneity of breast cancers across race/ethnicity.

Impact: These data suggest that HR status may be helpful in shaping strategies to reduce risk of a second breast cancer, while HER2 status seems uninformative for this purpose. Cancer Epidemiol Biomarkers Prev; 20(2); 389–96. ©2011 AACR.

Introduction

Despite progress in early diagnosis and treatment, cancer of the breast remains the most common cancer among U.S. women (1), the second most common cancer cause of death, and as such is a major concern for women’s health, health care providers, and public health policy. The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute puts the lifetime risk of invasive breast cancer for an American woman at just over 12% (2). Ninety-two percent of invasive cases are diagnosed at earlier stages (2), highlighting the importance of disease management to improve breast cancer outcomes.

Beyond surgical resection, choice of breast cancer therapy depends on stage at presentation, hormone-receptor (HR) status, and HER2/neu-receptor (HER2) status of the tumor, which are indicators for targeted therapies, (i.e., HR-positive status is used to recommend treatment with tamoxifen, raloxifene, aromatase inhibitors, or estrogen-receptor downregulators, whereas HER2-positive status determines eligibility for treatment with trastuzumab). Trial data show that tamoxifen significantly reduces risk of contralateral second primary tumors (3, 4) and aromatase inhibitors reduce the risk of recurrence in postmenopausal, HR-positive disease (5).

One recent analysis found that risk for contralateral second primary breast tumor significantly varied by HR status, citing a 10-fold elevated risk of HR-negative second primary tumor, following an HR-negative first tumor, relative to the general population (6), but this analysis of SEER data failed to capture HER2 information for either tumor. Another recent article described statistically significant marker concordance for HR/HER2-negative (so-called "triple-negative") first and second primary breast tumors (7), but they did not include cumulative risk estimates of the second breast tumor based on the HR/HER2 status of the first.

We aim to examine whether HR and HER2 status of the first breast cancer is associated with cumulative risk for second primary breast tumors. Using a historical prospective design and data from the population-based...
California Cancer Registry (CCR; ref. 8), we identify a cohort of women \( n = 106,331 \) in which invasive, locoregional breast cancer is the first cancer and follow them by using the registry for second breast cancers. Differences in risk of second primary breast tumor associated with HR and HER2 markers may inform disease management protocols for the first breast cancer tumor and may further explain etiology of second primary breast cancers.

### Materials and Methods

#### Incidence data

Cancer incidence data are from the CCR statistical extract of January 2007 (9). Cancer type and behavior are per the International Classification of Diseases for Oncology, second edition (10), and the cancer-type recoding scheme of the SEER program of the National Cancer Institute (11). The order of tumors within the same patient is given by the variable sequence number (12). The variables marker1, marker2, and markerca denote status on estrogen receptor, progesterone receptor, and HER2/neu, respectively (12). Stage of disease is given by the variable sumstage (12). Determination of major race/ethnic group is described elsewhere (13), resulting in 5 mutually exclusive categories: African American, Asian/Pacific Islander, Hispanic, Non-Hispanic white, and other. The variable lateralized identified laterality of primary and second breast tumors, recoded as right, left, and other (unilateral NOS, bilateral, unknown), with concordance signifying ipsilateral tumors and discordance signifying contralateral tumors. This study was conducted with Institutional Review Board approval (UCI IRB 95-203).

#### Study cohort

The cohort consists of all persons in the data set \( n = 2,775,646 \) cases in the registry extract) whose first cancer is locoregional invasive cancer \( n = 1,612,802 \) and who (a) are resident in California at diagnosis \( n = 1,527,543 \), (b) have breast as the index tumor \( n = 336,485 \), (c) were diagnosed from January 1, 1999, through December 31, 2005 \( n = 142,211 \), (d) are younger than 81 years at diagnosis \( n = 110,259 \), (e) alive at diagnosis \( n = 110,259 \), (f) have known race/ethnicity \( n = 109,505 \), (g) are female \( n = 108,893 \), and (h) attempting to avoid synchronous tumors, those whose second breast cancer is diagnosed within 6 months of the first diagnosis were excluded \( n = 106,331 \). The CCR collects marker status beginning with cases of 1999, and 2005 is the most recent year for which case ascertainment is reasonably complete in the data set. Our final cohort included 106,331 breast cancer cases.

#### HR and HER2/neu (HER2) status

We classify a case as HR\(^+\) if either the estrogen-receptor marker or the progesterone-receptor marker is positive and as HR\(^-\) if both markers are negative. Otherwise, cases are classified as HR unknown. Neither assay type nor titer is available in the data set for either of these markers. HER2 status was classified as positive or negative on the basis of the coding in the CCR, but the method of detection for HER2 status (i.e., FISH or immunohistochemistry) was not available (14).

#### Second primary

Second breast cancers are identified for a cohort member whose sequence number is 2, the age of diagnosis is below 85, and the diagnosis period is 1999–2005. For present purposes, both in situ and invasive diseases qualify as second tumors. Second breast cancers diagnosed at 85 years of age or greater are ignored because of difficulties in estimating risk above that age by these methods, although such patients contribute risk through age 84.

#### Risk of second cancer

Standardized incidence ratios (SIR; ref. 15) were used to estimate second cancer risk, for which expected numbers result from summing the cumulative risk of breast cancer (both in situ and invasive diseases) across cohort members (16, 17). The SIR method has also been used by the National Cancer Institute to estimate risk of new malignancies (16). For each individual, risk begins at diagnosis of the first cancer and ends at the earliest of (a) diagnosis of the second breast cancer, (b) loss to follow-up (including moving from California), (c) death, or (d) age 84. Risk estimates included patients with breast cancer as the second tumor (i.e., intermediate tumors between the primary breast cancer and subsequent breast cancers were not considered “second primaries” in our analysis). Cumulative risk is based on average annual age-, race/ethnic-, and sex-specific incidence rates estimated from the 5-year period centered on the U.S. Census of 2000 (viz. 1998–2002), using CCR incidence data and population data consistent with CCR publications (18, 19). Thus, the expected numbers of second breast cancers for the cohort account for age at first diagnosis, time at risk, sex, and race/ethnicity. Because calculations are based on ages in whole years, each patient contributes a minimum of 1 year of risk to the expected numbers of cases, which biases results toward the null hypotheses.

#### Computing and statistics

SIRs are evaluated by exact Poisson 95% CIs (15). Associations in contingency tables are tested by likelihood-ratio \( \chi^2 \) (20). Strength of associations are tested with the \( \kappa \) coefficient (21) or Sakoda’s adjusted contingency coefficient \( C^* \) (21). Interval estimates of proportions are by exact binomial methods. Programming and analyses are accomplished with SAS/STAT software (22).

### Results

#### Study cohort

Of the 106,331 women in the cohort, 68.3% are non-Hispanic white \( n = 72,658 \), 15.5% are Hispanic \( n = 16,479 \), 10.2% are Asian/Pacific Islander \( n = 10,808 \),
5.9% are African American (n = 6,291), and less than 1% are other race/ethnicity (n = 95). Mean age at diagnosis of the first tumor is 57.9 years (SD = 12.3, median = 58) whereas the mean age at follow-up is 60.9 years (SD = 12.5, median = 61). On average, each woman contributes about 4 years of risk for a cohort total of 423,852 person-years.

**HR status of first tumor**

Just over 81% (86,584/106,331) of the cohort have a known HR status for the first tumor. Among racial/ethnic groups, Hispanics have the lowest proportion of known HR status (78.1%) whereas non-Hispanic whites have the highest (82.3%). Proportions of known HR status among African Americans and Asian/Pacific Islanders are 81.3% and 80.7%, respectively. Table 1 shows the distribution of HR status stratified by race/ethnicity. The association between race/ethnicity and determined HR status (all CIs contain 1). Risk of second primary tumor when HR status is unknown is elevated (SIR = 1.16, 95% CI: 1.08–1.25). In contrast, those with HR-negative first tumors have elevated risks of a second primary (SIR = 1.92, 95% CI: 1.55–2.35; SIR = 1.84, 95% CI: 1.56–2.16 for HER2-positive and HER2-negative tumors, respectively). HER2 status does not differentiate risk for a second breast cancer.

Table 3 shows estimated relative risks for a second primary breast cancer by HR status of the first tumor, pooled across race/ethnicity. The cohort as a whole is at elevated risk for a second breast cancer (SIR = 1.13, 95% CI: 1.08–1.19). The magnitude of risk varies with HR status. Risks for those with HR-positive first tumors are not significantly elevated regardless of HER2 status (all CIs contain 1). Risk of second primary tumor when HR status is unknown is elevated (SIR = 1.16, 95% CI: 1.08–1.25). In contrast, those with HR-negative first tumors have elevated risks of a second primary (SIR = 1.92, 95% CI: 1.55–2.35; SIR = 1.84, 95% CI: 1.56–2.16 for HER2-positive and HER2-negative tumors, respectively). HER2 status does not differentiate risk for a second breast cancer.

**Risk of second breast cancer**

Table 2 shows estimated relative risks for a second primary breast cancer by HR and HER2 status of the first tumor, pooled across race/ethnicity. The cohort as a whole is at elevated risk for a second breast cancer (SIR = 1.13, 95% CI: 1.08–1.19). The magnitude of risk varies with HR status. Risks for those with HR-positive first tumors are not significantly elevated regardless of HER2 status (all CIs contain 1). Risk of second primary tumor when HR status is unknown is elevated (SIR = 1.16, 95% CI: 1.08–1.25). In contrast, those with HR-negative first tumors have elevated risks of a second primary (SIR = 1.92, 95% CI: 1.55–2.35; SIR = 1.84, 95% CI: 1.56–2.16 for HER2-positive and HER2-negative tumors, respectively). HER2 status does not differentiate risk for a second breast cancer.

**HER2/neu status of first tumor**

Just over 63% of the cohort have known HER2 status for the first tumor (67,136/106,331). Across race/ethnicity, African Americans have the smallest percentage of known HER2 status (58.3%; 3,670/6,291). Whites have the highest percentage (63.9%; 46,424/72,658), followed by Hispanics and Asian/Pacific Islanders at 61.9% and 62.7%, respectively. Table 1 shows the distribution of HER2 status stratified by race/ethnicity. While statistically significant (χ²(4) = 156.5, P < 0.0001) but only about 6% of the maximum possible (C* = 0.055).

**Second breast cancer**

To date, the cohort yields 1,613 second breast cancers, of which 389 (24.1%) are in situ and 1,224 (75.9%) are invasive disease. The proportion of in situ disease is not associated with race/ethnicity (χ²(4) = 4.52, P > 0.33). Of the 1,613 cases, 1,088 (67.5%) are non-Hispanic white, 256 (15.9%) are Hispanic, 143 (8.9%) are Asian/Pacific Islanders, and 125 (7.8%) are African American. Given that we omitted second diagnoses within 6 months of the first breast cancer, the mean number of months from first to second diagnoses is 31.4 (SD = 18.1, median = 27) and the mean age at second diagnosis is 60.6 (SD = 12.7, median = 61). Table 1 shows the distribution of HR and HER2 status, stage at diagnosis, and laterality of second tumors, stratified by race/ethnicity. Second tumors of all race/ethnicities are mostly localized, HR+, HER2+, and contralateral. Compared with non-Hispanic whites, more second tumors among Hispanic women were HR+ (>15%). Fewer African American women had HER2+ second tumors (7.2%) and contralateral second tumors (78.4%) than other race/ethnicity categories.
Table 1. Descriptive characteristics of participants from the CCR by race/ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Baseline cohort (n = 106,331)</th>
<th>Second breast tumor (n = 1,613)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Hispanic white</td>
<td>African American</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic white</td>
<td>African American</td>
</tr>
<tr>
<td>Total, n</td>
<td>72,658</td>
<td>6,291</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Stage at diagnosis, n (%)</td>
<td>In situ</td>
<td>Localized</td>
</tr>
<tr>
<td></td>
<td>59.5 (12.0)</td>
<td>55.6 (12.3)</td>
</tr>
</tbody>
</table>
| Stage of tumor, defined by CCR SUMSTAGE variable. Note that only invasive (local and regional), but not metastatic (remote), primary tumors were included in the cohort.

Abbreviation: n/a, not available.

aMean age at primary breast tumor diagnosis = 57.9 years (SD = 12.3)
bMean age at second breast tumor diagnosis = 62.3 years (SD = 12.8)
Discussion

In a large, population-based cohort of female primary breast cancer patients with nonmetastatic invasive disease, HR status significantly predicted risk of a second breast cancer in the full cohort and for the 2 largest race/ethnic groups. Among non-Hispanic whites and Hispanics, those with HR-negative first tumors show statistically significant elevations in risk for a second breast cancer, relative both to the race/ethnicity-specific general population of women.

Table 2. Estimated relative risk of second breast cancer by HR and HER2/neu status of the first tumor

<table>
<thead>
<tr>
<th>Status of first tumor</th>
<th>Number of patients</th>
<th>Observed cases</th>
<th>Expected cases&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% Confidence bounds&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR and HER2/neu</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR&lt;sup&gt;+&lt;/sup&gt;/HER2&lt;sup&gt;+&lt;/sup&gt;</td>
<td>9,830</td>
<td>116</td>
<td>124.21</td>
<td>0.93</td>
<td>0.77–1.12</td>
</tr>
<tr>
<td>HR&lt;sup&gt;+&lt;/sup&gt;/HER2&lt;sup&gt;−&lt;/sup&gt;</td>
<td>41,443</td>
<td>549</td>
<td>563.30</td>
<td>0.97</td>
<td>0.89–1.06</td>
</tr>
<tr>
<td>HR&lt;sup&gt;−&lt;/sup&gt;/HER2&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4,588</td>
<td>92</td>
<td>48.00</td>
<td>1.92</td>
<td>1.55–2.35</td>
</tr>
<tr>
<td>HR&lt;sup&gt;−&lt;/sup&gt;/HER2&lt;sup&gt;−&lt;/sup&gt;</td>
<td>8,332</td>
<td>155</td>
<td>84.12</td>
<td>1.84</td>
<td>1.56–2.16</td>
</tr>
<tr>
<td>Unknown</td>
<td>42,138</td>
<td>701</td>
<td>604.01</td>
<td>1.16</td>
<td>1.08–1.25</td>
</tr>
<tr>
<td>HR only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR&lt;sup&gt;+&lt;/sup&gt;</td>
<td>69,558</td>
<td>962</td>
<td>992.54</td>
<td>0.97</td>
<td>0.91–1.03</td>
</tr>
<tr>
<td>HR&lt;sup&gt;−&lt;/sup&gt;</td>
<td>17,026</td>
<td>344</td>
<td>186.94</td>
<td>1.84</td>
<td>1.65–2.05</td>
</tr>
<tr>
<td>Unknown</td>
<td>19,747</td>
<td>307</td>
<td>244.14</td>
<td>1.26</td>
<td>1.12–1.41</td>
</tr>
<tr>
<td>HER2/neu only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2&lt;sup&gt;+&lt;/sup&gt;</td>
<td>15,148</td>
<td>215</td>
<td>177.68</td>
<td>1.21</td>
<td>1.05–1.38</td>
</tr>
<tr>
<td>HER2&lt;sup&gt;−&lt;/sup&gt;</td>
<td>51,988</td>
<td>728</td>
<td>664.00</td>
<td>1.10</td>
<td>1.02–1.18</td>
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<td>Unknown</td>
<td>39,195</td>
<td>670</td>
<td>581.95</td>
<td>1.15</td>
<td>1.07–1.24</td>
</tr>
<tr>
<td>Total</td>
<td>106,331</td>
<td>1,613</td>
<td>1,423.62</td>
<td>1.13</td>
<td>1.08–1.19</td>
</tr>
</tbody>
</table>

<sup>a</sup>Figures are rounded to two places.

Table 3. Estimated relative risk of second breast cancer by HR status of the first tumor and major race/ethnic group

<table>
<thead>
<tr>
<th>HR status of first tumor</th>
<th>Number of patients</th>
<th>Observed cases&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Expected cases&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Relative risk&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% Confidence bounds&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic whites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR&lt;sup&gt;+&lt;/sup&gt;</td>
<td>49,655</td>
<td>685</td>
<td>827.47</td>
<td>0.83</td>
<td>0.77–0.89</td>
</tr>
<tr>
<td>HR&lt;sup&gt;−&lt;/sup&gt;</td>
<td>10,145</td>
<td>205</td>
<td>138.21</td>
<td>1.48</td>
<td>1.29–1.70</td>
</tr>
<tr>
<td>Unknown</td>
<td>12,858</td>
<td>198</td>
<td>193.74</td>
<td>1.02</td>
<td>0.88–1.17</td>
</tr>
<tr>
<td>Hispanics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR&lt;sup&gt;+&lt;/sup&gt;</td>
<td>9,564</td>
<td>135</td>
<td>72.72</td>
<td>1.86</td>
<td>1.56–2.20</td>
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<tr>
<td>HR&lt;sup&gt;−&lt;/sup&gt;</td>
<td>3,307</td>
<td>76</td>
<td>20.19</td>
<td>3.76</td>
<td>2.97–4.71</td>
</tr>
<tr>
<td>Unknown</td>
<td>3,608</td>
<td>45</td>
<td>24.62</td>
<td>1.83</td>
<td>1.33–2.45</td>
</tr>
<tr>
<td>Asian/Pacific Islanders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR&lt;sup&gt;+&lt;/sup&gt;</td>
<td>6,931</td>
<td>78</td>
<td>55.45</td>
<td>1.41</td>
<td>1.11–1.76</td>
</tr>
<tr>
<td>HR&lt;sup&gt;−&lt;/sup&gt;</td>
<td>1,789</td>
<td>29</td>
<td>12.88</td>
<td>2.25</td>
<td>1.51–3.23</td>
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<tr>
<td>Unknown</td>
<td>2,088</td>
<td>36</td>
<td>14.65</td>
<td>2.46</td>
<td>1.72–3.40</td>
</tr>
<tr>
<td>African Americans</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR&lt;sup&gt;+&lt;/sup&gt;</td>
<td>3,345</td>
<td>63</td>
<td>36.82</td>
<td>1.71</td>
<td>1.31–2.19</td>
</tr>
<tr>
<td>HR&lt;sup&gt;−&lt;/sup&gt;</td>
<td>1,771</td>
<td>34</td>
<td>15.65</td>
<td>2.17</td>
<td>1.50–3.04</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,175</td>
<td>28</td>
<td>11.11</td>
<td>2.52</td>
<td>1.68–3.64</td>
</tr>
</tbody>
</table>

<sup>a</sup>Other race/ethnicity category is excluded because there is only 1 observed second primary tumor case in this category.

<sup>b</sup>Figures are rounded to two places.
and to their race/ethnic peers whose first tumor is HR+. The numerically smaller Asian/Pacific Islander and African American groups (10.2% and 5.9% of cohort, respectively) show elevated risk for a second tumor relative to the race/ethnicity-specific general population of women, but that risk is not significantly altered by HR status of the first tumor. In these data, HER2 status of the first breast tumor is not associated with risk for a second primary tumor.

Our findings support and expand on the results of Kurian and colleagues (6, 7) in that our results indicate that women with HR-negative first breast tumors were at increased risk of second primary tumor whereas HER2 status of the first breast tumor did not differentiate risk for second primary breast cancers. The increased risk of second primary tumor was evident across all race/ethnicity groups for HR-negative first tumors, supporting the results of Kurian and colleagues. However, risk for a second breast cancer in our registry sample (SIR = 1.13, 95% CI: 1.08–1.19) was much lower than the second primary risk reported in the analysis of Kurian and colleagues (SIR = 2.46, 95% CI: 2.40–2.52; ref. 6). Kurian and colleagues excluded only the second tumors diagnosed within 2 months of the first, capturing more second primary tumors than diagnosed in our analysis. We excluded second primaries diagnosed within 6 months following trends in recent literature (23, 24). However, when we excluded only second primaries diagnosed within 2 months following Kurian and colleagues, the SIR becomes 1.29 (95% CI: 1.23–1.35), still substantially lower than the estimate of Kurian and colleagues. It is possible that the race/ethnicity distribution in our CCR-derived cohort may differ from the SEER-derived cohort of Kurian and colleagues, explaining the difference in SIR estimates.

Given the evidence that targeted therapies can reduce the risk of contralateral tumors (3, 4) or recurrent disease (5), our observed differences across race/ethnicity in the predictive value of HR-positive disease may reflect differences in access to quality care. A variety of treatment strategies have been associated with improved breast cancer outcomes. These include correct identification of HR status (25) and adherence to adjuvant hormonal therapy (26). Also, important are dose-dense and/or metronomic chemotherapy in specific subtypes and stages of breast cancer (27, 28), use of trastuzumab in specific subtypes (29), application of optimal scheduling (30), administration of radiation in patients with strong indication (31), and use of gene signatures to optimize treatment (32). Application of these strategies across races should reduce disparities in outcomes due to differential access to care.

In our data, a substantial proportion (95% CI: 37.2–50.8) of HR-negative first tumors are followed by a HR-positive second tumor, a risk also noted by Kurian and colleagues (SIR = 1.94, 95% CI: 1.77–2.13; ref. 6). Historically, hormone therapy has not shown a benefit for outcome in locoregional, HR-negative breast cancer (33, 34), so most HR-negative first tumors were presumably not treated with hormone therapy. However, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists estimate that up to 20% of immunohistochemical determinations of HR status worldwide may be inaccurate and recommend a threshold of less than 1% tumor cells staining positive for HR to classify the tumor as HR+(25). Assay titers for exact levels are not available in the CCR, nor is information on type, size, and handling of specimens, so a number of first tumors classified as HR+ in the registry might be better described as "HR poor." Perhaps, in some cases, the second primary HR-positive tumors may result from evolved HR-poor tumor clones that escape hormonal blockade. In addition, while some of the HR-positive second tumors may be biologically de novo disease, others may be manifestations of an imperfectly controlled first tumor.

Limitations include incomplete data on the use of tamoxifen or aromatase inhibitors. However, we acknowledge that treatment factors may confound our associations and this analysis does not account for specific treatment differences. An analysis based on detailed surgical and/or radiation treatment is beyond the scope of this article. Additional limitations include the relatively short follow-up period, the lack of centralized pathologic specimen review, and vagaries of classifying breast tumors by HR status (i.e., 20% unknown HR status, and 40% unknown HER2). Because of minor differences in missing receptor status by race/ethnicity, we cannot rule out the possibility that our failure to observe differences in SIR in minorities could be due to missing data. The lack of information on hormone therapies means we cannot separate marker status from therapy in our risk estimates or say to what degree race/ethnic variations in risk reflect only variations in treatment. A limitation of registry data is the lack of information on comorbidities and patients’ performance status (35–37) and these factors may play a role in second tumor risk. It is possible that case selection methods could explain the singular finding that white women with HR-positive first tumors are significantly protected from a second breast cancer. Strengths of this study include a large number of cases ascertained and followed by one of the larger population-based cancer registries in the world, reflecting a diverse population.

While all breast cancer patients require medical surveillance, our findings coupled with the results of Kurian and colleagues (6) show that HR-negative patients may be at relatively higher risk to develop a second primary breast tumor. Future research should investigate the degree to which this inequality is due to biological differences or differential access to care, and results of these studies will yield improvements in management strategies for breast cancer patients.

Disclosure of Potential Conflicts of Interest

The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended, nor should be inferred.
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