Familial Clustering of Breast and Prostate Cancer and Risk of Postmenopausal Breast Cancer in the Women’s Health Initiative Study

Jennifer L. Beebe-Dimmer, MPH, PhD1,2; Cecilia Yee, MS1,2; Michele L. Cote, MPH, PhD1,2; Nancie Petrucelli, MS1,2; Nynikka Palmer, MPH, DrPH3; Cathryn Bock, MPH, PhD1,2; Dorothy Lane, MD, MPH4; Ilir Agalliu, MD, ScD5; Marcia L. Stefanick, PhD6; and Michael S. Simon, MD, MPH1,2

BACKGROUND: Evidence suggests that the risk of breast and prostate cancer is increased among those with a family history of the same disease and particularly among first-degree relatives. However, less is known about the relationship between breast and prostate cancer within families and particularly among minority populations. METHODS: Analyses of participants in the Women’s Health Initiative observational cohort who were free of breast cancer at the time of their baseline examination were conducted. Subjects were followed for breast cancer through August 31, 2009. A Cox proportional hazards regression modeling approach was used to estimate the risk of breast cancer associated with a family history of prostate cancer, breast cancer, and both among first-degree relatives. RESULTS: There were 78,171 eligible participants, and 3506 breast cancer cases were diagnosed during the study period. A family history of prostate cancer was associated with a modest increase in breast cancer risk after adjustments for confounders (adjusted hazard ratio [aHR], 1.14; 95% confidence interval [CI], 1.02-1.26). In a separate analysis examining the joint impact of both cancers, a family history of both breast and prostate cancer was associated with a 78% increase in breast cancer risk (aHR, 1.78; 95% CI, 1.45-2.19). Risk estimates associated with a family history of both breast and prostate cancer were higher among African American women (aHR, 2.34; 95% CI, 1.09-5.02) versus white women (aHR, 1.66; 95% CI, 1.33-2.08). CONCLUSIONS: These findings suggest that prostate cancer diagnosed among first-degree family members increases a woman’s risk of developing breast cancer. Future studies are needed to determine the relative contributions of genes and a shared environment to the risk for both cancers. Cancer 2015;000:000-000. © 2015 American Cancer Society.

KEYWORDS: African American, aggregation, epidemiology, family history, genetics.

INTRODUCTION
Cancers of the breast and prostate are the most common invasive cancers diagnosed among women and men, respectively, in the United States. It has been estimated that 232,670 new cases of breast cancer and 233,000 new cases of prostate cancer will be diagnosed in the United States in 2014, and they will account for nearly 30% of all invasive cancers.1 A positive family history is a well-established risk factor for both cancers, particularly when they are diagnosed among first-degree family members.2,3 The risk increases with an increasing number of affected relatives and is inversely associated with the age at diagnosis of affected relatives.3,4 However, the relative risk for either breast or prostate cancer associated with the aggregation of both cancers within families has not been thoroughly investigated. Evidence indicates clustering of breast and prostate cancer in predominantly white populations5-8 and a similar or stronger phenomenon among African American families; however, the results for the latter are based on a relatively small number of participants.9,10 These epidemiological observations may be explained by shared environments and/or genetics. The rationale of such studies hinges on the 2 cancers having similar biological mechanisms, and these studies focus on exposure to endogenous sex-steroid hormone concentrations, insulin and insulin-like growth factors, and inflammatory mediators (eg, adipokines) with mitogenic and potentially genotoxic effects on target tissues.

The current investigation focuses on the family history of prostate cancer and breast cancer among first-degree relatives and the risk of postmenopausal breast cancer among participants in the Women’s Health Initiative (WHI) Observational Study (OS). The results of case-control studies investigating the relationships between family cancer history and
cancer risk can be influenced by recall bias. Thus, the WHI OS represents an opportunity to estimate the breast cancer risk associated with the reported family history while reducing the impact of such bias. Furthermore, the large sample size allows the examination of racial differences in the breast cancer risk associated with a positive family history of prostate and breast cancer.

MATERIALS AND METHODS

Study Population

The WHI consists of several clinical trials and an observational study with more than 168,000 US women enrolled. The study details of the WHI have been previously published. Briefly, the WHI enrolled healthy, postmenopausal women who were 50 to 79 years old into a randomized, controlled clinical trial of exogenous estrogen and progesterone with coronary artery disease as the primary outcome. Women unwilling to participate or considered ineligible for the initial clinical trial were given an opportunity to participate in the WHI OS. The OS was initially established to serve as a control for the clinical trial and collected detailed information on the following: demographics; medical history; family medical history at the baseline interview; and risk factors for a number of chronic diseases, including breast cancer.

The WHI OS enrolled 93,676 postmenopausal women through 40 clinical centers throughout the United States between October 1, 1993 and December 31, 1998. The WHI OS protocol was reviewed by the institutional review boards of each of the 40 centers, and informed consent was obtained from each participant locally. Each participant completed an interview and physical examination at the baseline and at 3 years. Women were deemed ineligible for the initial clinical trial were given an opportunity to participate in the WHI OS. The OS was initially established to serve as a control for the clinical trial and collected detailed information on the following: demographics; medical history; family medical history at the baseline interview; and risk factors for a number of chronic diseases, including breast cancer.

Baseline Data Collection

At the baseline, all OS participants had their height, weight, waist and hip circumference, and blood pressure measured, and their body mass index (kg/m²) was calculated from measures of weight and height. Participants also completed a comprehensive, standardized, self-administered questionnaire collecting information on their demographics (including self-reported race), occupation, lifestyle and behavioral risk factors (smoking, alcohol consumption, and physical activity), and reproductive, medical, and family history.

All participants were asked about their family medical history, including cancer. The most detailed cancer family history data gathered from women were for breast and colorectal cancer, primarily because of the impact of these cancers on morbidity and mortality but also because of their inclusion as secondary endpoints in 1 or more of the clinical trial components. For both breast and colorectal cancer, the number of affected first-degree relatives was recorded, the approximate age at diagnosis for each affected relative was recorded, and the relationship to the participant was recorded. For prostate cancer as well as endometrial, cervical, and ovarian cancers, only the number of affected first-degree, full-blood relatives was recorded.

Statistical Analysis

All analyses were conducted with Statistical Analysis Systems version 9.2 (SAS Inc, Cary, NC). Descriptive statistics, including age, race/ethnicity, education, WHI region, body mass index, smoking history, any hormone therapy use, parity, age at first birth, hysterectomy, oophorectomy, a history of benign breast disease, insurance coverage, mammography in the past 2 years, and general health, were used to characterize the baseline characteristics of the study population. To identify potential confounders, differences in the distribution of baseline characteristics between breast cancer cases and noncases were evaluated with chi-square tests and the associated P values. P values less than .05 were considered statistically significant. Cox proportional hazards regression was used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for breast cancer associated with having a family history of breast cancer and/or prostate cancer with adjustments for important confounders. Baseline characteristics that were significantly different between breast cancer cases and noncases were included individually in subsequent regression models. If the inclusion of those characteristics in the model changed the hazard ratios (HRs) related to a family history by ≥10%, then these characteristics were considered important confounding variables. Models were generated for all participants combined and were stratified by race; for the latter analysis, participants of non-white, non–African American, or unknown race were excluded. For all analyses, the family
history was restricted to first-degree, full-blood relatives. Because adjustments for the number of first-degree relatives did not change risk estimates, final models included mutual adjustments for a family history of breast cancer, prostate cancer, age, race, benign breast disease, hormone therapy use, and hysterectomy.

RESULTS
The 78,171 WHI OS participants included in this study were followed for a median of 132 months from the date of enrollment with a median of 60 months between enrollment and diagnosis for breast cancer cases. Table 1 describes the distribution of baseline characteristics between the 3506 incident breast cancer cases diagnosed between the baseline and August 31, 2009 and the 74,665 noncases followed during the same period in the WHI observational cohort. Breast cancer cases were more likely than noncases to be non-Hispanic white, college-educated, and hormone therapy users; to have a history of benign breast disease; and to have had a mammogram within 2 years of the baseline examination. The cases were also less likely to smoke, to have children, and to have undergone a hysterectomy. There were either marginal or nonsignificant differences between cases and controls with respect to the body mass index, WHI region, insurance coverage, and self-reported health. The median age at the baseline was 64 years for breast cancer cases and 63 years for noncases; the median age at the time of the breast cancer diagnosis was 69 years (range, 50-90 years).

Self-reported family histories of both breast and prostate cancer among first-degree family members in breast cancer cases and noncases are provided in Table 2. There were 11,608 women in the study who reported a positive family history of breast cancer; 48.7% of these women reported that their mother was diagnosed, 36.6% reported a diagnosis for a sister, 4.6% reported a diagnosis for a daughter, and the remaining 10.1% reported diagnoses for more than 1 first-degree relative. Cases were more likely than noncases to report a family history of breast cancer (20.5% and 14.6%, respectively), with an approximately 40% increase in risk associated with having a single family member affected after adjustments for potential confounders (aHR, 1.42; 95% CI, 1.30-1.55). Risk increased further with multiple family members being diagnosed with breast cancer (aHR, 1.66; 95% CI, 1.32-1.88). Breast cancer cases were more likely to report 1 or more relatives diagnosed with prostate cancer in comparison with noncases (11.6% vs 10.1%). A family history of prostate cancer in a first-degree relative (father, brother, or son) was associated with a significant, albeit modest, increase in breast cancer risk after adjustments for confounders, including a family history of breast cancer (aHR, 1.14; 95% CI, 1.02-1.26). Women at the greatest risk for breast cancer had a history of both breast and prostate cancer among first-degree family members, with an approximately 80% increase in breast cancer risk in comparison with women with no family history of either (aHR, 1.78; 95% CI, 1.45-2.19).

Table 3 provides race-stratified estimates of the breast cancer risk associated with a family history of breast and prostate cancer. Risk was greatest among African American women with multiple affected first-degree family members (aHR, 2.85; 95% CI, 1.33-6.09). Although a family history of prostate cancer was modestly predictive of breast cancer risk in both white and African American women, the association was statistically significant only in white women. Lastly, African American women with a family history of both breast and prostate cancer appeared to be at greater risk for developing breast cancer (aHR, 2.34; 95% CI, 1.09-5.02) than their white counterparts (aHR, 1.66; 95% CI, 1.33-2.08). However, the risk estimates were not significantly different as evidenced by the overlapping CIs.

We also considered the impact of a family history of other cancers (nonbreast, nonprostate) among first-degree relatives on breast cancer risk and found no increase in risk associated with a family history of any other cancer (HR, 0.99; 95% CI, 0.91-1.07). A family history of colorectal cancer was associated with a marginal increase in breast cancer risk (HR, 1.08; 95% CI, 0.99-1.18) after adjustments for a family history of breast and prostate cancer (Table 4). Interestingly, a family history among first-degree relatives that included breast, prostate, and colorectal cancer was associated with an approximately 2-fold increase in breast cancer risk (HR, 2.06; 95% CI, 1.38-3.08).

DISCUSSION
Findings from the WHI observational cohort suggest that independently of a family history of breast cancer, a positive family history of prostate cancer among first-degree relatives is associated with a modest increase in the risk of breast cancer diagnosed after the age of 50 years. We report, as have others, that women with a family history of breast cancer are at an increased risk, with risk estimates higher among women with multiple affected first-degree family members. Our results also suggest that African American women at the greatest risk for a diagnosis of breast cancer have a family history of both breast and prostate cancer.
Epidemiological studies consistently demonstrate that a family history of the same tumor, particularly among first-degree relatives, is a moderate to strong risk factor for both breast and prostate cancer, with concordant estimates of relative risk ranging from 2.0 to 4.5. Reported estimates are even higher with multiple affected relatives and/or relatives diagnosed with earlier onset disease (typically <50 years at the time of diagnosis for breast cancer and <60 years for prostate cancer). Interest-

ingly, the risk appears slightly higher for both cancers when a full-blood sibling instead of a parent is affected with the same disease, and this suggests some contribution from the environment (particularly the early environment) and/or an interaction between 1 or more genes and early environmental exposures playing an important role in carcinogenesis.

Comparatively, much less is known about the aggregation of breast and prostate cancer within families and the discordant estimates of risk associated with a positive

### TABLE 1. Baseline Characteristics of Breast Cancer Cases and Noncases Participating in the Women's Health Initiative Observational Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Breast Cancer Cases, n (%) or Median (Range)</th>
<th>Noncases, n (%) or Median (Range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>3506 (4.5)</td>
<td>74,665 (95.5)</td>
<td></td>
</tr>
<tr>
<td>Age at baseline, y</td>
<td>.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 y</td>
<td>1009 (28.8)</td>
<td>24,428 (32.7)</td>
<td></td>
</tr>
<tr>
<td>60-69 y</td>
<td>1653 (47.1)</td>
<td>32,785 (43.9)</td>
<td></td>
</tr>
<tr>
<td>≥70 y</td>
<td>844 (24.1)</td>
<td>17,452 (23.4)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50-59 y</td>
<td>403 (11.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69 y</td>
<td>1377 (39.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79 y</td>
<td>1417 (40.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80 y</td>
<td>309 (8.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>3129 (89.2)</td>
<td>62,555 (83.8)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>174 (5.0)</td>
<td>5627 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>194 (5.5)</td>
<td>6283 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (0.3)</td>
<td>200 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Education, n (%) or Median (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No high school diploma</td>
<td>113 (3.2)</td>
<td>3585 (4.8)</td>
<td></td>
</tr>
<tr>
<td>High school diploma/GED</td>
<td>489 (13.9)</td>
<td>12,054 (16.1)</td>
<td></td>
</tr>
<tr>
<td>College graduate or above</td>
<td>2879 (82.1)</td>
<td>58,450 (78.3)</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td>.19</td>
</tr>
<tr>
<td>Northeast</td>
<td>798 (22.8)</td>
<td>17,464 (23.4)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>879 (25.1)</td>
<td>18,952 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>747 (21.3)</td>
<td>16,458 (22.0)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>1082 (30.9)</td>
<td>21,791 (29.2)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td>.78</td>
</tr>
<tr>
<td>Underweight</td>
<td>1420 (40.5)</td>
<td>30,561 (40.9)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1180 (33.7)</td>
<td>25,171 (33.7)</td>
<td></td>
</tr>
<tr>
<td>(25.0-29.9 kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (≥30.0 kg/m²)</td>
<td>867 (24.7)</td>
<td>18,081 (24.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>39 (1.1)</td>
<td>853 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>Never</td>
<td>1679 (47.9)</td>
<td>37,897 (50.8)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>1579 (45.0)</td>
<td>31,390 (42.0)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>212 (6.0)</td>
<td>4558 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>36 (1.0)</td>
<td>820 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy use</td>
<td></td>
<td></td>
<td>.0001</td>
</tr>
<tr>
<td>Never</td>
<td>820 (23.4)</td>
<td>21,517 (28.8)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>621 (17.7)</td>
<td>14,580 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1984 (56.6)</td>
<td>37,174 (49.8)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>81 (2.3)</td>
<td>1394 (1.9)</td>
<td></td>
</tr>
<tr>
<td>None (nulliparous)</td>
<td>506 (14.4)</td>
<td>9271 (12.4)</td>
<td></td>
</tr>
<tr>
<td>1-2 term pregnancies</td>
<td>1269 (36.2)</td>
<td>26,261 (35.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;2 term pregnancies</td>
<td>1710 (48.8)</td>
<td>38,754 (51.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>21 (0.6)</td>
<td>379 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Age at first birth (full-term pregnancy)</td>
<td></td>
<td></td>
<td>.0001</td>
</tr>
<tr>
<td>Never</td>
<td>506 (14.4)</td>
<td>9271 (12.4)</td>
<td></td>
</tr>
<tr>
<td>&lt;30 y</td>
<td>2378 (67.8)</td>
<td>52,467 (70.3)</td>
<td></td>
</tr>
<tr>
<td>≥30 y</td>
<td>339 (9.7)</td>
<td>5603 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>283 (8.1)</td>
<td>7324 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>No</td>
<td>2219 (63.3)</td>
<td>43,591 (58.4)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: GED, general educational development.

* Percentages may not add up to 100% because of rounding.
* Chi-square test.
* Nonprostate, nonbreast cancer.
family history. Our findings are similar to those of Sellers et al, who reported that a family history of prostate cancer in a father or brother was associated with a modest increase in postmenopausal breast cancer risk independent of the family history of breast cancer (relative risk, 1.19; 95% CI, 0.90-1.56), but a family history of both breast and prostate cancer was associated with an approximately 2.0-fold increase in breast cancer risk. Both Turati et al and Gronberg et al reported an approximately 60% increase in the odds of a breast cancer diagnosis associated with a history of prostate cancer in any first-degree relative. However, other studies have not observed significant increases in breast cancer risk associated with a family history of prostate cancer. These discrepancies may be attributed to differences in study design and/or the composition of the study participants. In comparison, the majority of studies but not all, have reported a significant independent association between a positive family history of breast cancer among first-degree relatives and the risk of prostate cancer.

Few studies have reported on the impact of race and family history on the risk of breast and prostate cancer.

### TABLE 2. Baseline Reported History of Breast and Prostate Cancer Among First-Degree, Full-Blood Relatives and Breast Cancer Risk in the Women’s Health Initiative Observational Study

<table>
<thead>
<tr>
<th>Family History of Cancer Among First-Degree Relatives</th>
<th>Breast Cancer Cases, n (%)</th>
<th>Noncases, n (%)</th>
<th>Crude RR (95% CI)</th>
<th>Multivariate RR (95% CI)(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 78,171)</td>
<td>3506</td>
<td>74,665</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer(^{b})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2787 (79.5)</td>
<td>63,776 (85.4)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1 relative</td>
<td>636 (18.1)</td>
<td>9796 (13.1)</td>
<td>1.47 (1.35-1.60)</td>
<td>1.42 (1.30-1.55)</td>
</tr>
<tr>
<td>&gt;1 relative</td>
<td>83 (2.4)</td>
<td>1093 (1.5)</td>
<td>1.75 (1.41-2.18)</td>
<td>1.66 (1.32-2.08)</td>
</tr>
<tr>
<td>Prostate cancer(^{b})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3101 (88.4)</td>
<td>67,107 (92.9)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1 or more relatives</td>
<td>405 (11.6)</td>
<td>7568 (10.1)</td>
<td>1.14 (1.03-1.26)</td>
<td>1.14 (1.02-1.26)</td>
</tr>
<tr>
<td>Breast and prostate cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2480 (70.7)</td>
<td>57,459 (77.0)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Breast only</td>
<td>621 (17.7)</td>
<td>9648 (13.2)</td>
<td>1.48 (1.35-1.61)</td>
<td>1.42 (1.29-1.55)</td>
</tr>
<tr>
<td>Prostate only</td>
<td>307 (8.8)</td>
<td>6317 (8.5)</td>
<td>1.12 (0.99-1.26)</td>
<td>1.10 (0.98-1.24)</td>
</tr>
<tr>
<td>Both</td>
<td>98 (2.8)</td>
<td>1241 (1.7)</td>
<td>1.81 (1.48-2.21)</td>
<td>1.78 (1.45-2.19)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

\(^{a}\)Models included age, race, benign breast disease, hormone replacement therapy usage, and hysterectomy.

\(^{b}\)Models were also mutally adjusted for a family history of breast cancer and prostate cancer among first-degree relatives.

### TABLE 3. Race-Stratified Estimates of Breast Cancer Risk According to the Family History of Breast and Prostate Cancer in the Women’s Health Initiative Observational Study

<table>
<thead>
<tr>
<th>Family History of Cancer Among First-Degree Relatives</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast Cancer Cases, n (%)</td>
<td>Noncases, n (%)</td>
</tr>
<tr>
<td>Total (n = 71,485)</td>
<td>3129</td>
<td>62,555</td>
</tr>
<tr>
<td>Breast cancer(^{b})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2488  (79.5)</td>
<td>53,134 (84.9)</td>
</tr>
<tr>
<td>1 relative</td>
<td>578   (18.5)</td>
<td>8504 (13.6)</td>
</tr>
<tr>
<td>&gt;1 relative</td>
<td>63 (2.0)</td>
<td>917 (1.5)</td>
</tr>
<tr>
<td>Prostate cancer(^{b})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2766  (88.4)</td>
<td>56,151 (89.8)</td>
</tr>
<tr>
<td>1 or more relatives</td>
<td>363   (11.6)</td>
<td>6404 (10.2)</td>
</tr>
<tr>
<td>Breast and prostate cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2208  (70.6)</td>
<td>47,803 (76.4)</td>
</tr>
<tr>
<td>Breast only</td>
<td>558   (17.8)</td>
<td>8348 (13.3)</td>
</tr>
<tr>
<td>Prostate only</td>
<td>260   (8.9)</td>
<td>5331 (8.5)</td>
</tr>
<tr>
<td>Both</td>
<td>83 (2.7)</td>
<td>1073 (1.7)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

\(^{a}\)Models included age, benign breast disease, hormone replacement therapy usage, and hysterectomy

\(^{b}\)Models were also mutually adjusted for a family history of breast cancer and prostate cancer among first-degree relatives.
Among those focused on concordant risk, studies of prostate cancer have reported that African American men in the United States have a risk similar to that of white men with comparable family histories. Alternatively, studies of racial disparities in familial breast cancer are not as clear. The Black Women’s Health Study and the Women’s Contraceptives and Reproductive Experiences (CARE) study reported similar estimates of the relative risk associated with a positive family history of breast cancer in African American and white women. However, a subsequent report from the CARE study found that after the age of 50 years, risks diverge, with white women having a higher risk of breast cancer in comparison with black women; this was particularly true among those with more than 1 affected first-degree relative. Two case-control studies focusing on discordant risk in African Americans found that men with prostate cancer were more likely to report a family history of breast cancer in a sibling in comparison with controls. To our knowledge, the current investigation is the first to report on racial differences in the risk of breast cancer associated with a family history of prostate cancer.

A genetic explanation for the familial clustering of breast and prostate cancer is currently unknown, but researchers have naturally focused on breast cancer 1 early-onset (BRCA1) and breast cancer 2 early-onset (BRCA2) with the presence of prostate cancer in Ashkenazi Jewish families as well as those meeting criteria for hereditary breast and ovarian cancer syndrome. The results of studies examining the association between either of these genes and prostate cancer have been inconsistent. It has been predicted that germline mutations in BRCA1/2 can explain just a small proportion of the observed clustering of breast and prostate cancer within families, and BRCA2 has been linked to more aggressive prostate cancer clinical features.

The strengths of the current investigation primarily lie in the WHI OS resource. The large population allowed a precise estimation of the breast cancer risk associated with a history of breast and prostate cancer among immediate family members, particularly among those with a family history of both cancers, which is a relatively rare occurrence in the population. Any changes in family histories of cancer were not captured in this analysis.

In summary, a family history of breast cancer and a family history of prostate cancer were each independently associated with the risk of breast cancer diagnosed after the age of 50 years, with the greatest risk observed among women with a family history of both breast and prostate cancer among first-degree relatives. These findings deserve further investigation and may have significant

<table>
<thead>
<tr>
<th>Family History of Cancer Among First-Degree Relatives</th>
<th>Breast Cancer Cases, n (%)</th>
<th>Noncases, n (%)</th>
<th>Crude RR (95% CI)</th>
<th>Multivariate RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 78,171)</td>
<td>3506</td>
<td>74,665</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancerb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2787 (79.5)</td>
<td>63,776 (85.4)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1 relative</td>
<td>636 (18.1)</td>
<td>9796 (13.1)</td>
<td>1.47 (1.35-1.60)</td>
<td>1.42 (1.30-1.55)</td>
</tr>
<tr>
<td>&gt;1 relative</td>
<td>83 (2.4)</td>
<td>1093 (1.5)</td>
<td>1.75 (1.41-2.18)</td>
<td>1.66 (1.32-2.08)</td>
</tr>
<tr>
<td>Colorectal cancerb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2931 (83.6)</td>
<td>63,328 (84.8)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>1 or more relatives</td>
<td>575 (16.4)</td>
<td>11,337 (15.2)</td>
<td>1.08 (0.99-1.19)</td>
<td>1.08 (0.99-1.19)</td>
</tr>
<tr>
<td>Breast and colorectal cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2337 (66.7)</td>
<td>54,387 (72.8)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Breast only</td>
<td>594 (16.9)</td>
<td>8941 (12.0)</td>
<td>1.53 (1.39-1.67)</td>
<td>1.47 (1.34-1.61)</td>
</tr>
<tr>
<td>Colorectal only</td>
<td>450 (12.9)</td>
<td>9389 (12.6)</td>
<td>1.11 (1.01-1.23)</td>
<td>1.11 (1.00-1.23)</td>
</tr>
<tr>
<td>Both</td>
<td>125 (3.6)</td>
<td>1948 (2.6)</td>
<td>1.51 (1.26-1.80)</td>
<td>1.47 (1.22-1.77)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

Models included age, race, benign breast disease, hormone replacement therapy usage, and hysterectomy.

Models were also mutually adjusted for a family history of breast cancer and colorectal cancer among first-degree relatives.

<table>
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<tr>
<th>Baseline Reported History of Breast and Colorectal Cancer Among First-Degree, Full-Blood Relatives and Breast Cancer Risk in the Women’s Health Initiative Observational Study</th>
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<tr>
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<td>Breast only</td>
</tr>
<tr>
<td>Colorectal only</td>
</tr>
<tr>
<td>Both</td>
</tr>
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Abbreviations: CI, confidence interval; RR, relative risk.

Models included age, race, benign breast disease, hormone replacement therapy usage, and hysterectomy.

Models were also mutually adjusted for a family history of breast cancer and colorectal cancer among first-degree relatives.
implications because of the contribution of an inherited predisposition for both cancers. Familial clustering of these 2 cancers represents a unique phenotype in which to identify new susceptibility genes. Furthermore, because the contribution of a family history of prostate cancer to breast cancer risk among relatives (and vice versa) is more clearly elucidated, risk communication between the physician and the patient as well as the dissemination of this information from the patient to immediate relatives would be important in shaping the health behaviors (such as screening for early detection) of those family members, even among those of the opposite sex.

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**CONFLICT OF INTEREST DISCLOSURES**

The authors made no disclosures.

**REFERENCES**

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