Association Study of Prostate Cancer Susceptibility Variants with Risks of Invasive Ovarian, Breast, and Colorectal Cancer


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Abstract

Several prostate cancer susceptibility loci have recently been identified by genome-wide association studies. These loci are candidates for susceptibility to other epithelial cancers. The aim of this study was to test these tag single nucleotide polymorphisms (SNP) for association with invasive ovarian, colorectal, and breast cancer. Twelve prostate--associated tag SNPs were genotyped in ovarian (2,087 cases/3,491 controls), colorectal (2,148 cases/2,265 controls) and breast (first set, 4,339 cases/4,552 controls; second set, 3,800 cases/3,995 controls) case-control studies. The primary test of association was a comparison of genotype frequencies between cases and controls, and a test for trend stratified by study where appropriate. Genotype-specific odds ratios (OR) were estimated by logistic regression. SNP rs2660753 (chromosome 3p12) showed evidence of association with ovarian cancer [per minor allele OR, 1.19; 95% confidence interval (95% CI), 1.04–1.37; \( P_{\text{trend}} = 0.012 \)]. This association was stronger for the serous histologic subtype (OR, 1.29; 95% CI, 1.09–1.53; \( P = 0.003 \)). SNP rs7931342 (chromosome 11q13) showed some evidence of association with breast cancer (per minor allele OR, 0.95; 95% CI, 0.91–0.99; \( P_{\text{trend}} = 0.028 \). This association was somewhat stronger for estrogen receptor--positive tumors (OR, 0.92; 95% CI, 0.87–0.98; \( P = 0.011 \)). None of these tag SNPs were associated with risk of colorectal cancer. In conclusion, loci associated with risk of prostate cancer may also be associated with ovarian and breast cancer susceptibility. However, the effects are modest and warrant replication in larger studies. [Cancer Res 2008;68(21):8837–42]

Introduction

Breast and ovarian cancer are among the most frequent cancers in women in Western countries and colorectal cancer is one of the most prevalent cancers that affect both men and women. The known ovarian and breast cancer susceptibility genes, such as BRCA1 and BRCA2, explain <40% of the excess familial risk of ovarian cancer and <25% of the excess familial breast cancer risk (1, 2). Similarly, the known high penetrance colorectal cancer susceptibility genes, such as APC and the mismatch repair genes, account for <5% of the overall incidence; however, it has been estimated that 35% of colorectal cancer can be due to inherited susceptibility (3, 4). It is likely that the unexplained excess familial risks for ovarian, breast, and colorectal cancer are due to a combination of multiple low/moderate penetrance genetic variants, which are associated with relatively small effects on risk in the individual but contribute substantially to the overall risk in the population.

Genome-wide association studies (GWAS) using large sets of cases and controls have proven to be an effective approach to identify the common variants that are associated with common diseases without prior knowledge of position or function. This approach has successfully identified novel loci for breast, colorectal, and prostate cancer, as well as for other complex, late-onset disorders (5–12). It is clear that some loci confer risk for more than one type of cancer. For example, the high penetrance rare deleterious variants in BRCA1 and BRCA2 increase risk of breast, ovarian, prostate, and other cancers, and deleterious mutations in the mismatch repair genes cause a spectrum of cancers including colorectal, endometrial, gastric, and ovarian. In addition, a common allele on 8q24 identified through a prostate cancer GWAS has shown also be associated colorectal and varian cancer (9, 12, 13). More than a dozen other prostate cancer susceptibility loci have now been identified from GWAS (see Table 1; refs. 8, 14–16). The aim of this study was to test 12 of these loci for evidence of association with ovarian, colorectal, or breast cancer. These loci included seven identified by Eeles and colleagues (14), two additional loci identified by Thomas and colleagues (15), and one further locus identified by Godumundsson and colleagues (16), together with two previously identified loci on chromosome 17 (8).

Materials and Methods

Cancer case-control studies. Two UK breast cancer case-control studies were used for this analysis. SEARCH (breast; 6,640 cases and 6,832 controls) started in 1996. SEARCH is an ongoing, UK population--based

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study of different epithelial cancers ascertained through the Eastern Cancer Registration and Information Centre (formerly East Anglian Cancer Registry). Eligible cases were those diagnosed under the age of 55 between 1991 and 1996 and those diagnosed under age 70 y since 1996 (17). Controls were randomly selected from the Norfolk, United Kingdom, component of the European Prospective Investigation of Cancer study (EPIC). The ethnic composition of the cases was ascertained through regional cancer genetics clinics in the United Kingdom Collaborative Trial of Ovarian Cancer Screening as controls. The Genetics of Familial Breast Cancer Study (GFBCS; 1,499 cases and 1,499 controls) is randomly selected from the Norfolk, United Kingdom, component of the EPIC study. In the GFBCS study of different epithelial cancers ascertained through the Eastern Cancer Registry, the subjects were sex and frequency between 18 and 69 y and diagnosed since the year 1996. Cancer-free controls are White, and at least 98% of the controls were of White ethnicity.

To reduce genotyping costs, the studies were divided into two sets: the first set comprising 4,339 cases and 4,552 controls from SEARCH and the second set comprising a further of 2,265 cases and 2,280 controls from SEARCH and the GFBCS samples. Single nucleotide polymorphisms (SNP) that showed marginally significant association in the initial set ($P_{\text{trend}} < 0.05$) were also genotyped in the second set.

The colorectal study, also from SEARCH, comprises 2,148 cases ages 19 to 69 y and diagnosed since the year 1996. Cancer-free controls (2,265) were recruited from general practices from around the Eastern UK region (19). Eligible individuals were sex and frequency matched in 5-y age bands to cases. More than 98% of participants are White.

Invasive epithelial ovarian cancer cases and controls came from four different studies (total cases 2,085 and 3,486 controls) described in detail elsewhere (20, 21). Briefly, these were SEARCH (ovarian) from United Kingdom Collaborative Trial of Ovarian Cancer Screening as controls. MALOVA is a population-based study from Denmark comprises 681 incident cases diagnosed from 1994 to 1999 and 1,460 matching controls, from the municipalities of Copenhagen and Frederiksberg, and surrounding counties, 446 cases and 1,221 controls (all are White) were used in this analysis. Finally, the GEOCS study from the United States (325 cases and 429 controls, among them 293 cases and 600 controls are White) is recruiting incident cases from gynecological oncology National Health Service centers throughout the United Kingdom (January 2006 onwards) and healthy postmenopausal women from the United Kingdom Collaborative Trial of Ovarian Cancer Screening as controls. MALOVA is a population-based study from Denmark comprises 681 incident cases diagnosed from 1994 to 1999 and 1,460 matching controls, from the municipalities of Copenhagen and Frederiksberg, and surrounding counties, 446 cases and 1,221 controls (all are White) were used in this analysis. Finally, the GEOCS study from the United States (325 cases and 429 controls, among them 287 cases, 369 controls are White) is recruiting incident cases from gynecological oncology National Health Service centers throughout the United Kingdom (January 2006 onwards) and healthy postmenopausal women from the United Kingdom Collaborative Trial of Ovarian Cancer Screening as controls. MALOVA is a population-based study from Denmark comprises 681 incident cases diagnosed from 1994 to 1999 and 1,460 matching controls, from the municipalities of Copenhagen and Frederiksberg, and surrounding counties, 446 cases and 1,221 controls (all are White) were used in this analysis. Finally, the GEOCS study from the United States (325 cases and 429 controls, among them 287 cases, 369 controls are White) is recruiting incident cases from gynecological oncology National Health Service centers throughout the United Kingdom (January 2006 onwards) and healthy postmenopausal women from the United Kingdom Collaborative Trial of Ovarian Cancer Screening as controls. MALOVA is a population-based study from Denmark comprises 681 incident cases diagnosed from 1994 to 1999 and 1,460 matching controls, from the municipalities of Copenhagen and Frederiksberg, and surrounding counties, 446 cases and 1,221 controls (all are White) were used in this analysis. Finally, the GEOCS study from the United States (325 cases and 429 controls, among them 287 cases, 369 controls are White) is recruiting incident cases from gynecological oncology National Health Service centers throughout the United Kingdom (January 2006 onwards) and healthy postmenopausal women from the United Kingdom Collaborative Trial of Ovarian Cancer Screening as controls.

### Table 1. Association of prostate SNPs with colorectal, ovarian, and breast cancer

<table>
<thead>
<tr>
<th>SNPs</th>
<th>Base change*</th>
<th>Gene/Chr.</th>
<th>MAF †</th>
<th>Reported GWAS prostate cancer</th>
<th>Colorectal cancer (2,148 cases/2,265 controls)</th>
<th>Ovarian cancer (1,973 cases/3,419 controls)</th>
<th>Breast cancer (4,339 cases/4,552 controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs9545619</td>
<td>T/C</td>
<td>ChrX</td>
<td>0.36</td>
<td></td>
<td>1.19 (1.07–1.31)</td>
<td>1.01 (0.93–1.11)</td>
<td>1.06 (0.99–1.12)</td>
</tr>
<tr>
<td>rs2660753</td>
<td>G/A</td>
<td>Chr3</td>
<td>0.09</td>
<td></td>
<td>1.18 (1.06–1.31)</td>
<td>0.92 (0.83–1.02)</td>
<td>1.06 (0.96–1.17)</td>
</tr>
<tr>
<td>rs10993994</td>
<td>G/A</td>
<td>Chr10</td>
<td>0.39</td>
<td></td>
<td>1.25 (1.17–1.34)</td>
<td>0.95 (0.89–1.01)</td>
<td>1.05 (0.96–1.14)</td>
</tr>
<tr>
<td>rs7931342†</td>
<td>C/A</td>
<td>Chr11</td>
<td>0.49</td>
<td></td>
<td>0.84 (0.79–0.90)</td>
<td>0.96 (0.91–1.02)</td>
<td>1.01 (0.93–1.09)</td>
</tr>
<tr>
<td>rs9364554</td>
<td>C/T</td>
<td>SLCC22A3</td>
<td>0.30</td>
<td></td>
<td>1.17 (1.08–1.26)</td>
<td>0.98 (0.91–1.04)</td>
<td>1.06 (0.97–1.16)</td>
</tr>
<tr>
<td>rs2755839</td>
<td>G/A</td>
<td>Chr19</td>
<td>0.15</td>
<td></td>
<td>0.83 (0.75–0.91)</td>
<td>1.08 (0.99–1.17)</td>
<td>0.99 (0.98–1.11)</td>
</tr>
<tr>
<td>rs6465657</td>
<td>A/G</td>
<td>LMTK2</td>
<td>0.46</td>
<td></td>
<td>1.12 (1.05–1.20)</td>
<td>1.00 (0.94–1.06)</td>
<td>0.96 (0.89–1.04)</td>
</tr>
<tr>
<td>rs7501939</td>
<td>G/A</td>
<td>TCF2</td>
<td>0.40</td>
<td></td>
<td>0.84 (0.79–0.89)</td>
<td>1.02 (0.96–1.08)</td>
<td>0.96 (0.89–1.04)</td>
</tr>
<tr>
<td>rs1859962</td>
<td>T/G</td>
<td>Chr17</td>
<td>0.48</td>
<td></td>
<td>1.20 (1.14–1.27)</td>
<td>0.98 (0.92–1.04)</td>
<td>0.98 (0.90–1.06)</td>
</tr>
<tr>
<td>rs10486567</td>
<td>G/A</td>
<td>JAZF1</td>
<td>0.24</td>
<td></td>
<td>0.78 (0.71–0.85)</td>
<td>1.01 (0.94–1.09)</td>
<td>1.01 (0.92–1.12)</td>
</tr>
<tr>
<td>rs12769019</td>
<td>A/G</td>
<td>CTBP2</td>
<td>0.28</td>
<td></td>
<td>1.25 (1.16–1.35)</td>
<td>1.03 (0.97–1.11)</td>
<td>1.00 (0.90–1.10)</td>
</tr>
<tr>
<td>rs2710646</td>
<td>C/A</td>
<td>EHBP1</td>
<td>0.20</td>
<td></td>
<td>1.15 (1.10–1.21)</td>
<td>0.93 (0.87–1.01)</td>
<td>1.05 (0.94–1.19)</td>
</tr>
</tbody>
</table>

*The most common allele in controls is given first.
†MAF: minor allele frequency in breast cancer controls.
White subjects of European ancestry only.
Per rare allele ORs with 95% CI are presented. ORs for the first seven SNPs in the table are from Eeles and colleagues (14), rs7501939 and rs1859962 are from Gudmundsson and colleagues (8), rs10486567 and rs12769019 (in perfect LD with rs4962416) are from Thomas and colleagues (15), and rs2710646 (in perfect LD with 721048) is from Gudmundsson and colleagues (16).
Genotyping failed in the MALOVA and UKOPS ovarian cancer studies for rs12769019. Data highlighted with bold text are the statistically significant results.

OR (95% CI) P
0.012 1.06 (0.96–1.17) 0.26
0.028 1.01 (0.92–1.12) 0.98
0.20 1.15 (1.10–1.21) 0.22
0.07 1.03 (0.97–1.11) 0.94
0.98 1.03 (0.97–1.11) 0.97
A case-only analysis was used to compare genotype-specific risks by disease without a genotype-stratum interaction term using likelihood ratio tests. Between study strata by comparing logistic regression models with and estimated by unconditional logistic regression. We tested for heterogeneity for allele dosage and associated 95% confidence intervals (95% CI) were also logistic regression stratified by study where appropriate. Odds ratios (OR) ovarian, colorectal, and breast cancer. This was done using unconditional frequencies in cases and controls using a trend test for each SNP and control. The primary tests of association were comparison of genotype degree of freedom) for each set of controls as part of the genotyping quality association in controls between age and genotype frequency for sets are presented in Supplementary Table S1. There was no Table 1. The observed genotype frequencies for each of the data from HWE are likely to be chance observations. discrimination between genotypes, suggesting that these deviations (breast; $P=0.02$) compared with the common allele carrier. Figure 1 shows the genotype-specific ORs for each ovarian study and for the combined analysis for rs2660753. SNP rs7931342 was the only one associated with breast cancer risk in the first case-control set, with the minor allele of rs7931342 being associated with a decreased risk of breast cancer (per minor allele OR, 0.93; 95% CI, 0.87–0.98; $P_{\text{trend}} = 0.01$). We therefore genotyped this SNP in the validation samples. There was no association based on these data alone (per minor allele OR, 0.99; 95% CI, 0.92–1.05; $P_{\text{trend}} = 0.64$), but when the data were combined, the association remained significant at the 5% level (per minor allele OR, 0.95; 95% CI, 0.91–0.99; $P_{\text{trend}} = 0.028$). There was no between-study heterogeneity ($P = 0.82$). Morphology (ductal or lobular) and estrogen receptor (ER) status were available for 5,822 and 3,495 breast cancer cases, respectively, from SEARCH, and we carried out analyses based on these disease subgroups. SNP

### Table 2. Genotype-specific risks (95%CI) for serous-type invasive ovarian cancers in combined data for White subjects of European ancestry

<table>
<thead>
<tr>
<th>dbSNP</th>
<th>Controls AA*</th>
<th>Aa</th>
<th>aa</th>
<th>Total</th>
<th>Cases AA*</th>
<th>Aa</th>
<th>aa</th>
<th>Total</th>
<th>Per rare allele OR (95% CI)</th>
<th>$P_{\text{het}}$</th>
<th>$P_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs945619</td>
<td>1,355</td>
<td>1,565</td>
<td>433</td>
<td>3,353</td>
<td>362</td>
<td>407</td>
<td>139</td>
<td>908</td>
<td>1.07 (0.96–1.19)</td>
<td>0.18</td>
<td>0.24</td>
</tr>
<tr>
<td>rs2660753</td>
<td>2,760</td>
<td>525</td>
<td>18</td>
<td>3,303</td>
<td>717</td>
<td>170</td>
<td>14</td>
<td>901</td>
<td>1.29 (1.09–1.53)</td>
<td><strong>0.004</strong></td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>rs10993994</td>
<td>1,298</td>
<td>1,574</td>
<td>483</td>
<td>3,355</td>
<td>337</td>
<td>434</td>
<td>137</td>
<td>908</td>
<td>1.04 (0.93–1.15)</td>
<td>0.77</td>
<td>0.50</td>
</tr>
<tr>
<td>rs7931342</td>
<td>852</td>
<td>1,709</td>
<td>807</td>
<td>3,368</td>
<td>243</td>
<td>446</td>
<td>223</td>
<td>912</td>
<td>1.00 (0.90–1.11)</td>
<td>0.63</td>
<td>0.96</td>
</tr>
<tr>
<td>rs9364554</td>
<td>1,585</td>
<td>1,397</td>
<td>297</td>
<td>3,279</td>
<td>430</td>
<td>381</td>
<td>90</td>
<td>901</td>
<td>1.06 (0.94–1.18)</td>
<td>0.54</td>
<td>0.36</td>
</tr>
<tr>
<td>rs2735839</td>
<td>2,455</td>
<td>850</td>
<td>68</td>
<td>3,373</td>
<td>682</td>
<td>205</td>
<td>26</td>
<td>913</td>
<td>0.95 (0.82–1.10)</td>
<td>0.09</td>
<td>0.50</td>
</tr>
<tr>
<td>rs7501939</td>
<td>1,164</td>
<td>1,612</td>
<td>571</td>
<td>3,347</td>
<td>300</td>
<td>439</td>
<td>169</td>
<td>908</td>
<td>1.07 (0.96–1.19)</td>
<td>0.45</td>
<td>0.21</td>
</tr>
<tr>
<td>rs6463567</td>
<td>955</td>
<td>1,653</td>
<td>734</td>
<td>3,342</td>
<td>275</td>
<td>435</td>
<td>85</td>
<td>896</td>
<td>0.93 (0.84–1.04)</td>
<td>0.38</td>
<td>0.20</td>
</tr>
<tr>
<td>rs1859962</td>
<td>860</td>
<td>1,670</td>
<td>826</td>
<td>3,356</td>
<td>243</td>
<td>438</td>
<td>219</td>
<td>900</td>
<td>0.99 (0.87–1.07)</td>
<td>0.67</td>
<td>0.53</td>
</tr>
<tr>
<td>rs10486567</td>
<td>1,922</td>
<td>1,183</td>
<td>177</td>
<td>3,282</td>
<td>545</td>
<td>308</td>
<td>49</td>
<td>902</td>
<td>0.94 (0.83–1.07)</td>
<td>0.50</td>
<td>0.34</td>
</tr>
<tr>
<td>rs2710464</td>
<td>2,095</td>
<td>1,017</td>
<td>121</td>
<td>3,233</td>
<td>601</td>
<td>262</td>
<td>48</td>
<td>911</td>
<td>1.01 (0.89–1.15)</td>
<td>0.06</td>
<td>0.85</td>
</tr>
<tr>
<td>rs12769019</td>
<td>806</td>
<td>641</td>
<td>121</td>
<td>1,568</td>
<td>265</td>
<td>191</td>
<td>49</td>
<td>505</td>
<td>1.02 (0.87–1.20)</td>
<td>0.23</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*AA, common homozygote.
† Aa, heterozygote.
‡ aa, rare homozygote. Data highlighted with bold text are the statistically significant results.
rs7931342 was associated with decreased risks of ductal breast cancer (per minor allele OR, 0.94; 95% CI, 0.89–0.99; \( P_{\text{trend}} = 0.02 \)) but was not associated with lobular breast cancer (per minor allele OR, 1.03; 95% CI, 0.93–1.13; \( P_{\text{trend}} = 0.57 \)). This difference between ductal and lobular was not statistically significant (\( P = 0.074 \)). SNP rs7931342 was associated with decreased risk in ER-positive breast cancer (per minor allele OR, 0.92; 95% CI, 0.87–0.98; \( P_{\text{trend}} = 0.011 \)) but was not associated with ER-negative breast cancer (per minor allele OR, 1.02; 95% CI, 0.91–1.14; \( P_{\text{trend}} = 0.73 \)). Again, the difference between risk of ER-positive and ER-negative tumors was not statistically significant (\( P = 0.09 \)).

Discussion

We have evaluated 12 confirmed prostate cancer–associated loci with breast, colorectal, and ovarian cancer using tag SNPs. In all but two cases, we found no evidence of an association, and the 95% confidence limits exclude the estimated OR for prostate cancer. Thus, most of these susceptibility loci appear to be specifically associated with prostate cancer risk. Two loci, however, showed some evidence of association. We found the minor allele of rs2660753 was associated with an increased risks of invasive ovarian cancer and of serous ovarian cancer in particular. The same allele was also associated with increased prostate cancer risk, with a similar OR (Table 1). Support for a common genetic basis for prostate and ovarian cancer comes from the observation that ovarian cancer cases are more likely to report a first-degree relative with prostate cancer than controls (5.1% versus 2.4%; \( P = 0.00002 \)). The minor allele of rs7931342, associated with a reduced risk of prostate cancer, was also associated with a reduced risk of breast cancer (Table 1). These results, however, need to be treated with caution. A large number of reported positive associations have not been replicated by subsequent studies (22, 23). In the literature, it has been estimated that the fraction of false-positive findings is at least 0.95 for studies of association between genetic variants and disease risks (24). Even if these loci are treated as strong candidate loci, the level of statistical significance decreases short of what would be required to establish clear evidence of association. To explore the likelihood that these results represent true associations, we have computed the false-positive report probability (FPRP) under different assumptions. FPRP depends on the prior probability that a true association exists, the observed level of significance (\( \alpha \)), and the statistical power to detect the OR of the alternative hypothesis at the given \( \alpha \) (25). As the genome has a very large number of common SNPs, the prior probability of association of a random SNP is very low (<1 in a million). However, the prior probability is likely to be more favorable for rs2660753 and rs7931342 because these two SNPs have already been shown to be strongly associated with a hormonally related cancer, prostate cancer (14). Among ~30 common SNPs shown to
be associated with common cancers, one (rs6983267) has been shown to be associated with multiple cancer types, suggesting that the prior probability for such pleiotropy may be quite high. The FPRPs for the two associated SNPs under different prior probabilities and the power to detect the association at our observed significance level (α; assuming the true effect size is equal to that observed) are presented in Table 3. If, for example, we assume the prior to be 1 in 100, the FPRP for association of rs2660753 with serous type of ovarian cancer will be 0.33. This suggests that the association has a reasonable chance of being true and is worthy of additional follow-up (see Table 3). The evidence is weaker for rs7931342 with FPRPs of 0.21 and 0.75 for priors of 1 in 10 and 1 in 100, respectively.

Hidden population stratification is an alternative explanation for a spurious association. This occurs when allele frequencies differ between population subgroups and case and controls are drawn differentially from those subgroups. It seems unlikely that population stratification is important in this association study because we restricted our analysis to White subjects with European ancestry for the four ovarian cancer studies used. The two breast cancer studies reported here were both from United Kingdom and largely drawn from the same ethnic groups (>98% were of European ancestry). The extent of population stratification in the British population has been found to be generally modest (5).

Assuming the results represent true associations, they may either be due to a direct causative effect of the SNPs tested, or may be because these SNPs are markers in linkage disequilibrium (LD) with a functional variant. Neither SNP rs2660753 nor rs7931342 are located within known genes. rs2660753 is situated on chromosome 3p12. The nearest gene is VGLL3 (~70 kb away), which encodes colon carcinoma–related protein. The nearest alternative candidate gene is CHMP2B and POU1F1 in the same side of SNP rs2660753 and are 166 and 198 kb away, respectively. POU1F1 encodes POU domain class 1 transcription factor 1. POU1F1 is a pituitary-specific transcription factor centrally involved in regulating growth hormone (GH) synthesis. It is expressed in normal and human breast tumors and regulates GH secretion and cell proliferation (26). CHMP2B encodes chromatin-modifying protein 2B. CHMP2B belongs to the chromatin-modifying protein/charged multivesicular body protein family. It has been reported that a mutation in CHMP2B leads to aberrant mRNA splicing in tissue samples from affected individuals with familial frontotemporal dementia (27). SNP rs7931342 is situated on chromosome 11q13, an area where rearrangements are frequently observed in human cancers. The nearest gene, MYEOV, is 67 kb away but in different haplotype block with SNP rs7931342. MYEOV is a putative oncogene that is frequently amplified in breast tumors and esophageal carcinomas (28). It often comamplifies with the cell cycle control gene CCND1 (~360 kb away from MYEOV). MYEOV amplification is correlated with estrogen and progesterone receptor–positive breast cancer, the lobular carcinoma subtype, and axillary nodal involvement (29). This is consistent with our finding that the association was stronger for ER-positive cases but not with the observation that the association was restricted to cases of the ductal subtype. Increased MYEOV expression is also associated with cell proliferation and invasion in colon cancer cell lines (30). The effect of this SNP in colorectal cancer was in the same direction and of a similar magnitude to that in breast cancer, but our sample size was much smaller for colorectal cancer and the association was not significant. Although it is plausible that the effects of these functional variants at these loci is to regulate one or more of the local genes, only functional tests will determine if this is the mode of action and which genes are having an active role in cancer development.

We found no evidence of association with colorectal cancer for any of the other 11 SNPs analyzed in our study. Our colorectal cancer study (2,148 cases of 2,265 controls) was able to provide at least 86% power at a type I error of 0.01 to detect a codominant allele with a frequency of 0.3 that confers a relative risk of 1.2. Thus, at the present time, SNP rs6983267 on 8q seems to be unique in being strongly associated with both prostate and colorectal cancer. However, we cannot exclude the possibility that the alleles investigated are associated with smaller risks with colorectal cancer.

In conclusion, we have genotyped 12 prostate cancer–associated SNPs in colorectal, ovarian, and breast cancer case-control studies. We found some evidence for association of SNP rs2660753 on chromosome 3p12 with ovarian cancer and of SNP rs7931342 on chromosome 11q13 with breast cancer risk. None of the 12 SNPs tested were associated with colorectal cancer. The observed associations with ovarian and breast cancer warrant confirmation in larger studies.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Table 3. FPRP values for three disease associated SNPs

<table>
<thead>
<tr>
<th>SNP</th>
<th>Cancer type</th>
<th>OR 95% CI</th>
<th>Statistical power*</th>
<th>P (α)</th>
<th>Prior probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2660753</td>
<td>Ovarian</td>
<td>1.19 (1.04–1.37)</td>
<td>0.66</td>
<td>0.012</td>
<td>0.05</td>
</tr>
<tr>
<td>rs2660753</td>
<td>Serous type ovarian</td>
<td>1.29 (1.09–1.53)</td>
<td>0.70</td>
<td>0.0034</td>
<td>0.014</td>
</tr>
<tr>
<td>rs7931342</td>
<td>Breast</td>
<td>0.95 (0.91–0.99)</td>
<td>0.56</td>
<td>0.028</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Trend test P value (one degree of freedom). Data highlighted with bold text are FPRP < 0.5.
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