Evaluating the Utility of Polygenic Risk Scores in Identifying High-Risk Individuals for Eight Common Cancers

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Abstract

Background: Genome-wide association studies have identified common genetic risk variants in many loci associated with multiple cancers. We sought to systematically evaluate the utility of these risk variants in identifying high-risk individuals for eight common cancers. Methods: We constructed polygenic risk scores (PRS) using genome-wide association studies–identified risk variants for each cancer. Using data from 400,812 participants of European descent in a population-based cohort study, UK Biobank, we estimated hazard ratios associated with PRS using Cox proportional hazard models and evaluated the performance of the PRS in cancer risk prediction and their ability to identify individuals at more than a twofold elevated risk, a risk level comparable to a moderate-penetrance mutation in known cancer predisposition genes. Results: During a median follow-up of 5.8 years, 14,584 incident case patients of cancers were identified (ranging from 358 epithelial ovarian cancer case patients to 4,430 prostate cancer case patients). Compared with those at an average risk, individuals among the highest 5% of the PRS had a two- to threefold elevated risk for cancer of the prostate, breast, pancreas, colorectal, or ovary, and an approximately 1.5-fold elevated risk of cancer of the lung, bladder, or kidney. The areas under the curve ranged from 0.567 to 0.662. Using PRS, 40.4% of the study participants can be classified as having more than a twofold elevated risk for at least one site-specific cancer. Conclusions: A large proportion of the general population can be identified at an elevated cancer risk by PRS, supporting the potential clinical utility of PRS for personalized cancer risk prediction.

Globally, cancer is the second leading cause of death, following cardiovascular diseases. It is estimated that approximately 18.1 million cancer case patients were diagnosed and 9.6 million individuals died of cancer in 2018 worldwide (1). Over the years, a large number of deleterious germline mutations have been identified in cancer susceptibility genes (2-5). Among them, high-penetrance mutations have been associated with notably elevated cancer risk, but they explain only a small fraction of cancer events, because of their extremely low prevalence in the general population. For example, carriers of deleterious mutations in the BRCA1 gene are estimated to have around an 80% lifetime risk of developing breast cancer (6,7), but only 0.24% of women in the general population carry BRCA1 pathogenic mutations (8). More recently, moderate-penetrance mutations have been identified in multiple cancer predisposition genes. Most of them are associated with a two- to threefold elevated risk of cancer, and some have been included in genetic testing (5,9). For example, the CHEK2 mutation 1100delC is associated with about a twofold increased risk of breast or colorectal cancer, and deleterious ATM mutations are associated with a two- to threefold elevated risk of breast cancer (10-12). However, the frequency of these mutations is low in the general population (0.71% for CHEK2 1100delC, 1% to 2% for deleterious ATM mutations) (11,13).

Since 2005, genome-wide association studies (GWAS) have identified a large number of common genetic variants in relation to multiple site-specific cancers. Although the risk associated with each variant is small, individuals who carry multiple risk variants can be at a considerably elevated risk for the disease (14). Polygenic risk scores (PRS) can be used to summarize the combined effect of multiple variants to identify individuals at a high risk of site-specific cancer (15). Several studies have investigated the utility of PRS in risk prediction and stratification, but they typically study only one cancer at a time (16-18).
because it was the most common ovarian cancer, and the vast majority (8000, 8000, and 8010) (21). Epithelial ovarian cancer was selected because it was the most common ovarian cancer, and the vast majority of risk variants identified to date for ovarian cancer is from GWAS restricting to epithelial ovarian cancer.

Furthermore, many of the previous studies were limited by a small sample size. Herein, we evaluated the utility of PRS in predicting cancer risk for eight site-specific cancers (prostate, breast, pancreas, colorectal, kidney, bladder, lung, and ovary), which account for approximately 59% of the estimated number of all new cancer cases that will be diagnosed in the United States in 2019 (19). Furthermore, we sought to estimate the percentage of individuals in the general population who can be predicted to have an at least twofold elevated risk of cancer, a risk level comparable to the risk associated with many moderate-penetrance mutations in known cancer predisposition genes that are currently included in clinical genetic testing.

Methods

Study Subjects, Genotype, and Imputation

The UK Biobank is a population-based cohort study, which has recruited more than 500,000 adults across England, Scotland, and Wales. The design and methods of the UK Biobank study have been previously described (20). Data and diagnoses on site-specific incident cancers were provided by the National Health Service Information Centre for participants from England and Wales (follow-up through March 31, 2016) and by the NHS Central Register Scotland for participants from Scotland (follow-up through October 31, 2015). Cancers were coded by the International Classification of Diseases, Ninth Revision (ICD-9) or the International Classification of Diseases, Tenth Revision (ICD-10). Histological subtypes were classified according to the International Classification of Diseases for Oncology (ICD-O). Included in this study are investigations of the following cancers: prostate (ICD-9 = 185 or ICD-10 = C61), breast (ICD-9 = 174 or ICD-10 = C50), colorectal (ICD-9 = 153, 154.1 or ICD-10 = C18, C20), kidney (ICD-9 = 189.0 or ICD-10 = C64), bladder (ICD-9 = 188 or ICD-10 = C67), lung (ICD-9 = 162.2–162.9 or ICD-10 = C34), and epithelial ovary (ICD-9 = 183.0 or ICD-10 = C56; ICD-O: 8441, 8460, 8462, 8380, 8381, 8470, 8471, 8472, 8473, 8480, 8310, 8140, 8260, 8440, 8450, 9000, 8000, and 8010) (21). Epithelial ovarian cancer was selected because it was the most common ovarian cancer, and the vast majority of risk variants identified to date for ovarian cancer is from GWAS restricting to epithelial ovarian cancer.

Imputation data of 488,377 participants were acquired from UK Biobank. Samples were genotyped using two arrays sharing a 95% marker content, the UK BiLEVE Axiom (UKBL; 807,411 markers) and the UK Biobank Axiom (UKBB, 825,927 markers), and were imputed using reference panels of the Haploview Reference Consortium or UK10K and 1000 Genomes phase 3. We excluded individuals marked as outliers for heterozygosity, low call rates, and sex chromosome aneuploidy (n = 628). European individuals were identified from the genotype data by projecting all of the UK Biobank samples on the first two major principal components of four 1000 Genome populations (CEU, YRI, CHB, and JPT) (22). Individuals not falling in the neighborhood of the CEU cluster were excluded (n = 23,425). In the dataset from UK Biobank, a kinship coefficient was estimated for each pair of samples using KING’s robust estimator (23). We also excluded second-degree (or higher) related individuals (kinship coefficient > 0.0442; n = 37,590) and participants who had been diagnosed with cancer at baseline (n = 24,944). A total of 400,812 individuals (186,376 men and 214,436 women) remained after these exclusions (not mutually exclusive).

SNP Selection

We compiled the information for the genetic variants identified by previous GWAS in association with the risk of any of the eight site-specific cancers by reviewing the GWAS catalog and previous PubMed publications. Single-nucleotide polymorphisms (SNPs) specifically associated with the risk of a specific subtype of a given cancer were not included in the analysis, except for epithelial ovarian cancer. Cancer risk variants on the X chromosome, reported exclusively from non-European populations, or in high linkage disequilibrium ($r^2 \geq 0.2$ in data of European ancestry in the 1000 Genomes project database), were also excluded in this study. For some previously reported risk variants that were not available in the data from UK Biobank, SNPs in high linkage disequilibrium ($r^2 \geq 0.85$) were selected for the study. For breast cancer, we used a PRS of 313 SNPs reported by a recent study (18), and 288 of the 313 SNPs were available in our dataset. A total of 612 SNPs were retained to build PRS after these exclusions (Table 1). A detailed list of SNPs for the PRS of each cancer is shown in Supplementary Table 1 (available online).

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### Table 1. Number of cancer-associated SNPs used to construct the PRS and estimate AUC for each site-specific cancer

| Cancers | No. of SNPs | No. of Loci | Cases, mean (SD) | Noncases, mean (SD) | P† | PRS | AUC (95% CI)* |
|---------|-------------|-------------|------------------|---------------------|----|-----|-------------|
| Prostate| 147         | 117         | 12.03 (0.68)     | 11.63 (0.68)        | <.001| 0.662 (0.655 to 0.670) | 0.529 (0.522 to 0.535) | 0.669 (0.661 to 0.676) |
| Breast  | 288         | 183         | 16.33 (0.60)     | 16.05 (0.59)        | <.001| 0.628 (0.620 to 0.637) | 0.528 (0.521 to 0.534) | 0.633 (0.624 to 0.641) |
| Colorectal| 95          | 74          | 8.043 (0.47)     | 7.859 (0.47)        | <.001| 0.609 (0.598 to 0.620) | 0.523 (0.515 to 0.532) | 0.613 (0.602 to 0.624) |
| Lung    | 19          | 14          | 1.958 (0.37)     | 1.886 (0.37)        | <.001| 0.591 (0.576 to 0.606) | 0.589 (0.577 to 0.602) | 0.615 (0.600 to 0.629) |
| Kidney  | 15          | 14          | 2.257 (0.41)     | 2.171 (0.40)        | <.001| 0.567 (0.543 to 0.591) | —‡ | —‡ |
| Bladder | 14          | 13          | 1.963 (0.35)     | 1.868 (0.36)        | <.001| 0.583 (0.559 to 0.607) | —‡ | —‡ |
| Ovary   | 31          | 28          | 2.478 (0.34)     | 2.400 (0.32)        | <.001| 0.568 (0.537 to 0.598) | —‡ | —‡ |
| Pancreas| 22          | 18          | 3.892 (0.47)     | 3.680 (0.50)        | <.001| 0.639 (0.613 to 0.664) | —‡ | —‡ |

*Area under the receiver operating characteristic curve (AUC) was calculated by logistical models, adjusted for genotype array types. CI = confidence interval; PRS = polygenic risk score; SNP = single-nucleotide polymorphism.

†Two-sided, two-sample t tests were performed with a type I error of 0.05.

‡Data on family cancer history (first-degree relatives) were available for cancer of prostate, breast, lung, and colorectal only.

§P < .001 for the improvement of model performance by adding family history to the PRS-based model for all cancers.
Statistical Analysis

An additive genetic model was used to calculate each cancer-specific PRS, using previously reported regression coefficients as SNP-specific weights. For each site-specific cancer, a PRS was calculated as the sum of the product of the weight and the number of risk alleles for each risk variant per individual (24). Then, we checked the difference in distribution of standardized PRS (subtracted the mean and divided by the standard deviation) between case patients and noncase patients by two-sided, two-sample tests with a type I error of 0.05. We also divided the study participants into 50 groups according to the percentile of PRS (each 2%) and calculated the cumulative risk within each group for cancers of the prostate, breast, colorectal, and lung over the follow-up period. The PRS of each site-specific cancer was then categorized into quintiles. Hazard ratios (HRs) and 95% confidence intervals (CIs) associated with PRS were estimated by Cox proportional hazard models, using age as the time scale, and adjusted for age at the baseline survey, genotype array type (UKBL or UKBB), the 10 principal components for ancestry, sex (for nonsex-specific cancers), and stratified by birth cohorts. The assumption of proportional hazard was tested by adding time-dependent interaction term. We also estimated the hazard ratios of site-specific cancers for participants within the top and bottom 1% and 5% of each PRS, using the middle quintile (40%-60%) as the reference group. Two-sided Wald tests with a type I error of 0.05 were used for trend test. Then, we estimated the proportion of study participants in the cohort with a given relative risk of each site-specific cancer (HR = 2.0, 2.5, and 3.0). The area under the receiver operating characteristic curve (AUC) of the PRS for each cancer was calculated using logistical models that were adjusted for genotype array types. AUCs for models, including family history of cancer in first-degree relatives only, or both family history and PRS, were calculated for cancers of the prostate, breast, colorectal, and lung, because data on family history of these cancers in first-degree relatives were collected from a baseline survey in the UK Biobank. We calculated the absolute risks of site-specific cancer by PRS group using incidence and mortality rates in the United Kingdom, as described previously (25,26).

Results

During a median follow-up of 5.8 years of 400 812 participants (186 376 men and 214 436 women), there were 14 584 incident case patients of cancers, including 4430 with prostate cancer, 4340 with female breast cancer, 2453 with colorectal cancer, 1508 with lung cancer, 432 with pancreatic cancer, 545 with kidney cancer, and 358 with epithelial ovarian cancer.

Table 1 summarizes the number of SNPs and loci for the PRS for each site-specific cancer, and Figure 1 displays the
distribution of PRS for the four most common cancers: prostate, breast, colorectal, and lung. These PRS were all normally distributed, and the distribution curves for case patients were shifted to the right. Case patients had a higher mean value of each cancer-specific PRS than noncase patients, and the difference was highly statistically significant (Table 1). The PRS for prostate cancer had the largest AUC (0.662, 95% CI = 0.655 to 0.670), followed by pancreatic cancer (0.639, 95% CI = 0.613 to 0.664), and female breast cancer (0.628, 95% CI = 0.620 to 0.637). Kidney cancer has the lowest AUC (0.567, 95% CI = 0.543 to 0.591). The AUC derived from PRS was substantially higher than those derived using family history for cancers of the prostate, female breast, and colorectal, but not for lung cancer. Adding family history of cancer in first-degree relatives into the model slightly, but statistically significantly, improved the model performance in risk prediction.

The risk of developing cancer of the prostate, breast, colorectal, or lung during the 5.8-year follow-up period increased substantially with an increased PRS (Figure 2). For example, the cumulative risk of female breast cancer increased from 0.6% in the lowest 2% of PRS to 5.4% in the highest 2% of PRS. Similar results were observed for four other less common cancers (data not shown). Using Cox regression models, hazard ratios of each site-specific cancer were estimated in association with its PRS, with the quintile of the lowest PRS as reference (Table 2). The risk of each site-specific cancer was statistically significantly associated with its PRS, following a dose-response pattern (P < .001). Compared with individuals in the lowest PRS quintile, those in the highest quintile had a greater than threefold risk for cancer of the prostate (HR = 5.63, 95% CI = 5.00 to 6.35), breast (HR = 3.77, 95% CI = 3.39 to 4.21), pancreas (HR = 3.37, 95% CI = 2.39 to 4.76), and colorectal (HR = 3.08, 95% CI = 2.68 to 3.55), and a 1.7- to 2.2-fold elevated risk was observed for other cancers. Hazard ratios estimated with the middle quintile as the reference with or without additional adjustment of cancer family history are presented in Supplementary Table 2 (available online).

Compared with individuals in the middle quintile, individuals in the top 1% of the PRS had a threefold or higher risk of cancers of the prostate, breast, and colorectal, whereas individuals in the bottom 1% of the PRS had a 70% or greater reduced risk of these cancers (Table 3). Substantially elevated or reduced risks of other cancers in these extreme risk groups were also observed.

Figure 2. Cumulative risk of cancer over follow-up period by percentile of PRS. Study participants were divided into 50 groups according to the percentile of PRS (each 2%). Cumulative risk over a 5.8-year follow-up period of the UK Biobank cohort was displayed for cancers of the (A) prostate, (B) breast, (C) colorectal, (D) lung. PRS = polygenic risk score.
Figure 3 shows the estimated 5-year absolute risk of cancer of the breast, prostate, colorectal, and lung by PRS groups. In the United Kingdom, people become eligible for colorectal testing starting at the age of 60 years (50 years in Scotland), and people become eligible for breast cancer screening starting at the age of 50 years (47 years in parts of England) (27,28). The 5-year absolute risk is 1.2% for breast cancer and 0.2% for colorectal cancer for an individual aged 50 years in the United Kingdom with a median PRS (45-55 percentile group). However, people in the highest PRS group (>95%) reached the risk levels by ages 38 and 43 years for breast cancer and colorectal cancer, respectively, much earlier than the average-risk group.

We estimated the proportion of the study participants at a given elevated risk (HR ≥2.0, 2.5, or 3; Table 4). Compared with the middle quintile, 40.4% of participants were at a greater than twofold risk of at least one type of cancer, including prostate cancer (28% of men), female breast cancer (20% of women), pancreatic cancer (9%), colorectal cancer (10%), kidney cancer (0.6%), lung cancer (0.1%), and epithelial ovarian cancer (8% of women). A total of 5.7% of the study participants were at a greater than threefold risk (HR ≥3.0) of at least one type of these cancers.

**Discussion**

This is the first large prospective cohort study to systematically evaluate the performance of PRS that were constructed using...
GWAS-identified cancer risk variants for multiple major cancers. Although the discriminatory ability of PRS in classifying cancer case patients and noncase patients for any of the cancers evaluated in the study was moderate, as measured using AUCs ranging from 0.568 (for epithelial ovarian cancer) to 0.662 (for prostate cancer), these PRS can identify a large number of
individuals in the general population who are at a twofold or higher risk of developing cancer, which is a risk level that is often regarded as clinically actionable for some cancers (e.g., breast and colorectal cancers). For example, 28% of men and 20% of women were identified to have a greater than twofold risk of prostate cancer or female breast cancer, respectively. Overall, approximately 40.4% and 5.7% of study participants in the UK Biobank cohort had a greater than two- or threefold elevated risk of at least one site-specific cancer, compared with those who had an average risk of cancer in the total population.

For risk prediction, instead of obtaining information on the family history of cancer and other cancer risk factors, which could change over time, cancer-specific PRS can be assessed at any time in life. In the United Kingdom, current recommendations are to start breast cancer and colorectal cancer (in Scotland) screening at age 50 years (27,28). In the United States, the US Preventive Services Task Force also recommends starting breast and colorectal cancer screening at age 50 years (29,30). These guidelines are based on the average risk for the general population. Our results show that people in the highest PRS group reached the same risk level much earlier than the recommended age to start screening for the general population, which suggests that cancer-specific PRS can identify high-risk individuals who should receive screening tests earlier than the general population. The utility of PRS in identifying high-risk women for cost-effective breast cancer screening programs is currently under investigation in several ongoing studies (31,32). In addition, PRS can also be used to identify individuals at a low risk of cancer to postpone the age of receiving regular screenings to reduce the costs and complications related to cancer screenings. Certainly, further studies are needed to address issues related to the efficacy and ethics of selected screenings before they can be implemented in the general population.

In this study, the PRS was constructed based on the most updated GWAS-identified risk variants for each cancer. The AUC derived using PRS was substantially higher than that using family history for each site-specific cancer except for lung cancer. Fewer SNPs were included in the PRS for lung cancer compared with the PRS for prostate, breast, or colorectal cancers. In addition, the family history of lung cancer may reflect some shared smoking status in a family, which is a strong risk factor for lung cancer. Several previous studies have evaluated the association of various cancer-specific PRS. For example, Mavaddat et al. (18) built a PRS for breast cancer using 313 SNPs, with a P value less than $10^{-5}$ for hard-threshold stepwise forward regression and reported an AUC of 0.630 for overall breast cancer risk. For prostate cancer, Schumacher et al. (16) reported that men in the top 1% of PRS had a relative risk of 5.71 (95% CI: 5.04, 6.48) when compared with men in the 35-75 PRS percentiles. For epithelial ovarian cancer, Yang et al. (17) showed that women in the top 5% PRS category had a 1.78-fold and 2.14-fold elevated risk of overall epithelial and serous subtype ovarian cancer, respectively. These results are, in general, comparable to what we found in this study.

There are some limitations in our study. We built and evaluated PRS among individuals of European descent only. The clinical utility of PRS needs to be evaluated among populations of other races and ethnicities. A recent study has shown that PRS for breast cancer derived from non-Hispanic American-ancestry women performed well in Latina women (33). We also anticipate that the performance of PRS in cancer risk prediction and stratification will be further improved when combined with other lifestyle risk factors. In addition, the follow-up time (median = 5.8 years) of this cohort was relatively short, and a longer follow-up of this cohort could provide additional data to further evaluate cancer-associated PRS in the future. Nevertheless, our study suggests that we could start to consider using PRS to identify high-risk individuals for cost-efficient screenings.

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