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Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Association of Pancreatic Cancer Susceptibility Variants with Risk of Breast Cancer in Women of European and African Ancestry

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Abstract

Background: Pancreatic cancer mutation signatures closely resemble breast cancer, suggesting that both cancers may have common predisposition mechanisms that may include commonly inherited SNPs.

Methods: We examined 23 genetic variants known to be associated with pancreatic cancer as breast cancer risk factors in the Root genome-wide association study (GWAS; 1,657 cases and 2,029 controls of African diaspora) and GAME-ON/DRIVE GWAS (16,003 cases and 41,335 controls of European ancestry).

Results: None of the pancreatic cancer susceptibility variants were individually associated with breast cancer risk after adjustment for multiple testing (at $\alpha = 0.002$) in the two populations. In Root GWAS, a change by one SD in the polygenic risk score (PRS) was not significantly associated with breast cancer. In addition, we did not observe a trend in the relationship between PRS percentiles and breast cancer risk.

Conclusions: The association between reported pancreatic cancer genetic susceptibility variants and breast cancer development in women of African or European ancestry is likely weak, if it does exist.

Impact: Known GWAS-derived susceptibility variants of pancreatic cancer do not explain its shared genetic etiology with breast cancer. *Cancer Epidemiol Biomarkers Prev; 27(1); 116–8. ©2017 AACR.*

Introduction

Patients with pancreatic cancer have been found to carry rare germline deleterious variants in breast cancer susceptibility genes, such as *BRCA1*, *BRCA2*, *PALB2*, and *ATM* (1–3). In addition, a number of common SNPs were identified to be associated with common diseases, including pancreatic and breast cancers, by hypothesis-free genome-wide association study (GWAS) approach. Couch and colleagues evaluated the SNPs associated with breast cancer risk for influence on pancreatic cancer risk and found the SNP rs1045485 retained significance after adjusting for multiple testing (4). Furthermore, an interesting phenomenon indicated in the Catalogue of Somatic Mutations in Cancer was that the 7 mutational signatures of pancreatic cancer were all shared by those of breast cancer (http://cancer.sanger.ac.uk/signatures/matrix.png). These lines of evidence suggest that breast cancer and pancreatic cancer might have common predisposition mechanisms.

To date, many of the common variants associated with the risk of pancreatic cancer have been identified by the GWAS approach, and more than 20 loci reached the standard GWAS significance threshold (5), but no study has explored the possible associations between these SNPs and breast cancer risk. Here, we examined whether GWAS-identified genetic susceptibility to pancreatic cancer is related to breast cancer risk using GWAS datasets from two breast cancer consortia: Root and GAME-ON/DRIVE.

Materials and Methods

The Root consortium contained 1,657 cases and 2,029 controls of African diaspora, in which genotyping was conducted using the Illumina HumanOmni2.5-8v1 array, and imputation was conducted with the 1000 Genomes Project Phase 1 as reference panel (6). The GAME-ON/DRIVE GWAS is a meta-analysis of 12 breast cancer GWAS, including 16,003 cases and 41,335 controls of European ancestry (http://gameon.dfci.harvard.edu). Both studies were conducted in accordance of U.S. common rule, have been approved by their institutional review board, and obtained informed written consent from all the participants (6).

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A total of 23 known independent pancreatic cancer susceptibility loci ($P < 5 \times 10^{-8}$) were extracted from the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/, accessed on January 14, 2017). For Root GWAS, we used logistic regression with case status as the outcome and an additive model for genotype, adjusting for age (10-year groups), study site, and the first four eigenvectors from principal component analysis. For GAME-ON/DRIVE GWAS, fixed-effects meta-analysis was used and the SEs were adjusted by the inflation factors. We also constructed a polygenic risk score (PRS) based on risk allele frequencies across all loci and evaluated its relation to breast cancer risk in Root. The PRS was calculated as the log OR-weighted sum of risk allele counts, defined as $\text{PRS} = \sum_{i=1}^{23} n_i \times ln(OR_i)$, where n_i is the number of risk alleles carried by an individual at the i_{th} SNP with $n_i = \{0,\ 1,\ 2\}$, and OR_i is the per-allele OR associated with the i_{th} SNP. Adjusted ORs and 95% confidence intervals (CI) were used to measure the association of breast cancer risk with genetic variants or PRS. Statistical significance was declared at the 0.0022 (0.05/23) level for each SNP.

Results

For women of African ancestry, rs31490-G was a risk allele in both pancreatic and breast cancers, whereas the risk allele rs401681-T in pancreatic cancer became a protective allele in breast cancer (Table 1). Similarly, for women of European ancestry, rs11655237-T and rs2736098-C were found to be risk alleles in both pancreatic and breast cancers, but two pancreatic cancer risk alleles rs505922-C and rs687289-A turned to be protective for breast cancer (Table 1). The aforementioned SNPs were nominal significantly association with breast cancer risk; however, none of them remained significant after the adjustment for multiple testing.

Table 2. Performance of PRS based on pancreatic cancer susceptibility variants in the GWAS of breast cancer in the African diaspora

Percentile of PRS	Cases ($n = 1{,}657$)	Controls ($n = 2{,}029$)	OR[a] (95% CI)
<5	165	204	0.99 (0.76–1.27)
5–10	168	200	1.02 (0.79–1.32)
10–20	155	214	0.85 (0.66–1.10)
20–40	158	211	0.88 (0.68–1.13)
40–60	336	400	1.00 (ref)
60–80	171	199	1.00 (0.78–1.29)
80–90	166	201	0.98 (0.76–1.27)
90–95	173	197	1.01 (0.78–1.30)
>95	165	203	0.97 (0.75–1.25)
Continuous (per SD = 0.571)	—	—	1.01 (0.95–1.08)

[a]ORs are for different percentiles of the polygenic PRS relative to the middle quintile (40%–60%) and were adjusted for age, study site, and the first four eigenvectors from principal components analysis.

For Root GWAS, one SD change [0.571] in the PRS was not significantly associated with breast cancer. The ORs for developing breast cancer by percentiles of the PRS, relative to women in the middle quintile, showed no linear trend (Table 2). The discriminative accuracy of the pancreatic cancer PRS, as measured by the C-statistic, was 0.508 (95% CI, 0.489–0.526) for breast cancer.

Discussion

We found that known GWAS risk variants for pancreatic cancer do not have a significant association with breast cancer risk among women of African or European ancestry. It is also worth noting that the direction in the associations for half of the nominal significant SNPs was not consistent with those observed in the pancreatic cancer studies that identified these

Table 1. Association of pancreatic cancer susceptibility variants with risk of breast cancer

SNP	Reference/effect allele	Pancreatic cancer OR (95% CI)	Root			GAME-ON/DRIVE	
			Type[a]	OR (95% CI)	*P*	OR (95% CI)	*P*
rs10919791	G/A	1.27 (1.18–1.33)	Genotyped	1.01 (0.86–1.18)	0.940	1.02 (0.97–1.06)	0.465
rs11655237	C/T	1.26 (1.19–1.34)	0.96	0.97 (0.87–1.09)	0.643	1.09 (1.02–1.16)	0.007[b]
rs12413624	A/T	1.23 (1.16–1.31)	0.99	0.99 (0.85–1.15)	0.902	1.03 (1.00–1.08)	0.051
rs1486134	T/G	1.14 (1.09–1.19)	Genotyped	1.02 (0.90–1.16)	0.719	0.99 (0.95–1.03)	0.538
rs1547374	G/A	1.27 (1.19–1.35)	Genotyped	1.01 (0.92–1.11)	0.833	1.01 (0.97–1.04)	0.767
rs16986825	C/T	1.18 (1.12–1.25)	Genotyped	0.98 (0.76–1.26)	0.848	1.00 (0.96–1.05)	0.997
rs17688601	A/C	1.14 (1.09–1.19)	Genotyped	0.93 (0.74–1.15)	0.479	1.01 (0.97–1.05)	0.512
rs2736098	T/C	1.25 (1.18–1.32)	0.95	1.09 (0.92–1.28)	0.330	1.05 (1.01–1.11)	0.022[b]
rs31490	A/G	1.20 (1.14–1.27)	Genotyped	1.12 (1.02–1.23)	0.020[b]	0.99 (0.95–1.02)	0.491
rs372883	C/T	1.27 (1.19–1.33)	Genotyped	1.00 (0.91–1.10)	0.988	1.00 (0.96–1.03)	0.899
rs3790844	A/G	1.30 (1.19–1.41)	Genotyped	1.03 (0.89–1.20)	0.703	1.01 (0.97–1.05)	0.675
rs401681	C/T	1.20 (1.13–1.28)	1.00	0.89 (0.81–0.98)	0.018[b]	1.01 (0.98–1.05)	0.416
rs505922	T/C	1.27 (1.19–1.35)	1.00	1.04 (0.94–1.14)	0.458	0.96 (0.93–1.00)	0.032[b]
rs5768709	A/G	1.25 (1.17–1.34)	0.98	0.98 (0.89–1.09)	0.738	0.99 (0.95–1.03)	0.624
rs687289	G/A	1.27 (1.20–1.35)	Genotyped	1.06 (0.96–1.16)	0.264	0.96 (0.93–0.99)	0.021[b]
rs6971499	C/T	1.27 (1.19–1.35)	Genotyped	0.99 (0.87–1.14)	0.927	1.02 (0.96–1.08)	0.537
rs7190458	G/A	1.46 (1.30–1.65)	0.91	0.93 (0.83–1.04)	0.179	1.05 (0.97–1.15)	0.225
rs9543325	T/C	1.24 (1.16–1.32)	Genotyped	1.05 (0.89–1.25)	0.529	0.99 (0.96–1.03)	0.684
rs9554197	C/T	1.14 (1.10–1.19)	Genotyped	1.03 (0.91–1.17)	0.606	1.00 (0.97–1.03)	0.986
rs9573163	C/G	1.26 (1.18–1.34)	0.99	0.90 (0.79–1.04)	0.157	1.01 (0.97–1.04)	0.741
rs9581943	G/A	1.15 (1.10–1.20)	Genotyped	1.03 (0.87–1.22)	0.705	—	—
rs962856	T/C	1.12 (1.08–1.17)	Genotyped	1.09 (0.97–1.22)	0.164	1.00 (0.97–1.04)	0.954
rs9854771	A/G	1.12 (1.08–1.18)	Genotyped	1.06 (0.95–1.18)	0.276	0.97 (0.93–1.01)	0.107

[a]Numbers indicate the imputation scores.
[b]The *P* values are significant at nominal level (<0.05), but turn out to be nonsignificant after multiple correction.

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SNPs as risk factors (Table 1). Our result is consistent with a recently published study using cancer-specific GWAS summary statistics data based on subjects of European ancestry, which did not find significant genetic correlations between pancreatic and breast cancer (genetic correlation coefficient = 0.17, $P = 0.37$; ref. 7). In conclusion, the association between known GWAS-identified pancreatic cancer susceptibility variants and breast cancer risk is likely weak in women of African or European ancestry, if it does exist.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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