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Pleiotropic analysis of cancer risk loci on esophageal adenocarcinoma risk

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Abstract

Background—Several cancer-associated loci identified from genome-wide association studies (GWAS) have been associated with risks of multiple cancer sites, suggesting pleiotropic effects. We investigated whether GWAS-identified risk variants for other common cancers are associated with risk of esophageal adenocarcinoma (EA) or its precursor, Barrett's esophagus (BE).

Methods—We examined the associations between risks of EA and BE and 387 single nucleotide polymorphisms (SNPs) that have been associated with risks of other cancers, by using genotype imputation data on 2,163 control participants and 3,885 (1,501 EA and 2,384 BE) case patients from the Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study, and investigated effect modification by smoking history, body mass index (BMI), and reflux/heartburn.

Results—After correcting for multiple testing, none of the tested 387 SNPs were statistically significantly associated with risk of EA or BE. No evidence of effect modification by smoking, BMI, or reflux/heartburn was observed.

Conclusions—Genetic risk variants for common cancers identified from GWAS appear not to be associated with risks of EA or BE.

Impact—To our knowledge, this is the first investigation of pleiotropic genetic associations with risks of EA and BE.

Keywords

Pleiotropic analysis; esophageal adenocarcinoma; Barrett's esophagus

Introduction

The incidence of esophageal adenocarcinoma (EA) has increased substantially over the past four decades in western countries (1). Most EA arises within Barrett's esophagus (BE), a metaplastic transformation of the lower esophageal lining (1). Gastroesophageal reflux (GERD), high body mass index (BMI), and tobacco use are well-established risk factors for both EA and BE, although with some variations in the magnitudes of these associations. These risk factors, together with low consumption of fruits and vegetables, may explain about 70% of the EA cases (see references in (1)). Genetic factors are thought to play an etiologic role based on familial clustering (1). In addition, results from the Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study (BEAGESS) support a shared genetic susceptibility of EA and BE (2). In further analysis of the BEAGESS data, an estimated 25% of the variation in EA risk is due to common genetic variants (1). However, from genome-wide association studies (GWAS) to date, only 7 loci have been identified to be associated with risk of EA or BE (2, 3), and the effects of the individual genetic variants are small (2, 3). Motivated by studies investigating pleiotropic associations of GWAS-identified variants, some of which work has identified additional risk-associated loci for colorectal, endometrial, and pancreatic cancers (see references in (4)), we investigated in BEAGESS whether cancer-GWAS-identified variants could also influence the risk of EA and BE.

Materials and Methods

Details of the design and methods of BEAGESS have been described elsewhere (2). In brief, this ancillary study included 1,504 EA and 2,384 BE case patients and 2,163 control participants, all of European descent and for whom genome-wide genotyping and imputation was conducted and phenotype covariate data were available. We identified 407 single nucleotide polymorphisms (SNPs) that have previously been associated with one or more cancer sites at a P-value$<5\times10^{-8}$ in the National Human Genome Research Institute (NHGRI) GWAS catalog as of March 2014 (5). Genotyping was done using the Illumina Human Omni1-Quad platform. Imputation was performed using MaCH and Minimac software and a European reference panel from the 1000 Genomes project (2). This analysis included 387 of the 407 SNPs that had minor allele frequencies (MAF) >1% and passed genotyping and imputation quality control (e.g. imputation $r^2\geq0.3$) (2). We investigated associations with EA, BE, and for these conditions combined (EA/BE). Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using unconditional logistic regression of case status on additive SNP genotype score, with adjustments for age, sex, and the first four principal components analysis eigenvectors (2). We performed stratum-specific analyses by smoking status (never, former, or current), smoking intensity (never, <30 pack-years, or ≥30 pack-years), BMI (<25, 25-<30, or ≥30 kg/m^2), and history of reflux/heartburn (yes, no), and tested for the statistical significance of the interaction (product) term. Some SNPs included in the NHGRI catalog are in linkage disequilibrium with each other. Thus, we calculated 'P-values adjusted for correlated tests' to account for multiple testing of correlated SNPs (6). The adjusted P values (P_{adj}) < 0.05 are considered statistically significant. Analyses were conducted using SAS 9.2 (SAS Inc., NC) and R. All *P* values are two sided.

Results

After correcting for multiple testing, none of the 387 SNPs were associated with risk of EA, BE, or EA/BE combined (Table 1 and Supplementary Table S1). No evidence was seen for effect modification by smoking status or intensity, BMI, or reflux/heartburn history (data not shown).

Discussion

Studies investigating pleiotropic effects of GWAS-identified risk variants have revealed additional risk loci for endometrial, colorectal, and pancreatic cancer, but not for estrogen-receptor (ER)-negative breast cancer (ER-positive cancers were not investigated), prostate cancer, or non-Hodgkin lymphoma (4, 7-9). Some studies, including those of non-Hodgkin lymphoma, endometrial cancer, and colorectal cancer, investigated cancer GWAS hits while studies of pancreatic cancer, prostate cancer, and ER-negative breast cancer investigated cancer and non-cancer GWAS-hits (4, 7-9). Our investigation based on cancer GWAS SNPs is not supportive of shared genetic susceptibility between EA/BE and other cancer sites. To our knowledge, this is the first study to investigate pleiotropic associations of cancer GWAS loci on risks of EA and BE. Although our study sample size is moderate, the combined number of EA and BE cases is larger than that of most previous studies on cancer pleiotropy

(4, 7-9). For SNPs with MAF of 0.3 (the average MAF of all tested SNPs), we had 80% statistical power to detect an OR of 1.21 per minor allele for analyses on EA/BE combined, with a Bonferroni-corrected type I error rate of 5%. Given that nearly one-half (47%) of the NHGRI-catalogued cancer-GWAS SNPs were from studies of more common cancers (Supplementary Table S1), it may be fruitful to repeat this analysis when additional GWAS loci identified from less common cancers become available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Single nucleotide polymorphisms (SNPs) associated with risk of esophageal adenocarcinoma (EA), Barrett's esophagus (BE) risk, and EA/BE, with a nominal P-value < 0.01 and in the same direction as the GWAS-identified SNPs reported in the NHGRI[§].

			NHGRI catalog[¶]			BEAGESS results	
SNP (major/minor allele)	**MAF**	**Chromosome position**	**Risk allele**	**Odds ratios**	**Cancer site**	**Odds ratios[†] (95% confidence intervals)**	**P (P_{adj}[*])**
SNPs associated with EA							
rs7040024 (A/C)	0.24	chr9: 845516	A	1.70	Testicular	1.16 (1.04-1.30)	0.008 (0.88)
rs4712653 (T/C)	0.45	chr6: 22125964	C	1.40	Neuroblastoma	1.14 (1.03-1.25)	0.008 (0.89)
SNPs associated with BE							
rs616488 (A/G)	0.34	chr1: 10566215	A	1.10	Breast	1.14 (1.05-1.25)	0.003 (0.59)
rs1270884 (G/A)	0.50	chr12: 114685571	A	1.07	Prostate	1.12 (1.03-1.22)	0.008 (0.88)
SNPs associated with EA/BE							
rs616488 (A/G)	0.34	chr1: 10566215	A	1.10	Breast	1.13 (1.05-1.23)	0.002 (0.41)
rs1270884 (G/A)	0.50	chr12: 114685571	A	1.07	Prostate	1.12 (1.04-1.21)	0.004 (0.64)
rs2494938 (A/G)	0.48	chr6: 40536128	A	1.15/1.18	Multiple cancers / NCGC[††]	1.11 (1.03-1.20)	0.007 (0.84)
rs527616 (G/C)	0.36	chr18: 24337424	G	1.05	Breast	1.12 (1.03-1.21)	0.008 (0.87)

Abbreviations: MAF, minor allele frequency

[§]Results from 11 subgroup-specific analyses by smoking status and intensity, BMI, and reflux/heartburn are not presented. P_{adj} values for subgroup-specific analyses were further multiplied by 11; the smallest P_{adj} from subgroup-specific analyses was 0.22. All P for interaction values were above 0.05 after Bonferroni correction (i.e. multiplied by total number of interaction terms examined (387 × 4 = 1,548).

[¶]www.genome.gov/gwastudies

[†]Odds ratios for EA, BE, or EA/BE per risk allele reported in the NHGRI catalog

[††]Non-cardia gastric cancer

[*]P-values were corrected for multiple testing by calculating 'P-values adjusted for correlated tests' (6).