Published in final edited form as:
Eur J Cancer Prev. 2011 January ; 20(1): 54–57. doi:10.1097/CEJ.0b013e328341e320.

Possible association between a genetic polymorphism at 8q24 and risk of upper gastrointestinal cancer

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Abstract

Over recent years, genome wide association studies (GWAS) have contributed to our understanding of genetic susceptibility to sporadic cancer. In this study, we assessed the association between upper gastrointestinal cancer risk and four GWAS-identified single nucleotide polymorphisms (SNPs), previously implicated in prostate and colorectal cancer susceptibility. Genotyping for each SNP was performed in two, independent, Caucasian, population-based case-control studies. The first study comprised 290 gastric cancer cases and 374 controls. The second study included 185 non-cardia gastric cancers, 123 cardia cancers, 158 oesophageal cancers, and 209 controls. Odds ratios were computed from logistic models and adjusted for potential confounding variables. An inverse association was observed between the SNP rs1447295, located at 8q24, and gastric cancer risk in the first study population (odds ratio [OR] = 0.63; 95% Confidence Interval [CI], 0.41–0.97). A positive association was observed for the same SNP and oesophageal squamous cell carcinoma in the second study population (OR = 7.43; 95% CI, 1.37–49.98). No significant associations were detected in either study for the three remaining SNPs (rs6983297, rs10505477 and rs719725). Our data represent novel findings on heritable susceptibility to gastric and oesophageal cancer and warrant validation in additional populations.

Keywords

Gastric cancer; oesophageal cancer; genetic polymorphism; cancer susceptibiility

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Disclosure: The authors declare no conflicts of interest

INTRODUCTION

Gastric and oesophageal cancers are leading global causes of cancer-related mortality and together contribute to a significant burden of disease, particularly in economically lesser-developed countries [1]. The prognosis for individuals diagnosed with these tumours is usually bleak, with overall survival statistics remaining poor even in developed countries [2,3].

Several genome wide association studies (GWAS) have revealed associations between markers in the gene-poor 8q24 region, and risk for variety of solid tumours [4–7], most notably prostate cancer [8–11]. The 8q24 prostate cancer-associated single nucleotide polymorphisms (SNPs) include rs6983267 and rs1447295, which together are estimated to account for around one quarter of the population-attributable risk in Caucasian men [12,13]. In 2007, several independent groups identified variants at 8q24 that were associated with increased risk of sporadic colorectal cancer, including rs10505477 [14–16]. One of these groups also identified a colorectal cancer-associated SNP at 9p24 [16] that was later robustly validated in the colon cancer family registry [17]. The influence of genetic polymorphisms at 8q24 and 9p24 on upper gastrointestinal cancer susceptibility has not yet been assessed. We therefore performed a genotyping study to assess for associations between upper gastrointestinal cancer risk and three of the previously described SNPs located at 8q24 (rs6983267, rs10505477, and rs1447295), and the rs719725 SNP located at 9p24.

MATERIALS AND METHODS

Study Populations

Genotyping of all four SNPs was performed in two independent, Caucasian, population-based case-control studies of upper gastrointestinal cancer. The influence of lifestyle factors such as smoking, diet, and alcohol consumption on upper gastrointestinal cancer risk in these two studies has previously been extensively investigated [18–22].

The first study was a gastric cancer case-control study derived from a Polish population. Cases were residents of Warsaw who had been newly diagnosed with gastric cancer at one of 22 hospitals serving the study area. Controls were randomly selected from an electronic residency registry and frequency-matched by age and sex [18]. DNA samples were available from 290 gastric cancer cases and 374 control subjects. The second study was a multi-center oesophageal and gastric cancer study conducted in three distinct geographic regions of the United states holding population-based cancer registries [21]. Cases were residents of the three study regions who had been newly diagnosed with gastric or oesophageal cancer. Population-based controls were identified by random digit dialing or random sampling of Health Care Financing Administration (HCFA) rosters, and were frequency matched by age and sex. DNA samples were available from a total of 308 subjects with gastric cancer (122 cardia and 184 non-cardia, 90% Caucasian), 158 oesophageal cancer cases (51 squamous cell and 107 adenocarcinoma, 90% Caucasian), and 209 matched population controls (94% Caucasian). The institutional review boards of the participating centers approved the study, and written informed consent was obtained from all subjects.

Genotype Assays

Genotyping for the four SNPs (rs6983267, rs10505477, rs1447295 and rs719725) was performed by real-time PCR using pre-designed Taqman® assays with minor groove binding probes 5’ labelled with FAM or VIC fluorophores to detect the common and variant alleles (PE Applied Biosystems, Foster City, CA) [23]. Genotyping calls were possible in over 97% of samples using the StepOneplus allelic discrimination system (Applied Biosystems).

Statistical Analyses

Hardy-Weinberg equilibrium (HWE) of alleles at the four polymorphic loci was assessed by χ^2 statistics. Odds ratios (OR) with Cornfield 95% confidence intervals (CIs) were computed by logistic regression using STATA version 7.0 software (STATA Press, College Station, TX). Models were run to adjust for age, sex and (in the US study only) race.

RESULTS

For rs6983267, rs10505477 and rs719725, allele frequencies in both study control populations were in HWE with non-significant χ^2 values. For rs1447295, there was a heterozygote deficit in the Polish control population (chi-square = 7.43, p = 0.006), however allele frequencies were in HWE for the US study controls. For all four polymorphisms, minor allele frequencies were similar to those previously reported for Caucasians. Adjustment for age, sex and race made no material difference to the crude ORs.

No associations were found between rs6983267, rs10505477, or rs719725, and upper gastrointestinal cancer risk.

For the rs1447295 (A>C) polymorphism, an inverse association was observed between carriage of the minor allele (A) and risk of gastric cancer in the Polish study population (Table 1). This was only apparent in a dominant model, giving an OR of 0.63 (95% CI, 0.41–0.97). No similar association was seen for either gastric cardia or non-cardia cancer in the US study population (data not shown), where homozygosity for the A allele yielded an OR of 7.04 (95% CI, 1.29–46.63) for oesophageal squamous cell carcinoma (Table 2). A similar OR was observed in a recessive model. No association was observed between rs1447295 and oesophageal adenocarcinoma (data not shown).

DISCUSSION

Our data point toward the existence of novel associations between an 8q24 SNP, rs1447295, previously identified as a prostate cancer-associated polymorphism, and the risk of gastric cancer and oesophageal squamous cell carcinoma.

Whilst the observed inverse association with gastric cancer, only apparent in the Polish study, may reflect a population-specific effect, as has been described for other gastric cancer-associated polymorphisms [24,25], larger case-control series would be required to address this possibility. Interestingly, a recent publication reported that rs1447285 was not associated with common solid tumours, other than prostate cancer, in a Polish population [26]. This large case-control study did not, however, include any upper gastrointestinal cancer cases.

The finding of opposing risk effects of a single SNP for different cancers at different anatomic sites is not novel. Indeed, whilst being a risk factor for prostate and colorectal cancer, rs6983267 appears to confer a protective effect on bladder cancer risk [7].

The mechanism by which 8q24 SNPs, located in a non-protein-coding genomic region, modify cancer risk is not fully understood. Several hypotheses have been put forward; including the suggestion that 8q24 harbours *cis*-regulatory enhancers for the nearby *MYC* proto-oncogene. There is now mounting evidence to support an interaction between 8q24 loci and *MYC*. Tuupanen *et al.* have demonstrated that rs6982367 lies within a functional enhancer, and that the risk genotype leads to enhanced binding of the Wnt-regulated transcription factor TCF4 [27]. Data from Pomerantz *et al.* suggest that, not only does TCF4 bind to a transcriptional enhancer at the rs6983267 locus, but that this region physically

interacts with *MYC* [28]. This interaction is supported by data from a recent publication, which suggest that the formation of long-range chromatin loops with *MYC* is a tissue specific mechanism, common to the prostate, colon and breast cancer-associated 8q24 loci [29].

The present hypothesis-testing study has a number of limitations. Although only a small number of comparisons were made in this study, we cannot exclude that the significant findings may, through multiple testing, have arisen by chance. We acknowledge the possibility that violation of HWE for rs1447295 in the Polish controls could result in bias. Also, the numbers of oesophageal cancer cases in the US study is small, potentially leading to over or underestimation of the magnitude of the observed association. We feel that the findings of the study are, however, important enough to justify validation in additional case-control series. Furthermore, the influence of rs1447295 on the risk of solid tumours other than prostate cancer warrants further investigation.

A comprehensive knowledge of the genetic contribution to upper gastrointestinal cancer risk has the potential to facilitate the development of risk stratification models that could assist screening decisions in high-risk populations. Germline genetic polymorphisms are emerging as biomarkers of cancer prognosis and response to treatment, and could help inform clinical decision making in personalised cancer therapy [30,31].

In conclusion, our data represent novel findings on heritable gastric and oesophageal cancer risk, which merit validation in additional populations. Emerging data on the function of 8q24 SNPs will hopefully enhance our understanding of the pathways at play in upper gastrointestinal carcinogenesis.

Acknowledgments

Support: This study was supported by a grant from NHS Grampian endowments. PL is funded by a fellowship from the Scottish Government Chief Scientist Office. The US multi-centre esophageal and gastric cancer study was supported by the United States Public Health Service (U01-CA57983, U01-CA57949, U01-CA57923, P30ES10126) and by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services (N02-CP40501, N01-CN05230).

Abbreviations used in this paper

CI	confidence interval
GWAS	genome wide association study
OR	odds ratio
SNP	single nucleotide polymorphism

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Eur J Cancer Prev. Author manuscript; available in PMC 2012 January 1.

Table 1

Association between rs1447295 and risk of gastric cancer in the Polish study population. Per-genotype, dominant, and recessive models are shown with odds ratios (OR) and 95% confidence intervals (CI).

Genotype model	Number of Cases	Number of Controls	OR	95% CI	*p* value
Per-genotype					
C/C	244	287	reference		
A/C	39	67	0.68	0.43–1.07	0.083
A/A	3	11	0.32	0.06–1.24	0.069
Dominant					
C/C	244	287	reference		
A/C + A/A	42	78	0.63	0.41–0.97	0.029
Recessive					
A/C + C/C	283	354	reference		
A/A	3	11	0.34	0.06–1.31	0.086

Eur J Cancer Prev. Author manuscript; available in PMC 2012 January 1.

Table 2

Association between rs1447295 and risk of oesophageal squamous cell carcinoma in the US study population. Per-genotype, dominant, and recessive models are shown with odds ratios (OR) and 95% confidence intervals (CI).

Genotype	Number of Cases	Number of Controls	OR	95% CI	*p* value
Per-genotype					
C/C	40	169	reference		
A/C	6	36	0.70	0.29–1.75	0.458
A/A	5	3	7.04	1.29–46.63	0.003
Dominant					
C/C	40	169	reference		
A/C + A/A	11	39	1.19	0.50–2.63	0.647
Recessive					
A/C + C/C	46	205	reference		
A/A	5	3	7.43	1.37–49.98	0.002