Short Communication

Adiponectin gene and risk of colorectal cancer

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BACKGROUND: Genes of the adiponectin pathway are interesting candidates for colorectal cancer risk based on the potential association between colorectal cancer and obesity. However, variants of the adiponectin gene (ADIPOQ) have been demonstrated to be inconsistently associated with risk of colorectal cancer.

METHODS: The current study attempted to evaluate these findings by examining several single nucleotide polymorphisms (SNPs) that were previously genotyped as part of a genome-wide association study in the ADIPOQ gene. Genotyping was also performed for a previously reported risk variant, rs266729, in 1062 individuals with a diagnosis of colorectal cancer and 1062 controls matched on age, gender and ethnicity (Jewish or not Jewish) as part of a population-based case–control study in Israel.

RESULTS: No evidence was found for an association between ADIPOQ and risk of colorectal cancer. The single nucleotide variant previously associated with decreased risk of colorectal cancer, rs266729, revealed an adjusted odds ratio of 1.04; 95% confidence interval, 0.88–1.23.

CONCLUSION: The SNP, rs266729, was not strongly associated with colorectal cancer in patients of Ashkenazi Jewish descent or other ethnic groups in Israel.

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Decreased levels of circulating adiponectin, a hormone secreted by the adipose tissue, have been found to be directly associated with obesity and hyperinsulinemia (Vona-Davis et al, 2007). The combination of the association of adiponectin with insulin resistance, support for an association of obesity with risk of colorectal cancer, and a previous report which found that adiponectin levels were inversely associated with risk of colorectal cancer suggest that the adiponectin pathway may contribute to colorectal carcinogenesis (Wei et al, 2007; Moghaddam et al, 2007; Vona-Davis et al, 2007; Fenton et al, 2008; Williams et al, 2008). An association between genes of the adiponectin pathway and risk of colorectal cancer was recently reported in a multicenter case–control study (Kaklamani et al, 2008). Kaklamani et al identified a single nucleotide polymorphism (SNP, rs266729) in the adiponectin gene (ADIPOQ) that was associated with decreased risk of colorectal cancer. However, subsequent reports did not validate the findings of Kaklamani (Carvajal-Carmona et al, 2009; Pechlivanis et al, 2009). In response to this intriguing hypothesis and inconsistent data, we examined several SNPs in the ADIPOQ gene that were genotyped as part of an ongoing genome-wide association study (GWAS) (Gruber et al, 2007). We also specifically genotyped the variant rs266729 in 1062 colorectal cancer cases and 1062 matched controls.

MATERIALS AND METHODS

Histopathologically confirmed cases of all incident colorectal cancer diagnosed in northern Israel between 31 March 1998 and 31 March 2004 were recruited as part of the Molecular Epidemiology of Colorectal Cancer study. Population-based controls were identified from the Clalit Health Service database and matched to cases by year of birth, gender, clinic and Jewish/Arab ethnicity (Poynter et al, 2005). The study was approved by all relevant IRBs in the US and Israel, and written informed consent was given by study participants. SNPs within ADIPOQ were analysed as part of our GWAS to test the hypothesis that SNPs in linkage disequilibrium with the published risk variants of ADIPOQ were associated with risk (Table 1). Stage 1 of our GWAS (Gruber et al, 2007) used pooled DNA of cases (n = 500) and pooled DNA of controls (n = 500). Standard errors used for t-tests of pooled allele frequencies were corrected by adding a chip-specific constant to avoid biased selection of SNPs with small standard errors (Table 2b).

Our subsequent validation analysis had 95% power to detect an odds ratio (OR) of 0.73 by individually genotyping genomic DNA from 1062 matched pairs using Taqman SNP allelic discrimination (Table 1). Less than 5% of genotypes were scored as equivocal and 1% of the sample was genotyped in duplicate with 100% concordance. Conditional logistic regression was used to calculate ORs in R (version 2.11.1, R Development Core Team, http://www.R-project.org) and SAS (version 9.1, SAS Institute Inc., Cary, NC, USA). Analyses were adjusted for ethnicity (Ashkenazi Jewish, Sephardi Jewish, Arab) and APC I1307K.
RESULTS

Our GWAS study did not identify a significant association between any of the genotyped SNPs in the ADIPOQ gene and risk of colorectal cancer (Table 2a). Using the dominant model to replicate Kaklamani’s reported findings, SNP rs266729 revealed an adjusted OR (adjusted for age, gender, ethnicity and APCI1307K status) of 1.04; 95% confidence interval (95% CI), 0.88–1.23. The OR among Ashkenazi Jews was only 1.01 (95% CI 0.82–1.24). Excluding overlapping cases and controls used in both the initial pooled GWAS analysis and the individual genotyping of the subsequent validation study yielded an adjusted OR of 1.10, 95% CI (0.92, 1.32). Based on the current data we conclude that rs266729 in ADIPOQ is not associated with risk of colorectal cancer in a comparable population-based sample.

CONCLUSION

In contrast to one previous publication (Kaklamani et al., 2008) but consistent with two others (Carvajal-Carmona et al., 2009; Pechlivanis et al., 2009), we found no association with variants of ADIPOQ and risk of colorectal cancer. It should be noted that in the study by Carvajal-Carmona, genotypes at rs266729 were imputed in the CORGI cohort, but confirmed the absence of association with CRC risk. Based on the results from the current study, rs266729 was not associated with colorectal cancer in patients of Ashkenazi Jewish descent or other ethnic groups in Israel. It seems likely that the original publication represents a ‘winner’s curse’, or a chance observation in an initial study, as our study, rs266729 was not associated with colorectal cancer in a comparable population-based sample.

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