Genetic variation in adipokine genes and risk of colorectal cancer

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Abstract

Objective: Obesity has been related to an increased risk of colorectal cancer (CRC). Adipokines produced by the adipose tissue are directly linked to obesity and may thus contribute to the pathogenesis of CRC. We hypothesized that potentially functional polymorphisms in the adipokine genes leptin (LEP), leptin receptor (LEPR), resistin (RETN), and adiponectin (ADIPOQ) may be associated with CRC.

Design and methods: We studied the association of four putatively functional single nucleotide polymorphisms (SNPs) with CRC risk using a hospital-based study design with 702 cases and 752 controls from the Czech Republic. We used likelihood ratio tests to select the best model to represent the relationship between genotypes and risk of CRC. Age-adjusted odds ratios (ORs) under the best model were calculated for each SNP. Previous genotyping data on insulin (INS)-related genes were used to explore interactions between genes in obesity- and diabetes-related pathways by using two independent methods, logistic regression, and multifactor-dimensionality reduction.

Results: A trend to associate between the RETN SNP rs1862513 (C-420G) and CRC risk was observed (per allele OR 1.18, 95% confidence interval (0.99–1.40). Statistically, significant interactions were observed between the INS SNP rs3842754 (C1127INSpstI) genotypes and both the LEPR SNP rs1137101 (Q223R) and the ADIPOQ SNP rs266729 (C-11374G) genotypes.

Conclusions: Our results suggest that variants in the adipokine genes may affect CRC risk in combination with variants in diabetes-related genes.

European Journal of Endocrinology 160 933–940

Introduction

Obesity has been consistently associated with increased risk of cancer, including the risk of colorectal cancer (CRC) (1, 2). Both family-based and twin studies have indicated a strong heritable component for individual body mass index (BMI) (3, 4). The 2005 update of the human obesity gene map contains 253 quantitative-loci, and 22 gene associations, which have been replicated in at least five studies (5). Among these 22 genes are four adipokine genes, adiponectin (ADIPOQ), leptin (LEP), leptin receptor (LEPR), and resistin (RETN), which are expressed in and whose products are secreted by the adipose tissue. Adipokines can exert their biological actions on target cells by endocrine as well as by paracrine mechanisms. In addition to obesity, adipokines have been associated with several obesity-related disorders, such as type 2 diabetes, cardiovascular disease, inflammation, and CRC (6–9).

Plasma leptin levels are elevated in obesity and they increase with increasing fat mass (8). Leptin can also act as a mitogen, transforming factor or migration factor for many different cell types, including normal and neoplastic colon epithelial cells (8, 10, 11). Several prospective case–control studies have associated increased leptin levels with increased CRC risk (12–15). Leptin exerts its physiological action through the leptin receptor, which is expressed in colon cancer cell lines as well as in human normal colonic tissue and adenomatous polyps (10, 11). Resistin levels are also increased in both genetic and diet-induced obesity in mice (16). Recently, increased resistin protein expression has been observed in CRC tissue compared with the paired normal tissue (17). In contrast to high
leptin and resistin levels, low-adiponectin levels have been shown to associate with obesity and to confer a substantially increased risk for diabetes, cardiovascular diseases and several cancers, including CRC (6, 7, 18, 19), although in one study, no association with CRC was observed (20). However, a recent study suggests that the leptin/adiponectin ratio may be a better marker for factors of metabolic syndrome than any of the individual adipokines (14).

In humans, several single nucleotide polymorphisms (SNPs) have been identified in the LEPR, LEPR, RETN, and ADIPOQ genes. The G-2548A polymorphism (rs7799039) in the LEP gene has been shown to affect leptin secretion in vitro and the strength of a complex formation with a nuclear protein (21). Studies about the effects of the SNP on leptin levels and obesity have been contradictory (21–26). The glutamine to arginine effects of the SNP on leptin levels and obesity have been shown to associate with obesity and to confer a substantially increased risk for diabetes, cardiovascular diseases and several cancers, including CRC (6, 7, 18, 19), although in one study, no association with CRC was observed (20). However, a recent study suggests that the leptin/adiponectin ratio may be a better marker for factors of metabolic syndrome than any of the individual adipokines (14).

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The C-420G (rs1862513) SNP, in the promoter region of the RETN gene, has been associated with basal promoter activity in adipocytes and resistin mRNA levels in human abdominal s.c. fat (32). Several studies have found associations between the SNP and obesity, insulin sensitivity and insulin resistance (32–34). A high heritability has been observed for plasma adiponectin levels in French Caucasian families (35). Several investigators have characterized SNPs in the ADIPOQ gene and found one or more of these SNPs to be associated with adiponectin levels and obesity as well as with diabetes (35–38).

Here, we investigated the effect of SNPs in the adipokines on the CRC risk. We selected SNPs in the LEP, LEPR, RETN, and ADIPOQ genes based on their suggested effect on the gene expression or the protein function as described above. We investigated their association with the CRC risk in a Czech nationwide, hospital-based case–control population with 702 cases with histologically confirmed CRC and 752 controls with negative colonoscopic results for malignancy or idiopathic bowel diseases. Previously, we had studied the effect of SNPs in the INS, INSR, IGF1, IRS1, and IRS2 on CRC risk in the same population (39). As both insulin pathway and adipokines are associated with diabetes and obesity and adipokines directly affect insulin secretion (1), we additionally evaluated the effect of gene–gene interactions in these two groups of genes on the risk of CRC.

Materials and methods

Subjects

The present hospital-based case–control study is based on incident cases recruited between September 2004 and February 2006. Cases were CRC patients visiting one of the nine oncological departments distributed in all geographic regions of the Czech Republic (two in Prague, one each in Benesov, Brno, Liberec, Ples, Pribram, Ústí nad Labem, and Zlín), thus representing the population of the entire country. During the study period, a total of 968 cases were diagnosed with CRC in these hospitals. Sixteen individuals were initially excluded, because they met the Amsterdam criteria I and II for hereditary CRC. This study includes 702 (72.5%) patients, who provided biological samples of sufficient quality for genetic analysis. The lost cases were similar to those enrolled with respect to age and sex. All cases had positive colonoscopic results for malignancy, histologically confirmed as colon or rectal carcinomas.

Controls were recruited in the same period as the cases. They were subjects undergoing colonoscopy for various gastrointestinal complaints and in the frame of preventive examination in five large gastroenterological departments (Prague, Brno, Jihlava, Liberec, and Pribram). The distribution of controls from different parts of the Czech Republic was approximately the same as that of cases. The reasons for colonoscopic investigation were i) macroscopic bleeding, ii) positive fecal occult blood test (FOBT), and iii) abdominal pain of unknown origin. Owing to the high incidence of CRC in the Czech Republic, colonoscopy is largely recommended and practiced, and it is compulsory in case of positive FOBT. The most common findings for these subjects were hemorrhoids or idiopathic bowel diseases (IBD). Only subjects whose colonoscopic results were negative for malignancy, colorectal adenomas, benign polyps or IBD were chosen as controls. From 899 selected controls, 752 (83.6%) accepted to participate, gave a blood sample and were analyzed in this study; the lost controls were similar to those included to the study with respect to age and sex. DNA was isolated from peripheral leukocytes within 4 weeks after the blood sample was collected using the standard proteinase K digestion, phenol/chloroform extraction and ethanol precipitation, and stored at −80°C.

Study subjects provided information on their lifestyle habits (smoking, drinking, diet), BMI, diabetes and family/personal history of cancer, using structured questionnaires. Table 1 shows several characteristics of the study population at the time of recruitment. The median age of the cases was 62 (range 27–85) and of the controls 54 (range 29–91). Information on BMI at the time of diagnosis of cases and at the time of sample collection of the controls and on treatment for diabetes was available for 65.5% of cases and 66.9% of controls.
For other variables, information was available for \( \sim 67\% \) of cases and \( \sim 54\% \) of controls. All participants gave informed written consent and the design of the study was approved by the Ethical Committee of the Institute of Experimental Medicine, Prague, Czech Republic.

### Genotyping using TaqMan assay

The polymorphisms G-2548A (rs7799039) in the LEP gene, Q223R (rs1137101) in the LEPR gene, C-420G (rs1862513) in the RETN gene and C-11374G (rs266729) in the ADIPOQ gene were investigated using the allelic discrimination method. TaqMan primers and probes were ordered as Assay-on-Demand (Assay ID: C__1328079_10, C__8722581_10, C__1394112_10, and C__2412786_10 for the LEP, LEPR, RETN, and ACDC genes respectively) from Applied Biosystems (Foster City, CA, USA). The reaction was performed in 5 \( \mu l \) using 225 nM each primer, 50 nM each probe and 2.5 \( \mu l \) TaqMan Universal 2× PCR Master Mix (Applied Biosystems) per reaction. PCR was performed at 50 °C for 2 min, 95 °C for 10 min followed by 40–55 cycles at 92 °C for 15 s and 60 °C for 1 min.

### DNA sequencing

About 10% of the genotyped samples were sequenced in order to verify the results obtained by TaqMan. All sequencing results were concordant with the original results. PCR amplification and sequencing reaction were performed as described previously (39).

### Statistical analysis

The observed genotype frequencies in controls were tested for Hardy-Weinberg equilibrium (HWE). The best model to represent the relationship between the genotypes and the risk of CRC was selected based on likelihood ratio tests. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by logistic regression. Statistical significance for a different genotype distribution in cases versus controls was assessed using likelihood ratio tests.
determined by two-sided global \( \chi^2 \) tests. The ORs were considered statistically significant when the 95% CIs did not include unity. With the present sample size, our study had a power of 78% to detect a per allele OR of 1.3 for a SNP with a minor allele frequency (MAF) of 26% (the lowest MAF in the studied SNPs). The optimal combination of SNPs to describe the relationship between genotypes and risk of CRC was selected using Akaike’s information criterion (AIC) (40). In our calculations, the lower the AIC value, the better the model. To identify possible high-order gene–gene interactions among the adipokine genes, multifactor-dimensionality reduction (MDR) followed by permutation analyses was applied (41). This method has been developed to detect and characterize combinations of multi-locus genotypes that are associated with a specific disease. Shortly, MDR classifies multi-locus genotypes into high-risk and low-risk groups. The advantages of the method are that no mode of inheritance has to be assumed, and false-positive results due to multiple testing seem to be minimized.

Results

The genotype distributions of the four studied SNPs were according to HWE in the control population. The allele and the genotype distributions shown in Table 2 were concordant with the previously published studies for Caucasians (25, 31–33, 35, 36, 42) or for the CEPH (Utah residents with ancestry from northern and western Europe) population in the International HapMap Project (http://www.hapmap.org/index.html.en).

Data on BMI and diabetes was available from 65.5% of CRC cases and 66.9% of controls (Table 1). Among them, the median BMI was practically identical in the cases (26.4) and the controls (26.5; \( P = 0.79 \)), and the BMI did not depend on the genotypes (data not shown). Self-reported diabetes was more common among the CRC patients than the controls (\( P = 0.01 \)), but the investigated SNPs did not seem to modify susceptibility to diabetes. Among the lifestyle factors, the cases seemed to have slightly lower education level than the controls (\( P = 0.02 \)), but this result may be influenced by the different percentage of missing data in cases (33.5%) compared with controls (45.3%). Age-adjusted ORs under the best model, selected by likelihood ratio tests, were calculated for each SNP. As shown in Table 2, only the RETN genotypes showed a trend to association with CRC with a global \( \chi^2 \) value of 0.06 and the per minor allele G OR of 1.18 (95% CI 0.99–1.40). After additional adjustment for diabetes and education level, this association lost its statistical significance (OR 1.08, 95% CI 0.87–1.34).

We used logistic regression and MDR to evaluate interactions between the cytokine genes genotyped in this study and the insulin-related genes genotyped in our previous study (39). Based on the case–control

<table>
<thead>
<tr>
<th>Gene</th>
<th>Distribution of genotypes</th>
<th>Association analysis</th>
<th>Model selection</th>
<th>Model comparison</th>
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</thead>
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<tr>
<td>LEP</td>
<td>Three genotypes</td>
<td>AA versus GA versus GG</td>
<td>Dominant (AA) versus GG</td>
<td>( \chi^2 ) Global P OR (95% CI)</td>
</tr>
<tr>
<td>rs1370398</td>
<td>230 (36%)</td>
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<td>126 (18%)</td>
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study design with three-genotype models for each SNP, statistically significant interactions were observed between the SNPs in the LEPR and the INS genes (P value for multiplicative interaction 0.02) and between the ADIPOQ and the INS genes (P value 0.03; Supplementary Table 1, which can be viewed online at http://www.eje-online.org/supplemental/). The MDR analysis confirmed this finding and indicated that the best model to describe the case/control distribution was based on variants of the LEPR and the INS genes (Fig. 1). Permutation analyses revealed the statistical significance of this classification (P = 0.02). Subsequent likelihood ratio tests and AIC values suggested a model with three variants for the LEPR gene and dominant effects for the INS gene (Supplementary Table 2, which can be viewed online at http://www.eje-online.org/supplemental/). The association analysis indicated an increased CRC risk for carriers of the GG genotype of the LEPR gene and at least one variant allele of the INS gene compared with the carriers of the wild-type genotypes of these two SNPs (age-adjusted OR 1.64, 95% CI 1.02–2.65; Fig. 1), the association was slightly stronger after additional adjustment for diabetes and education level (OR 2.04, 95% CI 1.08–3.85). The MDR analysis confirmed this result and pointed to a complex interaction between the LEPR and the INS variants (Fig. 1, upper panel). The interaction between variants in the ADIPOQ and the INS genes was also complex (Fig. 1, lower panel). Compared with the wild-type genotype carriers, carriers of the variant allele of the ADIPOQ gene showed a decreased risk of CRC, when the INS genotype was CC (age-adjusted OR 0.73, 95% CI 0.55–0.98), and when the INS genotype was TT (age-adjusted 0.37, 95% CI 0.16–0.84). However, the last association should be taken with caution, because of low numbers of cases (n = 9) and controls (n = 22) carrying the genotype combination. These associations did not remain statistically significant after additional adjustment for diabetes and education level (Fig. 1).

**Discussion**

Adipokines, secreted by the adipose tissue, are strong candidates for the link between obesity and risk of CRC (1, 6). In order to investigate the influence of potentially functional genetic variation in the adipokine genes LEP, LEPR, RETN, and ADIPOQ on the CRC risk, we genotyped SNPs in these genes in a cohort of cases and controls from the Czech Republic. As adipokines regulate the function of insulin pathway and we have previously studied the effect of insulin-related genes on CRC in the same population (39), gene–gene interactions between genes in the two pathways were also investigated.

It is well known that the curse of dimensionality diminishes the usefulness of traditional, parametric methods and that no single approach is optimal for all

![Figure 1](https://www.eje-online.org)

**Figure 1** Interactions of LEPR and INS as well as of ADIPOQ and INS genotypes. On the left, the interactions according to multifactor-dimensionality reduction. The high risk genotype combinations (i.e., combinations with more cases than controls) are shown in dark grey boxes and the low risk combinations (with more controls than cases) in light grey boxes. In each box, left bars represent the number of cases and right bars the number of controls. On the right, distribution of the LEPR (rs1137101)-INS (rs3842754) genotype combinations and the ADIPOQ (rs266729)-INS (rs3842754) genotype combinations with age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs). The ORs were considered statistically significant, when the 95% CIs did not overlap unity, as indicated by bold.
data scenarios (43, 44). For example, in stepwise logistic regression, the standard method for analysis of data from case–control studies, only interaction terms of variables with significant main effects are tested for significance (45, 46). Therefore, logistic regression lacks by definition the ability to characterize purely interactive effects. In complex diseases, such as CRC, a majority of genes may be difficult to identify due to their modest individual effects and complex interactions (47). Multi-dimensionality reduction was developed to detect gene–gene interactions in the presence or absence of main effects in case–control studies and we decided to apply also this method to analyze our data. The present logistic regression data suggested that SNPs in the LEPR and the ADIPOQ genes interact with the SNP in the INS gene at a statistically significant level, but the two genes did not show independent main effects. The possible interaction between LEPR and INS was shown by MDR analysis, which also selected this combination of genes to describe the distribution of cases and controls. Likelihood ratio tests and the values of the AIC indicated that the best model to represent CRC risk consisted of three genotypes for the LEPR SNP and a dominant penetrance model for the INS SNP. For the possible interaction between the ADIPOQ and the INS genes the best model consisted of a dominant model for the ADIPOQ SNP and a three genotype model for the INS gene.

The reported functional effects of the studied SNPs support our observations about a link between the SNPs in adiposity-related adipokines, in the insulin pathway and risk of CRC. The LEPR SNP Q223R has been shown to affect serum leptin-binding affinity, with individuals homozygous for the R allele having higher serum leptin-binding affinity than carriers of the Q allele (27). Homozygosity for the R allele has also been associated with obesity and it has been reported to explain some 5% of the variance in percent fat mass and BMI (28). In another study, the R allele was associated with insulin sensitivity explaining about 6–7% of the variance in the trait (29). Since many studies, including two meta-analyses (30, 31), have failed to show an association with obesity phenotypes and the positive associations are mainly observed in young and/or healthy populations, Chiu et al speculated that this SNP may contribute to the initiation events leading to insulin resistance (29). A part of the inter-individual variation in adiponectin levels may be explained by the ADIPOQ promoter SNPs, including the C-11374G SNP (35). Although the low-level -11374G allele has been associated with obesity, its association with diabetes seems to depend on the level of obesity (35, 36, 38). The common partner of the gene–gene interactions observed in our study, the INS SNP +1127INS/7p11 (rs3842752) may regulate insulin production due to its location in the regulatory 3′-UTR (48) or due to its linkage disequilibrium with a variable number-tandem repeat (VNTR) locus in the promoter of the gene, which has consistently been associated with diabetes (49).

In the single SNP analysis, only the RETN SNP C-420G showed a trend to association with CRC risk based on an additive model (per allele OR 1.18; 95% CI 0.99–1.40). In the recent study by Wächter et al. no statistically significant difference in the genotype distribution between the cases (n=248) and the controls (n=256) was observed, although the GG genotype was more common among the cases (10.5%) than the controls (6.3%) (17). The effect of the G allele is biologically plausible, because the G allele has been associated with both increased basal promoter activity and higher resistin mRNA levels in human abdominal s.c. fat as well as in insulin resistance and obesity (32, 33). An alternative mechanism linking RETN with CRC is through inflammation, a known risk factor for CRC (50), because in humans resistin has been shown to be produced mainly in the macrophages within the adipose tissue (9).

In addition to the report about the relationship between the RETN SNP C-420G and the risk of CRC (17), only one study has addressed the question of an association between genetic variation in the adipokine genes and the risk of CRC (51). In that study, a decreased risk for the AA genotype carriers of the SNP rs2167270 in the 5′-UTR of the LEP gene was observed. Additionally, a decreased OR was observed for a combination of the LEP SNP rs21672709 and the SNP rs6588147, located in intron 2 of the LEP gene. Slattery et al. (51) observed an interaction between the LEP and the LEPR SNPs and polymorphisms in the insulin-like growth factor-1 and the IRS2 genes. According to HapMap (http://www.hapmap.org/index.html.en) the SNP rs2167270 in the LEP gene is in a partial linkage disequilibrium with the SNP rs7799039 (D′ = 1.0, r2 = 0.47) analyzed in our study, and the SNP rs6588147 in the LEP gene shows low linkage disequilibrium with the SNP rs1137101 (D′ = 0.70, r2 = 0.34) genotyped by us. Thus, although the SNPs studied by Slattery et al. (51) and by us are different and do not show high linkage disequilibrium with each other, both studies suggest an interaction of the adipokine and the IRS-related genes in the etiology of CRC.

The strengths of our study include the relatively large sample size, 702 cases and 752 controls, and the selection of SNPs based on previous functional data. Additionally, we were able to study gene–gene interactions between genes in two obesity- and diabetes-related pathways, because the genotyping data on insulin-related genes in the same population were available from our previous study. The limitations of our study include the difference in age between the cases and the controls. However, no age or gender specific differences in the genotype distributions were observed. Another limitation was the presence of missing data on BMI, diabetes, and lifestyle habits.
which may be related to work overload in some of the participating departments. Especially, for lifestyle habits, the answering rate was much lower among the controls (about 55%) than among the cases (about 67%). BMI data were recorded in the cases at the time of diagnosis and diabetes was self-reported, thus probably restricting the adequacy of this information. When individuals without information on age, genotype, diabetes or education were excluded from the analyses, the reduction in sample size resulted in non-significant associations. It should be kept in mind that different patterns of missing data in cases and controls may have resulted in spurious associations. Regarding the statistical methods used, it has been reported that standard methods for gene–gene interaction studies are not feasible and the results may be difficult to interpret (41). In our study, this was especially clear for the interaction between the ADIPOQ and the INS genes, where both wild-type and variant homozygous genotypes of the INS gene together with at least one variant allele of the ADIPOQ gene associated with decreased risk of CRC.

In conclusion, our results suggest that SNPs in the adipokine genes may affect the risk of CRC together with SNPs in other genes related to obesity or diabetes. This observation is relevant from both a practical and a scientific point of view and it warrants further studies using both large, independent cohorts, and a population-based approach.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This study was supported by a grant from EU (LSHC-CT-2004-503465), B Pardini, A Naccarati, I Vodickova, J Novotny, and P Vodicka were recipients of the following grants: GACR 310/07/1430 and IGA MZ NR8563-5/2005.

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Received 26 February 2009
Accepted 8 March 2009

www.eje-online.org