Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

GWAS-Identified Common Variants for Obesity Are Not Associated with the Risk of Developing Colorectal Cancer

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Abstract

Background: Observational studies have consistently associated obesity with colorectal cancer risk. Because both traits are genetically determined and share some metabolic biomarkers, we hypothesized that obesity-related polymorphisms could also influence the risk of developing colorectal cancer.

Methods: We conducted a comprehensive population-based case–control study in 1,792 German colorectal cancer cases and 1,805 controls to explore associations between 28 obesogenic variants identified through genome-wide association studies (GWAS) and colorectal cancer risk. We also evaluated interactions between polymorphisms and body mass index (BMI), type II diabetes (T2D), and gender.

Results: No evidence of association between obesogenic variants and colorectal cancer risk was observed after correction for multiple testing. There was only a remarkable interaction between the $LTA_{rs1041981}$ polymorphism and gender, which modified the risk of colorectal cancer [$P_{interaction} = 0.002$; males: odds ratio (OR), 1.14; 95% confidence intervals (CI), 1.00–1.30 vs. females: OR, 0.83; 95% CI, 0.71–0.97].

Conclusions: Our findings showed that obesogenic variants are not a major pathogenetic risk factor for colorectal cancer.

Impact: This comprehensive population-based case–control study does not provide evidence of a shared genetic component between obesity and colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 23(6); 1125–8. ©2014 AACR.*

Introduction

Obesity as one of the main environmental risk factors of colorectal cancer has not only been associated with colorectal cancer risk, but may also influence clinical outcome (1). Because obesity and colorectal cancer share metabolic biomarkers and both traits are influenced by genetic factors, obesity-related variants may also influence the risk of developing colorectal cancer. Recent genome-wide association studies (GWAS) have identified a number of obesogenic loci (2); some of them have already been evaluated as risk factors for colorectal cancer in the multiethnic cohort (3), with mainly negative outcome. We conducted a comprehensive population-based case–control study in a Caucasian population (1,792 German colorectal cancer cases and 1,805 controls) and investigated the role of 28 obesity-related genetic variants in 23 genes identified through GWAS in determining the risk of developing colorectal cancer. We also evaluated interactions between alleles and body mass index (BMI), type II diabetes (T2D) and gender.

Materials and Methods

The Darmkrebs: Chancen der Verhütung durch Screening (DACHS) study is a population-based case–control study that has been previously described in detail (4, 5). Characteristics of cases and controls recruited between 2003 and 2007 and included in this analysis are summarized in Table 1. The single-nucleotide polymorphisms (SNPs) were selected through an extensive literature search of relevant GWAS and meta-analyses published by February 2009 using publicly available online databases. Additional criteria were potential functionality and linkage disequilibrium between the reported SNPs. Finally, 28 SNPs in 23 genes were selected for this study. Genotyping was performed using KASPar assays (LGC Genomics) according to previously reported protocols (6).

Statistical analyses were conducted using the SAS 9.2 software (SAS institute). Hardy–Weinberg equilibrium (HWE) was assessed in the control group ($P > 0.01$) and the association between colorectal cancer and SNPs was tested using a multivariate unconditional logistic regression analysis adjusted for matching variables (age, sex, and county of residence). Associations were reported as per-allele odds ratios (ORs) with 95% confidence intervals (CIs). SNP–BMI, -T2D, and -gender interaction analyses

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Table 1. Distribution of selected epidemiological variables in the DACHS study population

Value	Cases ($N = 1,792$) *N* (%)	Controls ($N = 1,805$) *N* (%)	*P*
Age (y)			
30 to <40	17 (0.95)	5 (0.28)	0.02
40 to <50	58 (3.24)	60 (3.32)	
50 to <60	269 (15.01)	260 (14.40)	
60 to <70	622 (34.71)	574 (31.80)	
70 to <80	568 (31.70)	615 (34.00)	
80+	258 (14.40)	295 (16.30)	
Gender			
Female	743 (41.46)	732 (40.55)	0.60
Male	1,049 (58.54)	1,073 (59.45)	
BMI (kg/m^2) ≥5 years before diagnosis/date of interview			
≥18.5 to <25	551 (30.75)	667 (36.95)	<0.01
≥25 to <30	835 (46.60)	845 (46.81)	
≥30	361 (20.15)	268 (14.85)	
Unknown	45 (2.51)	25 (1.39)	
Average alcohol intake in last 12 months (g/day)[a]			
None	529 (29.52)	466 (25.82)	<0.01
0< to <6.1 g/day	261 (14.56)	300 (16.62)	
≥ 6.1 to <13.2 g/day	287 (16.02)	335 (18.56)	
≥ 13.2 to <25.5 g/day	302 (16.85)	334 (18.50)	
≥ 25.5 g/day	392 (21.88)	325 (18.01)	
Unknown	21 (1.17)	45 (2.49)	
Average lifetime pack years of regular smoking			
Nonsmoker	837 (46.71)	935 (51.80)	<0.01
>0 to <10	298 (16.63)	314 (17.40)	
10 to <20	219 (12.22)	201 (11.14)	
20 to <30	187 (10.44)	160 (8.86)	
≥30	232 (12.95)	180 (9.97)	
Unknown	19 (1.06)	15 (0.83)	
First degree family history of colorectal cancer			
No	1,529 (85.32)	1,600 (88.64)	0.01
Yes	259 (14.45)	202 (11.19)	
Unknown	4 (0.22)	3 (0.17)	
Ever been diagnosed with diabetes (through a physician)[a]			
No	1,452 (81.03)	1,553 (86.04)	<0.01
Yes	324 (18.08)	247 (13.68)	
Unknown	16 (0.9)	5 (0.28)	
Ever colorectal endoscopy[b]			
No/unknown	1,419 (79.19)	847 (46.93)	<0.01
Yes	372 (20.76)	958 (53.07)	
Unknown	1 (0.06)	0 (0.00)	
Ever use of hormone replacement therapy[c]			
No	500 (67.29)	357 (48.77)	<0.01
Yes	238 (32.03)	373 (50.96)	
Unknown	5 (0.67)	2 (0.27)	
Ever regular use of NSAIDs 2+ times/week ≥ 1 year[a]			
No	1,381 (77.06)	1,249 (69.20)	<0.01
Yes	403 (22.49)	549 (30.42)	
Unknown	8 (0.44)	7 (0.39)	
Colorectal cancer localization			
Colon	1,094 (61.05)	n/a	n/a
Rectum	698 (38.95)	n/a	

Abbreviation: n/a, characteristic only available for cases.

[a]Before reference date, which equals date of diagnosis among cases and date of recruitment among controls.

[b]For cases excluding endoscopies conducted as part of the diagnostic process.

[c]In women only.

Table 2. Association between obesogenic variants and colorectal cancer risk in the DACHS population

Variant_dbSNP	Gene	Nucleotide substitution	Position[a]/ variant	Risk allele[b]	OR (95% CI)[c]	P_{trend}	BMI × SNP $P_{interaction}$	T2D × SNP $P_{interaction}$	Sex × SNP $P_{interaction}$
rs6265	*BDNF*	G/A	V66M	G	1.05 (0.93–1.17)	0.44	0.25	**0.02**[e]	0.49
rs1919127	*C2orf16*	T/C	V685A	n/s	1.00 (0.90–1.11)	0.95	0.91	0.53	0.19
rs2679120	*CLIP*	G/C	Intron 5	G	0.97 (0.88–1.07)	0.55	0.65	0.45	0.74
rs2572106	*FBXL4*	A/C	5′-UTR	C	1.04 (0.94–1.15)	0.42	0.88	0.85	0.36
rs9939609	*FTO*	T/A	Intron 1	A	0.96 (0.87–1.05)	0.35	0.34	0.48	0.79
rs8050136	*FTO*	C/A	Intron 1	A	0.96 (0.88–1.06)	0.45	0.28	0.69	0.78
rs1260326	*GCKR*	C/T	P446L	n/s	0.91 (0.83–1.00)	0.06	0.18	0.18	0.35
rs10938397	*GNPDA2*	A/G	5′-UTR	G	1.10 (1.00–1.21)	**0.04**	0.85	0.16	0.34
rs4623795	*ITIH5*	G/C	Intron 3	G	0.98 (0.86–1.12)	0.78	0.30	0.93	0.51
rs11084753	*KCTD15*	G/A	3′-UTR	G	1.05 (0.95–1.16)	0.35	0.79	0.23	0.71
rs1041981	*LTA*	C/A	T60N	A	1.00 (0.91–1.11)	0.99	0.34	0.91	**0.002**[f]
rs1424233	*MAF*	G/A	5′-UTR	A	1.00 (0.91–1.10)	0.92	0.27	0.54	0.81
rs17782313	*MC4R*	T/C	3′-UTR	C	0.93 (0.84–1.04)	0.19	0.22	0.45	0.39
rs17700633	*MC4R*	G/A	3′-UTR	A	0.91 (0.83–1.01)	0.08	0.73	0.71	0.98
rs12970134	*MC4R*	G/A	3′-UTR	A	0.94 (0.84–1.04)	0.22	0.41	0.76	0.25
rs10838738	*MTCH2*	A/G	Intron 1	G	1.00 (0.91–1.11)	0.93	0.51	0.17	0.51
rs7336049	*MYO16*	C/G	5′-UTR	G	0.99 (0.90–1.10)	0.91	**0.04**[d]	0.67	0.46
rs2568958	*NEGR1*	A/G	5′-UTR	A	0.97 (0.88–1.07)	0.54	0.55	0.62	**0.04**[i]
rs1805081	*NPC1*	A/G	H215R	n/s	0.98 (0.89–1.07)	0.62	0.08	0.05	**0.03**[g]
rs6235	*PCSK1*	G/C	S690T	n/s	0.97 (0.87–1.08)	0.55	0.57	0.13	**0.03**[k]
rs6232	*PCSK1*	A/G	N221D	n/s	1.05 (0.85–1.30)	0.65	0.40	0.84	0.13
rs7212681	*RABEP1*	T/G	Intron 1	G	1.00 (0.91–1.10)	0.97	0.98	0.68	0.07
rs7498665	*SH2B1*	A/G	T484A	G	0.93 (0.85–1.02)	0.13	0.37	0.98	**0.03**[j]
rs10769908	*STK33*	T/C	Intron 5	C	1.01 (0.92–1.11)	0.88	0.44	0.77	0.17
rs35859249	*TBC1D1*	C/T	R125W	T	0.99 (0.84–1.17)	0.93	0.89	0.25	0.91
rs6548238	*TMEM18*	C/T	3′-UTR	C	1.00 (0.89–1.13)	0.99	0.32	0.95	**0.04**[h]

Abbreviations: n/s, not specified; UTR, untranslated region.

[a]Position denotes the location of an SNP in relation to the gene, i.e., 5′-UTR, 3′-UTR, or within the gene.

[b]BMI-increasing allele according to recent GWAS on obesity risk.

[c]Estimates were adjusted for age, sex, and county of residence. $P < 0.05$ in bold.

[d]*MYO16*$_{rs7336049}$ ($OR_{BMI<25\ kg/m^2}$, 0.94; 95% CI, 0.78–1.14; $OR_{BMI\geq25<30\ kg/m^2}$, 1.12; 95% CI, 0.95–1.31; and $OR_{BMI\geq30\ kg/m^2}$, = 0.75; 95% CI, 0.58–0.99).

[e]*BDNF*$_{rs6265}$ ($OR_{Diabetic}$, 1.50; 95% CI, 1.06–2.13 vs. $OR_{Nondiabetic}$, 0.98; 95% CI, 0.86–1.12).

[f]*LTA*$_{rs1041981}$ (OR_{Female}, 0.83; 95% CI, 0.71–0.97 vs. OR_{Male}, 1.14, 95% CI, 1.00–1.30).

[g]*NPC1*$_{rs1805081}$ (OR_{Female}, 0.86; 95% CI, 0.74–1.00 vs. OR_{Male}, 1.06; 95% CI, 0.94–1.20).

[h]*TMEM18*$_{rs6548238}$ (OR_{Female}, 1.17; 95% CI, 0.96–1.42 vs. OR_{Male}, 0.90; 95% CI, 0.77–1.06).

[i]*NEGR1*$_{rs2568958}$ (OR_{Female}, 0.86; 95% CI, 0.75–1.00 vs. OR_{Male}, 1.06; 95% CI, 0.94–1.20).

[j]*SH2B1*$_{rs7498665}$ (OR_{Female}, 0.82; 95% CI, 0.71–0.95 vs. OR_{Male}, 1.01; 95% CI, 0.90–1.15).

[k]*PCSK1*$_{rs6235}$ (OR_{Female}, 1.11; 95% CI, 0.95–1.31 vs. OR_{Male}, 0.88; 95% CI, 0.76–1.01).

were assessed by including multiplicative interaction terms in unconditional logistic regression models. All tests were two-sided and were considered statistically significant with $P \leq 0.05$.

Results

The study population comprised 1,792 German colorectal cancer cases (743 women and 1,049 men) and 1,805 controls (732 women and 1,073 men). Colorectal cancer cases were slightly younger than controls, had a higher BMI, and were more frequently diagnosed with T2D (Table 1).

All selected polymorphisms were in HWE in the control group ($P < 0.01$), with the exception of *FTO*$_{rs1421085}$ and *PRL*$_{rs4712652}$ that were excluded from further analyses. We did not find evidence of any association between obesity-related variants and the risk of developing colorectal cancer (Table 2). Only carriers of the *GNPDA2*$_{rs10938397G}$ allele had a nominally increased risk of developing colorectal cancer when compared with the wild-type allele carriers (per-allele OR, 1.10; 95% CI, 1.00–1.21). The risk estimates did not change substantially after adjustment for BMI.

Next, we investigated whether gender, obesity, and T2D modify the association of obesity-related variants with the risk of colorectal cancer (Table 2). We observed several nominally significant ($P < 0.05$) interactions between the SNPs and gender, BMI, and T2D, with the interaction of the $LTA_{rs1041981}$ SNP by gender being the strongest one ($P_{interaction} = 0.002$). While male carriers of the $LTA_{rs1041981A}$ allele had an increased risk of colorectal cancer (OR, 1.14; 95% CI, 1.00–1.30), an opposite effect was observed in women (OR, 0.83; 95% CI, 0.71–0.97). None of these findings remained statistically significant after Bonferroni correction for multiple testing, with threshold $P = 0.002$ (0.05/28) for the risk analysis and $P = 0.0006$ [$0.05/(28 \times 3)$] for interaction analysis.

Discussion

In this comprehensive case–control study, we did not observe any strong association between the studied 28 obesity-related variants and colorectal cancer risk in a Caucasian population, supporting the results observed earlier in the multiethnic cohort (3). We observed several interactions between the SNPs and gender; however, only the one with $LTA_{rs1041981}$ had ORs with nonoverlapping 95% CIs between males and females. We had an 80% power to detect an OR of 1.23 at $\alpha = 0.002$ (multiple testing threshold) for a polymorphism with a minor allele frequency of 0.25. However, as obesity was hypothesized to be an intermediate phenotype for colorectal cancer susceptibility, and the effect sizes of the GWAS-based SNPs were expected to be small, it is likely that some existing genetic effects were not detected because of insufficient power.

In summary, these results do not suggest that the obesity-related genetic variants are the underlying link between obesity and colorectal cancer. However, we cannot rule out the possibility that other obesity-related SNPs, affecting, e.g. adipokine, insulin-like growth factor-1 (IGF-I) or steroid hormone levels, may have an impact on colorectal cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J. Sainz, J. Chang-Claude, K. Hemminki, A. Försti
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.I. da Silva Filho, H. Brenner, A. Försti
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