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Insulin receptor variants and obesity-related cancers in the Framingham Heart Study

Niyati Parekh^{1,2}, Guia Guffanti³, Yong Lin⁴, Heather M. Ochs-Balcom⁵, Nour Makarem¹, Richard Hayes⁶

¹Department of Nutrition, Food Studies and Public Health, Steinhardt School, New York University, 411 Lafayette Street, 5th Floor, Room 542, New York, NY 10003, USA

²Department of Population Health, NYU Langone School of Medicine, 650 First Avenue, New York, NY 10016, USA

³Department of Psychiatry, Columbia University, Harkness Pavilion 180 Ft. Washington Avenue, New York, NY 10032, USA

⁴Rutgers School of Public Health, Rutgers The State University of New Jersey, 683 Hoes Lane West, Piscataway, NJ 08854, USA

⁵Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY 14214, USA

⁶Division of Epidemiology, Department of Population Health, NYU Langone School of Medicine, 650 First Avenue, New York, NY 10016, USA

Abstract

Purpose—The insulin-signaling pathway plays a pivotal role in cancer biology; however, evidence of genetic alterations in human studies is limited. This case-control study nested within the Framingham Heart Study (FHS) examined the association between inherited genetic variation in the insulin receptor (INSR) gene and obesity-related cancer risk.

Methods—The study sample consisted of 1,475 controls and 396 cases from the second familial generation of the FHS. Participants who provided consent were genotyped. Nineteen single-nucleotide polymorphisms (SNPs) in the INSR gene were investigated in relation to risk of obesity-related cancers combined and breast, prostate and colorectal cancers. Generalized

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Niyati Parekh, niyati.parekh@nyu.edu.

NP developed the overall research plan, contributed to manuscript writing, reviewed the manuscript for important intellectual content and had primary responsibility for the final content. NP was responsible for overseeing the entire study. YL performed the statistical analyses and reviewed the manuscript for statistical accuracy of results. GG provided guidance for statistical analyses, interpretation of data and contributed to manuscript writing and intellectual content. NM conducted literature searches and contributed to manuscript writing and preparation. HOB and RH provided insights toward reviewing and revising the manuscript for important intellectual content. All co-authors provided substantive comments and editorial review and approved the final version of the manuscript.

Conflict of interest

This research was supported by the American Cancer Society Research Scholar Grant (#RSG-12-005-01-CNE) awarded to Niyati Parekh, PhD RD. The American Cancer Society did not have a role in study design, collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. The authors have no conflicts of interest to report.

estimation equation models controlling for familial correlations and include age, sex, smoking and body mass index as covariates, assuming additive models, were used.

Results—Three SNPs, rs2059807, s8109559 and rs919275, were significantly associated with obesity-related cancers (p value < 0.02) with the most significantly associated SNP being rs2059807 (p value = 0.008). Carriers of two copies of SNP rs2059807 risk allele T were significantly less prevalent among subjects with obesity-related cancers [$f(TT)_{\text{cases}} = 14$ vs. $f(TT)_{\text{controls}} = 18$ %; OR 1.23]. In exploratory analyses evaluating site-specific cancers, the INSR rs2059807 association with these cancers was consistent with that observed for the main outcome (ORs colorectal cancer = 1.5, breast cancer = 1.29, prostate = 1.06). There was no statistically significant interaction between the INSR-SNP and blood glucose in relation to obesity-related cancer.

Conclusions—The INSR gene is implicated in obesity-related cancer risk, as 3 of 19 SNPs were nominally associated, after false discovery rate (FDR) correction, with the main outcome. Risk allele homozygotes (rs2059807) were less prevalent among subjects with obesity-related cancer. These results should be replicated in other populations to confirm the findings.

Keywords

Genetic polymorphisms; INSR gene; Insulin-signaling pathway; Cancer; Framingham Heart Study

Introduction

There is sufficient evidence in the literature to support the obesity-cancer link [1, 2]. It was estimated that more than 1.5 million new cases of cancer were diagnosed in the USA in 2010, with over 50 % in sites in which obesity was implicated [3]. Cancer is a complex disease characterized by a combination risk factors including metabolic dysregulation [4]. Intake of refined carbohydrates can influence blood glucose and insulin secretion [5], and activate ‘nutrient-sensing pathways’ that support cell proliferation and survival [6]. The insulin-signaling pathway plays a pivotal role between energy balance and cancer biology coupled with its influence on cell growth [7]. Although dysregulation of the insulin-signaling pathway has been implicated in carcinogenesis in laboratory and human studies [7–10], evidence for key susceptibility genes in the insulin-signaling pathway is limited in humans.

Dysregulation of the insulin-signaling pathway has been demonstrated in numerous cancers including breast, prostate, colon and uterus (reviewed in [9]). A key mechanism through which insulin may increase cancer risk is by activation of target genes downstream of the insulin receptor, which comprise a signaling network that dictates cell growth, survival, proliferation and anti-apoptotic activities (reviewed in [7, 11]). The insulin-signaling pathway is critical for ‘sensing nutrients’ [6] and ultimately determines cell fate (e.g., proliferation, protein synthesis, angiogenesis, or apoptosis). Altered gene and protein expression (in the absence of gene amplifications or mutations) has been observed. Therefore, other genetic alterations such as single-nucleotide polymorphisms (SNPs) may explain changes in gene expression or protein function in relation to cancer [12].

Insulin exerts its physiologic action by binding to the transmembrane receptor on the cell surface. The receptor undergoes structural changes due to phosphorylation of tyrosine residues and subsequently leads to the downstream activation of effector proteins that mediate cell survival and growth [13]. To date, few studies have examined INSR gene variation specifically, and we believe this is a necessary step to further our understanding of the role of insulin receptor and insulin signaling in obesity-related cancers.

Herein, we examined the association of inherited genetic variation in the insulin receptor gene (SNPs) and obesity-related cancers in the Framingham Heart Study (FHS) offspring cohort. The present analyses will provide data on potential genetic targets for future clinical trials designed for cancer prevention.

Methods

The Framingham offspring cohort

The FHS is an ongoing study based in Framingham, Massachusetts, consisting of data from three familial generations [14]. The original cohort was initiated in 1948 and consisted of 5,209 men and women aged between 28 and 62 years. Clinical exams were conducted on average every 2 years for this generation. The Framingham offspring (FOS) cohort was initiated in 1971 and includes 5,124 offspring (of the original cohort) and their spouses. Clinical exams were conducted, on average, every 4 years from 1971 to 2008 for the FOS [15, 16]. For the purpose of this analysis, we studied biological descendants of the first generation (excluding their spouses) for a total of 1,871 individuals; 850 males and 1,021 females.

Genotyping in the Framingham Heart Study

Genotyping was conducted through the FHS SNP Health Association Resource (SHARe) initiated in 2007 on all FHS participants with DNA available. Overall 9,232 FHS participants were genotyped using the Affymetrix Gene-Chip Human Mapping 500 K Array and the 50 K Human Gene Focused Panel, including 1,529 FHS participants from the original cohort, 3,753 from the FOS, 3,893 from the third generation and 535 singletons.

Single-nucleotide polymorphism selection

After removal of singleton participants, there were 8,697 participants. We used the full sample (including parental generation) to screen for Mendelian errors. Families were discarded if there were more than 5 % Mendelian errors (considering all SNPs) and SNPs were removed if Mendelian error rate was more than 10 % (i.e., based on the number of trios). This initial quality control measure yielded a sample of 8,577 participants. We studied biological descendants of the first generation (excluding their spouses) resulting in an analytical sample of 1,871 participants. Then, we selected SNPs mapping to the gene INSR to test our research hypothesis. In particular, we derived the genomic coordinates of the INSR gene consulting the publicly available database GeneCards [17]. SNPs mapping to the interval between chr19: 7,112,266 (–5 Kb) and chr19: 7,294,045 (+5 Kb) were extracted from the whole-genome data, which provided us with 25 SNPs.

We performed quality control analysis of the 25 INSR SNPs using PLINK [18]. We removed SNPs that did not meet the significance threshold of p value $>10^{-3}$ for the Hardy-Weinberg equilibrium tests, if the minor allele frequency (MAF) was $<1\%$ and genotyping rate was $<95\%$. These quality checks resulted in the removal of 2 SNPs that failed HWE and 4 SNPs due rare MAF, for a final set of 19 INSR SNPs for analysis.

Data collection for other variables

Anthropometric measures were obtained by trained personnel, and height and weight were used to calculate body mass index (BMI). Demographic and lifestyle characteristics including race/ethnicity, age, smoking status and physical activity were self-reported during in-person interviewing. Physical activity levels of participants were assessed by querying the hours spent engaging in sedentary, light, moderate and heavy physical activity, and subsequently computing a physical activity index by multiplying the time spent at each activity by its metabolic cost as previously published [19]. Menopausal status was determined using a standardized medical history questionnaire, while hormone use was ascertained by a physician at the clinical exam. Dietary intake was measured using the validated semi-quantitative Harvard food frequency questionnaire (FFQ) that queried the frequency of food intake with standard serving sizes [20]. FFQ data were analyzed using the US Department of Agriculture nutrient database.

Obesity-related cancer diagnosis

Obesity-related cancers were defined as cancers identified by the American Cancer Society as clearly or possibly linked to excess adiposity [21]. This definition encompasses cancers of the gastrointestinal tract, reticuloendothelial system (blood, bone and spleen), female reproductive tracts, genitourinary organs and the thyroid gland. Pathology reports were used to ascertain cancer cases though some diagnoses based solely on death certificates or clinical diagnoses. Diagnoses not confirmed by pathology reports were excluded. Patient medical records were used to determine cancer type and date of diagnosis. In these analyses, there were 396 subjects affected by obesity-related cancers and 1,475 healthy controls.

Statistical analysis

We performed association tests to analyze the association of INSR SNPs and obesity-related cancers using generalized estimation equation (GEE) models that allow for control for familial correlations using GWA R package [22]. We assumed additive genetic models. The GEE model included the following covariates: age, sex, smoking and BMI. We also performed a GEE model including age, sex and smoking as covariates but no BMI. The false discovery rate (FDR) was investigated by calculating q values, i.e., FDR analogs of p values, with the R package QVALUE [23], aiming at less than one false discovery among the significant findings. Given that there is no evidence for major population substructure in FHS [24], we did not include any population substructure correction in our population-based GEE models.

Results

General characteristics of the study participants

General demographic and clinical characteristics in addition to dietary variables of the cases and controls are summarized in Table 1. The majority of cases and controls were former or current smokers (63.68 and 65.29 % respectively); there were no significant differences in smoking status between the two groups. The distribution by sex also did not vary significantly between the cases and controls (52.27 and 55.19 % female respectively). In general, the study sample was young to middle-aged though the cases were significantly older than the controls (39.44 vs. 37.25 years; $p < 0.001$). On average, both cases and controls were in the overweight category. The mean BMI of the controls was significantly higher than that of the cases ($p < 0.001$), though the difference between the two groups was not clinically significant (27.78 vs. 27.58 kg/m²). There were significant differences in menopausal status between cases and controls, as cases were more likely to be postmenopausal (49.76 vs. 40.79 %; $p = 0.02$). Cases and controls had a similar physical activity index corresponding to high levels of physical activity. There were no significant differences in total energy, carbohydrate, protein and fat intake. However, controls reported significantly higher intakes of alcohol than cases (12.60 vs. 10.13 g/day; $p = 0.038$).

Association of SNPs mapping to INSR gene with obesity-related cancers

The association between obesity-related cancers and the INSR SNPs is shown in Table 2. Three SNPs, rs2059807, s8109559 and rs919275, were significantly associated with obesity-related cancers at the threshold of p value < 0.02 . The most significantly associated SNP, rs2059807, yielded a p value = 0.008. Carriers of two copies of SNP rs2059807 risk allele T were significantly less prevalent among subjects with a diagnosis of obesity-related cancers [$f(TT)_{\text{cases}} = 14$ vs. $f(TT)_{\text{controls}} = 18$ %; OR 1.24]. All three SNPs were still associated at the significance threshold of q value < 0.05 after FDR correction (< 1 false positive among them). The rs2059807 SNP is an intronic variant. Two SNPs, rs4804416 and rs10416429, were marginally significant with p value of 0.037. We also performed a GEE model without adjustment for BMI. The significance of the association of INSR SNPs with obesity-related cancers changes only slightly without adjustment for BMI.

The bioinformatics analysis of potential functional role of this SNP revealed a functional score (FS) of 0.28 and indicated that the substitution C > T might play a role in transcriptional regulation processes.

In exploratory analysis, we performed the association analysis between SNP rs2059807 and the three most commonly diagnosed types of obesity-related cancers, breast, prostate and colorectal cancer. Although the sample size differs across these three analyses, both in consideration of the prevalence and the sex specificity of single cancers, the ORs were consistently significant and > 1 ranging from 1.06 to 1.5 for the three sites, thus providing support for an INSR association with these specific individual obesity-related cancers (data not shown). Finally, we tested the hypothesis that glucose levels were moderating the relationship between the INSR SNP and odds of obesity-related cancer, but the analysis did not reveal any significant interaction (data not shown).

In silico analysis of the genome/epigenome annotations of INSR SNPs associated with obesity-related cancers

We performed an in silico computational analysis using the current genome/epigenome annotations available at UCSC Genome Browser (ENCODE regulation). SNP rs2059807 maps to intron 8 of the INSR gene, only ~50 bp from exon 8. The region harboring the top associated SNP is characterized by evidence of moderate levels of the histone marks H3K4Me1 and the identification of a weak enhancer through the ChIP-seq chromatin state segmentation of the endothelial cells of blood vessels. SNP rs4804416 maps to intron 2 in a region characterized by moderate to intense levels of the histone marks H3K4Me1 and the identification of an enhancer through the ChIP-seq chromatin state segmentation enhancer in blood cells. Although far from conclusive, data for both of these SNPs annotation analyses support a potential functional role for transcriptional regulation of the region harboring them. SNP rs919275 (intron 2) and SNP rs8109559 (intron 5) map to regions that do not reveal any evidence of transcriptional regulation based on current annotations.

Discussion

In this study, we provided evidence of the potential role of the insulin receptor gene in the genetic susceptibility to obesity-related cancers. We found 3 out of 19 SNPs nominally associated after FDR correction with the main outcome. Risk allele homozygotes were less prevalent among subjects with a diagnosis of obesity-related cancers. Although intronic, the most significantly associated SNP, rs2059807, revealed a potential role in transcriptional regulation processes after bioinformatics in silico function analysis for non-coding SNPs.

The INSR gene has been linked to cancer, because SNP polymorphisms influence gene expression and protein function in the insulin-signaling pathway [7, 12]. Dysregulation of this pathway plays a pivotal role in cancer etiology [9]. Insulin is associated with increased risk of obesity-related cancers [4], potentially through its impact on genes downstream that promote cell proliferation growth, survival, and anti-apoptotic activity (reviewed [7, 11]). For instance, insulin may regulate cell growth and apoptosis by binding to its INSR receptor. Moreover, previous evidence indicates that mutations in the INSR gene may lead to moderate or severe insulin resistance [25, 26]. In turn, hyperinsulinemia and obesity are associated physiologic and biochemical changes in INSR expression that may impact cancer risk.

A total of four previous studies have evaluated polymorphisms in the INSR gene in relation to cancer risk [27–30]. One study evaluated INSR SNP polymorphisms in relation to breast cancer [28], two studies in relation to colorectal adenomas/cancer [27, 29] and one study in relation to papillary thyroid cancer [30]. There are no previous studies evaluating INSR gene polymorphisms in relation to prostate cancer and the remaining obesity-related cancers. The studies evaluating INSR in relation to colorectal cancer were both conducted in largely Caucasian samples and provided different results. A Czech case-control study [29] showed a significant association between the A-603G polymorphism in the INSR gene corresponding to the rs3842752 SNP and colorectal cancer. Under dominance, a protective impact of the variant allele carriers of INSR gene was observed. In particular, there was a 29 % reduction in colorectal cancer risk for the GG/AG versus AA genotype (OR 0.71; 95 % CI 0.54–0.93).

On the other hand, a nested case-control within the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial [27] showed that heterozygosity at the INSR exon 17–4 locus, corresponding to the rs1799817 SNP, was associated with increased risk of advanced left-sided colorectal adenoma, a precursor for cancer (OR 1.27; 95 % CI 1.01–1.61). Moreover, this study found a statistically significant interaction between INSR genotypes and BMI in relation to colorectal adenoma risk, though for some SNPs genotype-specific associations differed according to BMI. Results were also suggestive of an interaction between glycemic load and INSR genotypes in risk of colorectal adenoma. These results did not change upon restricting the sample to Whites and non-diabetics or stratification by adenoma location (colon vs. rectum).

A case-control study using the US Radiologic Technologists cohort [30] investigated INSR polymorphisms in relation to cancer of the thyroid. This study showed no association between the INSR SNP rs919275 and risk of papillary thyroid cancer. Similarly, only one study evaluated SNP polymorphisms in the INSR gene in relation to postmenopausal breast cancer risk [28]. The study was conducted among 488 matched case-control pairs from the American Cancer Society's Cancer Prevention Study II Nutrition Cohort. Women who were homozygous for the T allele of INSR H1085H corresponding to the rs1799817 SNP had a statistically significant 69 % lower risk of breast cancer (OR 0.31; 95 % CI 0.11–0.85).

The results of three of these studies [27–29] are consistent with our finding of a significant association between certain INSR SNP polymorphisms and cancer risk. However, in the present study being homozygous for the SNP rs2059807 risk allele was associated with decreased risk of obesity-related cancers in general and breast and colorectal cancer in site-specific analyses. These results have not been observed in any previous studies.

We need to consider our work within the context of several limitations. First, sample size is limited and replication in an independent sample is warranted. Second, the associated SNPs are non-coding and little is known on the actual functional effects of these genetic variations on INSR expression. Further studies are needed to explore the functional impact of these polymorphisms. However, this study has some notable strengths. Medical records and pathologic reports were used to diagnose and confirm cancer cases. The availability of cancer data for all sites allowed the evaluation of INSR polymorphisms in relation to obesity-related cancers combined and three of the most common site-specific cancers. The Affymetrix 100 K chip with 112,990 autosomal SNPs was used to genotype participant DNA, and quality control analysis was done for the 25 identified INSR SNPs in this analysis. Additionally, multiple SNPs of the INSR gene were analyzed which increases the probability of identifying a signal from a causal variant.

In conclusion, our results suggest reduced risk of obesity-related cancers, in general, and colorectal and breast cancer, in particular, among risk allele homozygotes. However, these results should be confirmed in other independent sample sets. Additionally, the present study and most studies thus far have been conducted in largely Caucasian samples. Similar studies are warranted in other ethnic groups, as associations may vary by race. Moreover, studies thus far have focused on prostate, colorectal, breast and thyroid cancers as study outcomes. Associations with other cancers merit further investigation. Because of the role of insulin

dysregulation in cancer risk, polymorphisms in the INSR gene may have a more prominent impact on individuals with insulin-related chronic conditions such as diabetes and obesity. Future studies should focus INSR SNPs and other genetic variants of the insulin transduction pathway in relation to cancer risk among overweight, obese and diabetic individuals.

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Table 1

Demographic characteristics of cases and controls

Characteristics	Controls (<i>n</i> = 1,475)		Cases (<i>n</i> = 396) ^a		<i>p</i> values
	Percentage (%)	Mean (SD)	Percentage (%)	Mean (SD)	
Sex (%)					
Male	44.81		47.73		0.301
Female	55.19		52.27		
Smoking status (%)					
Smoker	65.29		63.68		0.481
Non-smoker	34.71		36.62		
Age (years)		37.25 (9.22)		39.44 (8.04)	<0.001
BMI (kg/m ²)		27.78 (5.49)		27.58 (4.71)	<0.001
Physical activity index		34.15 (5.57)		34.04 (5.79)	0.76
Menopausal status (%)					
Premenopausal	59.21		50.24		0.02
Postmenopausal	40.79		49.76		
Total energy intake (kcal)		1820.69 (611.28)		1836.23 (614.81)	0.69
Protein intake (% kcal)		16.55 (3.43)		16.53 (3.50)	0.68
Carbohydrate intake (% kcal)		51.31 (8.32)		51.20 (8.86)	0.94
Fat intake (% kcal)		27.46 (5.92)		26.94 (6.11)	0.97
Alcohol intake (g/day)		12.60 (19.08)		10.13 (16.16)	0.038

^a A total of 396 obesity-related cancers were included in these analyses. There were 111 breast cancer, 123 prostate cancers, 77 colorectal cancers and 85 other obesity-related cancers

Associations between SNPs in the INSR gene and obesity-related cancer risk in the Framingham health study

Table 2

SNP (rs#) ^a	Affy SNP name	Chr	Coordinate	Alleles (major/minor)	MAF	<i>f</i> (risk genotype) cases	<i>f</i> (risk genotype) controls	OR (95 % CI)	<i>p</i> values	<i>q</i> values (FDR)
rs2059807	ss66472545	19	7,117,109	C/T	0.395	0.187	0.143	1.24 (1.057–1.455)	0.008	0.020
rs3815902	ss66279670	19	7,117,138	C/T	0.228	0.056	0.051	1.054 (0.875–1.271)	0.578	0.120
rs8109559	ss66230095	19	7,122,629	G/A	0.203	0.018	0.050	1.269 (1.033–1.557)	0.019	0.020
rs8108622	ss66230096	19	7,133,753	T/A	0.215	0.053	0.050	1.025 (0.846–1.241)	0.839	0.137
rs10500204	ss66089952	19	7,133,963	A/C	0.285	0.077	0.082	1.023 (0.859–1.218)	0.838	0.137
rs7245757	ss66044517	19	7,138,628	C/T	0.291	0.102	0.078	1.078 (0.905–1.284)	0.466	0.111
rs1035940	ss66036602	19	7,150,978	G/C	0.286	0.097	0.080	1.082 (0.907–1.291)	0.409	0.111
rs2042901	ss66342531	19	7,155,394	G/T	0.265	0.092	0.066	1.069 (0.893–1.281)	0.454	0.111
rs3745546	ss66493296	19	7,162,816	G/C	0.216	0.041	0.045	0.925 (0.759–1.128)	0.575	0.120
rs3745545	ss66525709	19	7,162,841	A/G	0.165	0.016	0.022	0.876 (0.703–1.093)	0.158	0.079
rs7245562	ss66179389	19	7,169,135	C/T	0.072	0.011	0.004	1.065 (0.780–1.456)	0.799	0.137
rs7508679	ss66284257	19	7,173,832	C/T	0.400	0.153	0.155	0.902 (0.767–1.060)	0.427	0.111
rs4804416	ss66484547	19	7,174,848	T/G	0.440	0.220	0.184	0.836 (0.714–0.979)	0.059	0.037
rs7248104	ss66379676	19	7,175,431	G/A	0.398	0.152	0.153	0.895 (0.761–1.053)	0.376	0.111
rs4804424	ss66049909	19	7,180,677	G/A	0.322	0.100	0.112	1.124 (0.947–1.334)	0.209	0.081
rs10416429	SS66246208	19	7,181,438	C/A	0.320	0.096	0.116	1.187 (0.994–1.418)	0.058	0.037
rs890862	ss66435005	19	7,184,604	C/T	0.322	0.100	0.114	1.136 (0.957–1.348)	0.179	0.079
rs919275	ss66479946	19	7,212,441	A/G	0.431	0.232	0.163	1.231 (1.050–1.442)	0.016	0.020
rs8101064	ss66198791	19	7,244,119	C/T	0.040	0.003	0.000	1.141 (0.744–1.750)	0.623	0.121

^aLocation of the all SNPs relative to gene is intron

SNP= single nucleotide polymorphism; Chr= chromosome; MAF= minor allele frequency