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Recreational physical activity modifies the association between a common GH1 polymorphism and colorectal cancer risk

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Abstract

Growth hormone may be associated with the development of colorectal cancer directly and/or indirectly via increased serum level of IGF-I. Regular physical activity can decrease insulin-resistance and modulates IGF-I production. A common polymorphism in the GH1 gene, rs2665802, was previously shown to be associated with lower IGF-I levels and decreased colorectal cancer (CRC) risk. We investigated the association of this polymorphism and physical activity with colorectal cancer risk in a case-control study.

Methods—The analysis includes 3041 (1402 cases and 1639 controls) participants in the Molecular Epidemiology of Colorectal Cancer study, a population-based case-control study in Northern Israel. Analysis was carried out separately in two sets. The first set included 1248 subjects (625 cases, 623 controls), and the second validation set consisted of 1793 subjects (777 cases, 1016 controls).

Results—No association was found between the studied polymorphism and CRC risk. However, evaluation of gene-environment interactions revealed an interaction between leisure time physical activity and the GH1 polymorphism, which was consistent in both sets(p-*interaction*=0.005). The genotype AA was associated with decreased risk of CRC among individuals who did not engage in any such activity; OR=0.76(0.52–0.98), whereas the same genotype was marginally associated with increased risk among individuals who reported physical activity; OR=1.38(0.98–1.94).

Conclusions—We found that the A allele of the rs2665802 polymorphism is associated with reduced risk of CRC only among physically inactive individuals, indicating an interaction between physical activity and the GH/IGF-I system. A replication of the observed findings and further investigation of the underlying mechanism is warranted.

Introduction

Growth hormone (GH) might be directly associated with colorectal cancer, as the expression of the GH receptor is upregulated during tumorgenesis of human colorectal cancer [1] and acromegaly, a disorder characterized by high circulating levels of growth hormone, has been associated with the presence of hyperplastic colonic polyps and carcinoma[2,3].

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Further, GH is indirectly associated with colorectal cancer as it is the primary determinant of insulin-like growth factor I (IGF-I) levels. IGF-I has anti-apoptotic and mitogenic actions[4–6], and several prospective studies support a positive association between IGF-I and colorectal cancer risk[7–11]. However, some studies have not shown this association[12] and one recent study reported an inverse association with colorectal adenoma recurrence[13].

Circulating levels of IGF-I and its binding proteins are determined both by genetic and lifestyle factors.. There have been reports of altered levels of IGF-I and its binding protein in response to exercise[4,14–16].

Physical activity is one of the strongest risk factors for colon cancer. It has been estimated that 13–14% of colorectal cancer may be attributed to physical inactivity, an attributable risk greater than family history[17]. Despite the wealth of evidence for reducing colon cancer risk, physical activity has been inconsistently associated with rectal cancer. While it has been found to be similarly protective for colon and rectal cancers in some studies[18–21], others support a protective effect on colon but not rectal cancer[22,23].

A common polymorphism at intron 4 of the GH1 gene (rs2665802) has been found to be significantly associated with IGF-I levels and colorectal cancer colorectal cancer risk[24,25]. We assessed the association of the GH1 polymorphism with colorectal cancer risk in a large case-control study an its interaction with risk factors. Based on previous findings we hypothesized that the A allele of the GH1 polymorphism will reduce the risk of colorectal cancer in our study population.

Materials and Methods

Study subjects

Subjects were drawn from among participants in the Molecular Epidemiology of Colorectal Cancer study (MECC). Detailed description of the study was previously published[26].

In brief, the MECC Study is a population-based study of all incident colorectal cases diagnosed in northern Israel between 1998 and 2004, and population-based controls identified from the same source population with the use of the Clalit Health Services (CHS) database, and matched for age, gender, primary care clinic and religion. As Israel has a mandatory governmental health insurance coverage, all study participants (patients and controls) had similar health insurance and similar access to health services. The study utilizes a structured questionnaire to obtain information on demographic factors, family history, reproductive history, prior disease history, medications use, dietary habits, and health related behaviors including physical activity. Blood samples are obtained from subjects that complete the in-person interview. The study was approved by the institutional review boards at the University of Michigan and Carmel Medical Center in Haifa. Participants provided written informed consent at the time of enrollment.

The present analysis includes a total of 3041 (1402 cases and 1639 controls) participants in the MECC study, that were genotyped and initially analyzed as two independent sets, for test validation, followed by joint analysis. The first set included 1248 subjects (625 cases and 623 controls), and the second set 1793 (777 cases and 1016 controls). These participants were drawn from among a total of 4,225 participants in the phase I of the MECC study. The participation rate of all eligible patients in phase I was 67.5%.

Genotyping

Genotyping was done using a custom Taqman- based SNP genotyping assay on the ABI Prisms 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA), in 96-well format.

The reaction mix for each sample included 1μl genomic DNA, 0.1 μl primer/probe mix, 4.7 μl master mix (Applied Biosystems), and 9.3 μl of double distilled water, in a final volume of 15 μl. The thermocycling included: a pre-run of 2 min at 50°C followed by 10 min at 95°C; then 40 cycles with 10 s at 95°C followed by 60 s at 60°C. Primer sequences were as follows: forward 5′-GAGAAACACTGCTGCCCTCTT-3′; Reverse 5′-GAGAAAGGCCTGGAGGATTCAC-3′; and probes as VIC TTTAGCAG**A**CAGGCCCT and FAM TTAGCAG**T**CAGGCCCT.

Genotyping was done separately for two independent sets. Cases and controls were genotyped on the same assay run. Each assay run included two negative controls (without DNA), one positive control (confirmed by sequencing), and two samples that were duplicated on separate runs. For additional quality control, genotyping for 304 randomly selected samples, was repeated. The genotype concordance rate was 97%.

Variable definition

Physical activity was assessed using questions from a previously validated questionnaire[27]. Leisure-time physical activity was quantified from the self-reported types and duration of activities. The reported time spent at each activity per week was multiplied by its typical energy expenditure requirements expressed in metabolic equivalents (METs) and added together to yield a MET-hours per week score. Based on the MET-hours per week score, participants were categorized as being either inactive (a score less or equal to 3) or active (a score higher than 3).

Body mass index (BMI) was calculated as an individual's reported weight (in kilograms) a year prior to the interview, divided by height (in meters) squared. Age at interview was included as a continuous variable. Individuals were ethnically categorized as Ashkenazi, Sephardi and Arabs based on self-reported ethnicity/religion.

Statistical analysis

The current analysis was not confined to matched cases. However, to address the main research question, both conditional and unconditional multivariate logistic regression models were developed.

Established risk factors were included in the logistic regression model to adjust for potential confounding. Interactions were pre-defined to biologically plausible ones, namely gender, ethnic group, physical activity and BMI, and were reported only if the interaction term was statistically significant. The Chi-square test for goodness of fit was also employed to test for Hardy Weinberg equilibrium among controls. All Statistical tests were two-sided, with 5% significance level. Analysis was carried out using SPSS version 14.

The effect of leisure-time activity was tested separately on colon and rectal cancer, and was combined only after demonstrating a similar effect on both sites. Further, data were analyzed separately for each set, and only if the results were consistent, an analysis of the combined set was undertaken.

Results

Leisure time physical activity was found to have an equally protective effect on colon and rectal cancer; the odds ratio (OR) and 95% confidence interval (95%CI), adjusted for age, gender, BMI and ethnicity, were 0.63 (0.53–0.75) for colon and 0.60 (0.44–0.81) for rectum. The ratio of odds ratios (ROR) was 0.92 (0.69–1.22). The two sites were combined for the remaining of the analysis. In the univariate analysis for both sites combined we found 36% reduction in risk; OR=0.64 (0.55–0.75) which was attenuated in the multivariate model

including the interaction parameter with the GH1 polymorphism; 0.73 (0.54–1.00). Although Jewish/non-Jewish ethnicity was matched for in the study design, cases were more likely to be of Ashkenazi Jewish origin ($p<0.0001$), which is in line with ethnicity-specific incidence rates reported by the Israeli Cancer Registry. Differences in BMI did not reach statistical significance in the multivariate model (Table 1).

The distributions of the GH1 rs2665802 genotypes were consistent with the Hardy-Weinberg equilibrium among controls in both study sets, as well as in the overall group ($p=0.36$).

As shown in Table 1, there was no apparent association between the rs2665802 polymorphism and colorectal cancer risk in any of the groups. Nevertheless, evaluation of gene-environment interactions revealed a significant interaction of the studied polymorphism with leisure time sports participation. This interaction was consistent in both sets, as well as in the combined group (p-*interaction*=0.005).

Stratified analysis by sports participation status is presented in Table2. The genotype AA was associated with a decreased risk of colorectal cancer only among inactive individuals; OR=0.76 (0.52–0.98). The same genotype was associated with increased risk of colorectal cancer in active individuals, OR=1.38 (0.98–1.94), although the risk estimate was of borderline significance in the combined group.

Discussion

We sought evidence for the association of a common polymorphism in the GH1 gene and colorectal cancer risk. This polymorphism has been previously documented to be associated with IGF-I, IGFBP1 plasma levels, and IGF-1/IGFBP-3 ratio, as well as with colorectal cancer risk[25].

In accordance with previous findings the rs2665802 polymorphism was common, “A” was the minor allele, and its frequency differed between the three ethnic groups in the study. The frequency of the A variants of the polymorphism in our population overall was 47%, (50% in Ashkenazi, 44% in Sephardi, and 39% in Arabs) similar to the frequencies reported previously[25].

Our study did not confirm a previously reported association between genetic variation in GH1 and risk of colorectal cancer, although we had an 80% power to detect a minimum OR of 1.3. However, we found a statistically significant interaction between the studied polymorphism and sports participation.

We observed a risk reduction of both colon and rectal cancer associated with leisure-time physical activity. In the univariate analysis the magnitude of risk reduction conferred by leisure-time physical activity was in line with previous studies that averaged 40–50%[28]. However, it was somewhat attenuated in the multivariate model including the interaction parameter with the GH1 polymorphism.

Several mechanisms that link between physical activity and cancer development in general and colorectal in particular, have been suggested. One mechanism is through interactions with the insulin-like growth factor axis[17,29].

Regular physical activity can decrease insulin-resistance[30] and hence, serum insulin levels, which modulates the growth hormone stimulus for IGF-I production. Further, some studies have demonstrated reductions in IGF-I levels in response to chronic exercise[14,31].

We found that leisure time physical activity modifies the association of the GH1 rs2665802 polymorphism with colorectal cancer. The A allele of the GH1 polymorphism, which has been previously shown to decrease circulating IGF-I levels[25], seems to decrease risk of colorectal cancer only among the physically inactive.

Our findings support the hypothesis that physical activity may modify the effect of genes involved in the development of colorectal cancer. Two studies has previously shown that physical activity modifies the association of polymorphisms in the IGF-I gene with colorectal cancer[32,33]. Nevertheless, the observed findings need to be replicated in future studies.

Further the studied polymorphism has been previously shown to alter IGF-I levels[24,25]. However, the evidence relating IGF-I levels and risk of colorectal neoplasia may be more complex than initially thought. A study of adenoma recurrence found an inverse association[13]. Thus, further investigation of the mechanism underlying this interaction is warranted.

Given the obesity epidemic in much of the Western world, these data provide potential insight into understanding the complex relationships between physical activity, body mass index, genetic variation in the insulin-like growth factor axis and risk of colorectal cancer.

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Table 1

The association between GH1, physical activity and colorectal cancer risk in the MECC study*

	First set (n=1248)			Second set (n=1793)			Overall group (n=3041)		
	Cases (n=625)	**Controls (n=623)**	**OR (95% Confidence interval)**	**Cases (n=777)**	**Controls (n=1016)**	**OR (95% Confidence interval)**	**Cases (n=1402)**	**Controls (n=1639)**	**OR (95% Confidence interval)**
GH1 genotype									
TT	197 (31.5)	191 (30.7)	1.0 (reference)	209 (26.9)	283 (27.9)	1.0 (reference)	**406 (29.0)**	**474 (28.9)**	**1.0 (reference)**
TA	295 (47.2)	298 (47.8)	0.77 (0.56–1.07)	390 (50.2)	482 (47.4)	0.91 (0.68–1.20)	**685 (48.9)**	**780 (47.6)**	**0.84 (0.68–1.04)**
AA	133 (21.3)	134 (21.5)	0.71 (0.47–1.06)	178 (22.9)	251 (24.7)	0.84 (0.60–1.17)	**311 (22.2)**	**385 (23.5)**	**0.77 (0.59–0.99)**
Sport participation – no. (%)	196 (31.4)	252 (40.4)	0.83 (0.50–1.37)	264 (34.0)	427 (42.0)	0.63 (0.42–0.95)	**460 (32.8)**	**679 (41.4)**	**0.73 (0.54–1.00)**
GH1 X Sports interaction term			P=0.05			P=0.07			**P=0.005**
Age (years)- mean ± SD**	69.5±11.8	69.9±11.9	0.99 (0.98–1.00)	69.9±11.04	71.3±11.3	0.98 (0.97–0.99)	**69.7±11.4**	**70.7±11.6**	**0.98 (0.98–0.99)**
Sex – no. (%)**									
Male	330 (52.8)	341 (54.7)	1.0 (reference	417 (53.7)	531 (52.3)	1.0 (reference)	**747 (53.3)**	**872 (53.2)**	**1.0 (reference)**
Female	295 (47.2)	282 (45.3)	1.01 (0.81–1.28)	360 (46.3)	485 (47.7)	0.90 (0.74–1.09)	**655 (46.7)**	**767 (46.8)**	**0.94 (0.81–1.09)**
Body mass index (kg/m^2) – no. (%)									
<25	215 (34.4)	236 (37.9)	1.0 (reference	275 (35.4)	387 (38.1)	1.0 (reference)	**490 (35.0)**	**623 (38.0)**	**1.0 (references)**
25-<30	253 (40.5)	256 (41.1)	1.16 (0.89–1.49)	321 (41.3)	400 (39.4)	1.09 (0.88–1.36)	**574 (40.9)**	**656 (40.0)**	**1.14 (0.94–1.3)**
>=30	157 (25.1)	131 (21.0)	1.32 (0.97–1.78)	181 (23.3)	229 (22.5)	1.01 (0.78–1.3)	**338 (24.1)**	**360 (22.0)**	**1.12 (0.92–1.36)**
Ethnicity – no. (%)**									
Ashkenazi Jews	404 (64.6)	352 (56.5)	1.0 (reference	599 (77.1)	725 (71.4)	1.0 (reference)	**1003 (71.5)**	**1077 (65.7)**	**1.0 (reference)**
Sephardi Jews	84 (13.4)	131 (21.0)	0.48 (0.35–0.67)	160 (20.6)	262 (25.8)	0.64 (0.51–0.81)	**244 (17.4)**	**393 (24.0)**	**0.58 (0.48–0.71)**
Arabs	137 (21.9)	140 (22.5)	0.66 (0.49–0.90)	18 (2.3)	29 (2.9)	0.61 (0.33–1.13)	**155 (11.1)**	**169 (10.3)**	**0.77 (0.60–0.98)**

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* Estimated from a model including GH1 genotype, age, sex, BMI, ethnicity, sports participation, and the interaction term GH1 genotype*sports participation.

** Variables used for matching in the original study design, and ORs do not reflect risk of colorectal cancer.

Table 2

The association of GH1 rs2665802 genotype with colorectal cancer risk, by level of physical activity

	Genotype	Overall (n=3041)			First Set (n=1248)			Second Set (n=1793)		
		Cases No. (%)	Controls No. (%)	OR* (95% Confidence interval)	Cases No. (%)	Controls No. (%)	OR* (95% Confidence interval)	Cases No. (%)	Controls No. (%)	OR* (95% Confidence interval)
Inactive	TT	302 (32.1)	272 (28.3)	1.0 (reference)	149 (34.7)	109 (29.4)	1.00 (reference)	153 (29.8)	163 (27.7)	1.00 (reference)
	TA	440 (46.7)	463 (48.2)	0.84 (0.68–1.04)	199 (46.4)	182 (49.1)	0.77 (0.56–1.07)	241 (47.0)	281 (47.7)	0.90 (0.68–1.19)
	AA	200 (21.2)	225 (23.4)	**0.76 (0.52–0.98)**	81 (18.9)	80 (21.6)	0.69 (0.46–1.04)	119 (23.2)	145 (24.6)	0.83 (0.59–1.16)
Active	TT	104 (22.6)	202 (29.7)	1.0 (reference)	149 (34.7)	109 (29.4)	1.00 (reference)	56 (21.2)	120 (28.1)	1.00 (reference)
	TA	245 (53.3)	317 (46.7)	1.52 (1.14–2.04)	199 (46.4)	182 (49.1)	1.46 (0.93–2.29)	149 (56.4)	201 (47.1)	1.34 (0.91–1.97)
	AA	111 (24.1)	160 (23.6)	1.38 (0.98–1.94)	81 (18.9)	80 (21.6)	1.77 (1.03–3.03)	59 (22.3)	106 (24.8)	0.84 (0.53–1.33)

*Adjusted for age, gender, ethnic group, and BMI