Insulin-like Growth Factor Polymorphisms and Colorectal Cancer Risk

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Abstract

Several modifiable lifestyle factors, such as physical activity, obesity, and postmenopausal hormone use, have been associated with colorectal cancer risk. It has been hypothesized that some or all of these factors may mediate their effects through alterations in insulin-like growth factor-1 (IGF-1) and its binding proteins (IGFBP). To evaluate the role of IGFs in colorectal cancer, we examined the relationship of two common genetic polymorphisms in *IGF-1* (a cytosine-adenosine dinucleotide repeat) and *IGFBP-3* (a G → C single nucleotide polymorphism) with colorectal cancer risk, as well as their potential modification by physical activity, body mass index (BMI), and postmenopausal hormone use. Subjects included 782 male and female colorectal cancer cases diagnosed between 1998 and 2002 and reported to the statewide registry in the metropolitan Seattle area, and 503 age- and sex-matched cancer-free population controls. Colorectal cancer was modestly associated with having an *IGF-1* genotype other than homozygous for 19 repeats (odds ratio, 1.3; 95% confidence interval, 1.0-1.6) and having the *GG IGFBP-3* genotype (odds ratio, 1.3; 95% confidence interval, 1.0-1.8). There was evidence that *IGF-1* genotype modified the relationship between BMI and colorectal cancer among women, such that high BMI increased risk of colorectal cancer only among those with the *19/19* genotype ($P_{interaction}$ = 0.02). *IGFBP-3* genotype was also a significant effect modifier of the relationship between risk factors and colorectal cancer: The positive association between BMI and colorectal cancer was observed only among men ($P_{interaction}$ < 0.01) and women ($P_{interaction}$ = 0.06) with the *GG* genotype; the inverse association between postmenopausal hormone use and colorectal cancer was observed only among women with the *GG* genotype (P = 0.01) and the inverse association between physical activity and colorectal cancer was observed only among men who carried the *C* allele (P < 0.01). The current study provides some support for a role of IGFs in colorectal cancer etiology, particularly in mediating the relationship of common risk factors (physical activity, BMI, and postmenopausal hormone use). (Cancer Epidemiol Biomarkers Prev 2005;14(5):1204–11)

Introduction

Several aspects of a ''Western lifestyle'' are associated with risk of colorectal cancer (1). Factors strongly related to such a lifestyle include low levels of physical activity, obesity, and the use of postmenopausal hormones (2, 3). Physical activity has been consistently associated with decreased risk of colon cancer in studies that have concentrated on occupational activity, recreational activity, and total activity (4). Obesity increases the risk of colon cancer, particularly in men (1); the risk of colon cancer in obese men may be as much as 2-fold that of leaner men (2). Finally, the use of postmenopausal hormone reduces risk of colorectal cancer in women, a 40% to 50% reduction among current users (5, 6). A recent theory proposes that the common biological denominator relating these lifestyle factors and colorectal cancer risk may involve alterations in insulin-like growth factor (IGF) physiology (3, 7).

IGF-1 is a potent mitogen and antiapoptotic agent, the action of which is partly regulated by IGF binding protein-3 (IGFBP-3), which has itself been observed to both inhibit and enhance IGF-1 bioactivity (8, 9). Disruptions in the expression of either may be related to changes in the rates of cell division and cell death, resulting in, over generations of cell divisions, the accumulation of genetic errors and the acquisition of a neoplastic phenotype (10). Physical inactivity and obesity (especially central adiposity) are associated with elevated insulin levels and insulin resistance (3, 11-13). Besides having its own growth-promoting effects, insulin enhances the growth hormone–stimulated expression of IGF-1 (14) and increases the bioavailability of IGF-1 via decreased synthesis of IGFBPs (15). In postmenopausal women, obesity is also related to increased bioavailable endogenous estrogens (16, 17), and both epidemiologic and *in vitro* studies have shown that endogenous and exogenous estrogens reduce serum IGF-1 (18-23). This estrogen-induced suppression of IGF-1 synthesis is one proposed mechanism underlying the observed inverse relationship between current postmenopausal hormone use and colorectal cancer risk among women (5, 24). Recent epidemiologic studies evaluating the relationship between circulating IGF-1 and IGFBP-3 and colorectal cancer support a role of IGFs in tumorigenesis, although the magnitude and direction of these associations have been inconsistent (25-32).

The biological interactions between these lifestyle factors and IGFs suggest several mechanisms through which these factors may influence colorectal cancer risk, although studies that define and characterize these relationships have been limited. Several of the genes involved in IGF bioactivity and signal transduction are polymorphic in the Caucasian population (33-39) and have been observed to confer functional differences in circulating IGF-1 and IGFBP-3 (39-41). Studying the role of these common variants in colorectal cancer risk and

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their interaction with environmental factors may provide insight into the etiologic pathways underlying colorectal cancer epidemiology. In a population-based case-control study, we evaluated the role of two potentially functional variants, a microsatellite polymorphism in *IGF-1* and a single nucleotide polymorphism in exon 1 in *IGFBP-3*, in colorectal cancer risk and their possible role in modifying the relationship of body mass index (BMI), physical activity, postmenopausal hormone use, and colorectal cancer risk.

Materials and Methods

Study Subjects. Subjects for the current analysis consisted of a sequential sample of cases and controls enrolled in the Seattle Colon Cancer Family Registry (C-CFR) (U01 CA74794), part of the multisite collaborative Colorectal Cancer Family Registry (C-CFR). Eligible population-based cases included all male and female residents ages 20 to 74 years diagnosed with incident invasive colon or rectal cancer [International Classification of Diseases for Oncology (ICDO) C18.0, C18.2-.9, C20.0-.9] from October 1998 to February 2002. Cases were identified through the Puget Sound Surveillance Epidemiology and End Results (SEER) registry (N01-CN-05230). Only cases resident in the greater Seattle Metropolitan counties (King, Snohomish, and Pierce counties) were included in this study. SEER registry reports include information on stage, grade, first course of treatment, and demographics. Eligible cases had no previous personal history of colorectal cancer, had an available telephone number, and were capable of completing the study interview in English. Of the 2,185 eligible case patients identified for the parent study, 131 were deceased (6%), 66 (3%) had physicians who refused contact, 22 (1%) could not be located, and 240 (11%) refused to participate resulting in a final sample size of 1,726 cases (overall response proportion of 79%).

Community controls were male and female residents in the greater Seattle metropolitan area and randomly selected from two sampling frames. Washington State driver's license files were used to identify eligible controls 20 to 64 years of age, and Centers for Medicare and Medicare Services lists were used to identify those over age 64. These files include information on name, birth date, address, and race. Phone numbers for these subjects were obtained from published directories on CD-ROM or professional tracing services. As with cases, eligibility was limited to men and women with available phone numbers, who could complete the interview in English and who had no prior colorectal cancer diagnosis. Controls were selected on a monthly basis to represent the age and sex distribution of cases enrolled in the study. Of the 1,889 potential control subjects identified for the parent study, 38 (2%) had died, 19 (1%) could not be located, and 510 (27%) refused to participate. The final study sample included 1,322 controls (overall response proportion 70%).

Interview Data and Biospecimen Collection. After consent was obtained according to a protocol approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, trained study interviewers administered the structured C-CFR interview by telephone. Interview data were collected and stored using a computer-assisted telephone interview system (Ci3, Sawtooth Software, v4.1). The Seattle C-CFR instrument included questions on family history of cancer, current and past body size, screening practices, medical history, reproductive experiences, medication use, vitamin and supplement use, alcohol intake, smoking, limited diet history, and demographics. Of particular interest to this study was history of exogenous hormone use, recent and past body size, and recent history of vigorous physical activity. At the conclusion of the telephone interview, permission for a blood specimen by venipuncture was requested from a sample of subjects and, for consenting subjects, an appointment was arranged for a trained phlebotomist to obtain 20 mL of venous blood. If a subject refused, a buccal-cell specimen (obtained using a mouthwash protocol; ref. 42) was requested.

Sample Collection and Processing. Blood samples were collected per C-CFR protocol and returned to the Fred Hutchinson Cancer Research Center Specimen Processing Lab for processing. Whole blood samples were collected in EDTA vacuum tubes to prevent coagulation and were processed within 48 hours of being drawn. White cells, red cells, and plasma were separated according to a standardized protocol. Plasma was aliquoted and stored at −70°C. White cells were stored in appropriate cell culture medium at −70°C for DNA extraction or preparation of cell lines. DNA was extracted from buffy coats or buccal cells at SPL using the PureGene DNA isolation kit (Gentra Systems, Inc., Minneapolis, MN). DNA was quantified and examined for purity by UV absorption at 260 and 280 nm.

Genotyping

IGF-1. Genotyping of the *IGF-1* microsatellite polymorphism (cytosine-adenosine, or CA, repeat) was determined by PCR amplification of the polymorphic region (40) followed by rapid fragment length detection using the ABI3100 DNA Sequencer (Applied Biosystems, Foster City, CA). PCR primers were 5′-GCTAGCCAGCTGGTGTTATT-3′ and 5′-ACCACTCTGGGAGAAGGGTA-3′; the forward primer was 5′-labeled with a fluorescent dye (FAM). The PCR reaction contained 10× AmpliTaq buffer (supplied with enzyme, Applied Biosystems), 2.0 mmol/L $MgCl_2$, 200 μmol/L deoxynucleotide triphosphate, 200 nmol/L forward primer, 200 nmol/L reverse primer, 0.5 units AmpliTaq DNA polymerase (Applied Biosystems), and 40 ng genomic DNA. Cycling was at 94°C for 5 minutes and 35 cycles of 94°C for 30 seconds, 62°C for 45 seconds, and 72°C for 1 minute, followed by 72°C for 5 minutes, using an MJ thermal cycler (MJ Research, Inc., Waltham, MA). The length of amplified fragments was determined relative to GeneScan-500 size standard, using GeneScan and Genotyper Analysis Software (Applied Biosystems). Representative homozygotes (*18/18*, *19/19*, *20/20*, and *21/21*) were sequenced to determine $(CA)_n$ repeat number from base pair length.

IGFBP-3. Genotyping of the Gly32Ala single nucleotide polymorphism in *IGFBP-3* was done by PCR-RFLP. A fragment containing the mutation was amplified using primer 5′-TTCCTGCCTGGATTCCACAGCTT-3′ and G5-GGCACTAGCGTTGACGCAGA-3′. The PCR reaction contained 10× AmpliTaq buffer (supplied with enzyme, Applied Biosystems), 2.0 mmol/L $MgCl_2$, 200 μmol/L deoxynucleotide triphosphates, 200 nmol/L forward primer, 200 nmol/L reverse primer, 5% DMSO, 0.5 units AmpliTaq DNA polymerase (Applied Biosystems), and 40 ng genomic DNA. Cycling was at 96°C for 5 minutes and 35 cycles of 96°C for 30 seconds, 60°C for 45 seconds, and 72°C for 1 minute, followed by 72°C for 5 minutes. The amplified fragment was then digested with *Ava*1 (New England BioLabs, Beverly, MA). The 40 μL reaction contained 20 μL PCR fragment, 10× NEB buffer 4 (New England Biolabs, supplied with enzyme), and 2 units of *Ava*1 enzyme. The products were separated on a 2% NuSieve agarose gel (BioWhittaker Molecular Applications, Rockland, ME) and stained with ethidium bromide; the fragments were photographed on a UV transilluminator. The fragment sizes were 187 and 263 bp for the G allele and 450 bp for the C allele. Quality control measures for all genotyping included blinded repeat genotyping of 10% of samples; concordance for QC repeats was 100%.

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Subjects for Analysis. Subjects for the current analysis included a sequential sample of male and female controls who gave a blood or buccal sample from August 1999 through December 2001. One thousand three hundred and twenty subjects were eligible for the current analysis. For three individuals (<1%), DNA quality was insufficient for genotyping. Only individuals with complete genotyping information were included in this analysis; genotyping of at least one polymorphism was missing for 20 individuals (1.5%). The final study population consisted of 782 cases (335 males, 447 females) and 503 controls (153 males, 350 females).

Variable Definitions. BMI was calculated as an individual's reported weight (in kilograms) divided by their height (in meters) squared and dichotomized based on the median BMI among controls, separately for men and women. Categories of recent vigorous physical activity (hours per month of physical activity of at least 6.0 metabolic equivalents, or METs (76), over the most recent decade of life) were based on dichotomized distributions among controls, separately for men (low = <12 h/mo; high = 12+ h/mo) and women (low = <10 h/mo; high = 10+ h/mo) or categorized as ''none'' for those who reported no vigorous activity. Postmenopausal hormone use (never, formerly, or currently) was defined as use of postmenopausal hormones containing estrogen for at least 6 months. Age at interview was categorized into four groups (20-49, 50-59, 60-69, and 70-79). Individuals were categorized as non-Hispanic White or other based on self-reported race/ethnicity. Family history of colorectal cancer was defined as having at least one first degree (parent, sibling, child) with colorectal cancer. Sigmoidoscopy screening was defined as having had a sigmoidoscopy (regardless of indication). To account for the clustering of tests that may have occurred shortly before diagnosis (cases), we categorized individuals as having never had a test, had a test <2 years before diagnosis (or reference) date, or had a test 2+ years before diagnosis date (43). Smoking status was defined as never, formerly, or currently smoking at least one cigarette a day for at least 3 months. Regular use of nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin), multivitamins, and calcium supplements was defined as at least twice a week for >1 month, and individuals were categorized as either never, former, or current users.

Cases were also categorized according to the subsite of their lesions. Cases whose tumor was in the cecum (ICDO C18.0), ascending colon (C18.2), hepatic flexure (C18.3), transverse colon (C18.4), or splenic flexure (C18.5) were classified as proximal cases. Cases whose tumor was in the descending colon (C18.6), sigmoid colon (C18.7), rectosigmoid junction (C19.9), or rectum (C19.9) were considered distal cases. There were two cases whose pathology data were not specific enough (C18.9 = colon NOS) to classify into subsite and were excluded only from subsite-specific analyses.

IGF-1 genotype was summarized two ways. First, individuals were dichotomized into the most common genotype, homozygosity for the 19-repeat allele (*19/19*) and having any other *IGF-1* genotype (other). Next, individuals were categorized into 10 genotypes based on the six most common alleles occurring in our population (out of 10 alleles, ranging from 11 to 24 CA repeat). One thousand two hundred and one of our 1,285 study participant genotypes were categorized into 1 of these 10 genotypes. *IGFBP-3* was evaluated as a codominant model, with individuals being categorized as having a *CC*, *GC*, or *GG* genotype.

Statistical Analyses. Data were analyzed using unconditional logistic regression to evaluate the association between IGF polymorphisms and risk of colorectal cancer. Multivariate-adjusted odds ratios (OR) and 95% confidence intervals (CI) were used to assess associations. Potential confounders in the genotype-disease relationship were evaluated by comparing the models with and without the potential confounder, to evaluate their effect on the OR of interest (separately for *IGF-1* and *IGFBP-3*). Only age and covariates that altered the main OR by 10% were included as confounders. Covariates evaluated as potential confounders were sex, race/ethnicity, family history of colorectal cancer, sigmoidoscopy testing, postmenopausal hormone use, BMI, vigorous physical activity, smoking status, regular NSAID use, multivitamin use, calcium supplementation, and frequency of milk consumption. Postmenopausal hormone use was the only covariate evaluated that changed the OR estimates for *IGF-1* genotype by at least 10% and was therefore included (along with age) in multivariate models. No covariates confounded the *IGFBP-3*/colorectal cancer relationship, and subsequent models for *IGFBP-3* included only age (as a categorical variable) for adjustment. The association of the *IGF* genotypes and colorectal cancer according to sex and subsite (i.e., proximal versus distal tumors) was also evaluated.

Effect modification by *IGF-1* genotype (*19/19*, $n = 513$; other, $n = 772$) and *IGFBP-3* genotype (*CC*, $n = 430$; *GC*, $n = 587$; *GG*, $n = 268$) was also assessed in the relationships of BMI, physical activity, postmenopausal hormone use, and colorectal cancer risk. In stratified analyses, the association between each lifestyle factor and colorectal cancer was evaluated using unconditional logistic regression, adjusting for standard colorectal cancer risk factors [age, race/ethnicity, family history of colorectal cancer, screening sigmoidoscopy, smoking, NSAID use, BMI, vigorous physical activity, and postmenopausal hormone use (women)]. A P value for interaction was calculated as the significance of the multiplicative interaction term of the dichotomous group (*IGF-1* genotype) variable and the risk factor variable coded as a trend variable (i.e., 0, 1, 2. . ., etc.). The interaction between *IGFBP-3* genotype and each risk factor was evaluated by the significance of the likelihood-ratio test, comparing the maximum log likelihoods of a model containing the interaction terms (genotype was coded as a categorical variable and risk factors coded as a trend variable) with a reduced model with no interaction terms.

All analyses were completed using STATA 7.0 for Windows (STATA Corporation, College Station, TX) statistical software; all significance tests were two-sided.

Results

Cases were more likely than controls to be older, to be male, to be non-Caucasian, to have a family history of colorectal cancer, and much less likely to have had a recent screening sigmoidoscopy (Table 1). Among both men and women, cases were heavier and had fewer hours per month of strenuous physical activity. Female cases were less likely than controls to be postmenopausal hormone users. Cases were more likely to be current smokers and less likely to be regular NSAID users than controls; there was little difference in multivitamin and calcium supplementation use.

Homozygosity for the 19-repeat allele was the most common *IGF-1* genotype among both cases (37.9%) and controls (43.1%), and the relative frequency of other genotypes was also similar between cases and controls; the *19/20* genotype was the second most common (27.4% among cases, 23.4% among controls), followed by the *19/21* genotype (11.2% among cases, 9.2% among controls) and the *18/19* genotype (6.4% among cases, 9.4% among controls). For *IGFBP-3*, cases were somewhat more likely to be homozygous for the G allele (22.1%) than controls (18.9%; Table 2). All alleles were in Hardy-Weinberg equilibrium among Caucasian controls.

Main Effect of Polymorphisms. Having an *IGF-1* genotype other than the most common (homozygous for the 19-repeat

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Table 1. Distribution of cases and controls on selected demographic and lifestyle characteristics

	Controls, *n* (%)	Cases, *n* (%)
Age		
20-49	73 (14.5)	97 (12.4)
50-59	134 (26.6)	195 (24.9)
60-69	152 (30.2)	291 (37.2)
70-79	144 (28.6)	199 (25.4)
Sex		
Male	153 (30.4)	335 (42.8)
Female	350 (69.6)	447 (57.2)
Race		
White	470 (93.8)	719 (92.1)
Other	31 (6.2)	62 (7.9)
Family history of colorectal cancer		
No	461 (91.7)	647 (82.7)
Yes	42 (8.3)	135 (17.3)
Sigmoidoscopy		
Never	280 (56.2)	357 (46.9)
In last 2 y	86 (17.3)	292 (38.4)
≥2 y ago	132 (26.5)	112 (14.7)
BMI (kg/m^2)		
Males		
<26.5	78 (51.0)	133 (39.7)
26.5+	75 (49.0)	202 (60.3)
Females		
<25.6	174 (50.0)	201 (45.1)
25.6+	174 (50.0)	245 (54.9)
Vigorous physical activity (h/mo)		
Males		
0	63 (41.2)	164 (49.0)
Low	46 (30.1)	101 (30.1)
High	44 (28.8)	70 (20.9)
Females		
0	139 (39.7)	221 (49.4)
Low	99 (28.3)	117 (26.2)
High	112 (32.0)	109 (24.4)
Menopausal status		
Post	295 (84.8)	388 (87.2)
Pre	53 (15.2)	57 (12.8)
Postmenopausal hormone use		
Never	116 (39.3)	179 (46.6)
Former	33 (11.2)	42 (10.9)
Current	146 (49.5)	163 (42.4)
Regular NSAID use		
Never	236 (47.2)	387 (50.0)
Former	108 (21.6)	163 (21.1)
Current	156 (31.2)	224 (28.9)
Smoking status		
Never	247 (49.2)	306 (39.1)
Former	208 (41.4)	381 (48.7)
Current	47 (9.4)	95 (12.1)
Multivitamins		
Never	131 (26.2)	230 (29.7)
Former	264 (52.8)	351 (45.3)
Current	105 (21.0)	194 (25.0)
Calcium		
Never	262 (52.6)	490 (62.9)
Former	163 (32.7)	184 (23.6)
Current	73 (14.7)	105 (13.5)

allele) was associated with a very modestly increased risk of colorectal cancer (OR, 1.3; 95% CI, 1.0-1.6; Table 2). For individual genotypes, only the *19/20* genotype (OR, 1.4; 95% CI, 1.0-1.9) and the *18/20* genotype (OR, 2.3; 95% CI, 1.0-5.6) were associated with increased risk, although there was limited power to evaluate the rarer *IGF-1* genotypes. *IGFBP-3* genotype was weakly associated with colorectal cancer risk; the *GG* genotype was associated with an OR of 1.3 (1.0-1.8) relative to the *CC* genotype. There was a suggestion of an allele-dose effect, with risk increasing with the number of G alleles (P = 0.06). Stratified analyses showed no statistically significant differences by subsite (data not shown). Analyses stratified by sex suggested that the association with *IGF-1* genotype may be limited to women ($P_{interaction}$ = 0.08); there was no evidence that the relationship of *IGFBP-3* genotype and colorectal cancer differed by sex ($P_{interaction}$ = 0.62).

Effect Modification by *IGF-1*. There was little evidence of gene-environment interactions for BMI or physical activity and colorectal cancer risk among men (Table 3). However, among women, there was significant evidence that the BMI-colorectal cancer relationship was modified by *IGF-1* genotype ($P_{interaction}$ = 0.02); the increase in risk of colorectal cancer associated with increasing BMI occurred among women only with the *19/19* genotype (OR, 2.0; 95% CI, 1.2-3.2). Slim women with other *IGF-1* genotypes were at higher risk of colorectal cancer than slim women with the *19/19* genotype, but BMI itself was unrelated to risk among women with the non-*19/19* genotypes. There was no evidence of effect modification by *IGF-1* genotype of the relationship between either physical activity or postmenopausal hormone use and colorectal cancer risk among women.

Effect Modification by *IGFBP-3*. There was evidence of effect modification by *IGFBP-3* genotype in the relationship of BMI and colorectal cancer among men ($P_{interaction}$ < 0.01), as well as among women ($P_{interaction}$ = 0.06; Table 4). The elevation in risk due to high BMI was strongest among those with the *GG* genotype: among males, the OR for high BMI relative to low BMI was 8.1 (2.5-26.5); for women, it was 2.3 (1.1-4.8; data not shown in table). Whereas there was no evidence of effect modification by *IGFBP-3* genotype of the relationship between physical activity and colorectal cancer among women, *IGFBP-3* genotype modified the relationship among men (P < 0.01), such that the reduction in risk was observed only among individuals who carried the C allele and was particularly strong among heterozygotes (OR, 0.3; 95% CI, 0.1-0.7 comparing high physical activity to none; data not shown in table). The relationship of postmenopausal hormone use and colorectal cancer was also modified by *IGFBP-3* genotype ($P_{interaction}$ = 0.01): the inverse relationship of postmenopausal hormone and colorectal cancer was observed only among women with the *GG* genotype (OR, 0.3; 95% CI, 0.1-0.6 comparing never users to current users), and postmenopausal hormone use was unrelated to risk among other genotypes.

Discussion

In this population-based analysis of male and female colorectal cancer cases and community controls, we observed that common variants in the *IGF-1* and *IGFBP-3* genes were modestly related to risk of colorectal cancer. There was a weak, statistically significant association between the *IGF-1* genotype and colorectal cancer, with individuals with a genotype other than the *19/19* genotype having a 30% increased risk of colorectal cancer relative to those with the *19/19* genotype. There was a similar relationship between the *IGFBP-3* genotype and colorectal cancer for those with *GG* versus *CC* genotype. Additionally, the polymorphisms in both *IGF-1* and *IGFBP-3* modified the relationship of BMI, physical activity, and postmenopausal hormone use with colorectal cancer risk. The association of high BMI with colorectal cancer risk was observed only among women with the *19/19 IGF-1* genotype and was strongest among both men and women with the *IGFBP-3 GG* genotype. Among men, the reduction in colorectal cancer risk associated with vigorous physical activity seemed to be restricted to carriers of the *C IGFBP-3* allele. The association of current postmenopausal hormone use with reduced risk of colorectal cancer among women was observed only among those with the *GG* genotype. Our confidence in these results is enhanced by the population-based design of the study, the standardized collection of lifestyle factors, the size of the population, and the excellent reproducibility of our lab results.

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Table 2. IGF-1 and IGFBP-3 genotype and colorectal cancer risk

	Controls *n* (%)	All cases *n* (%)	Male cases *n* (%)	Female cases *n* (%)	All cases OR (95% CI)	Male cases OR (95% CI)	Female cases OR (95% CI)
IGF-1 genotype*,†							
19/19	217 (43.1)	296 (37.9)	138 (41.2)	158 (35.3)	1.0	1.0	1.0
Other	286 (56.9)	486 (62.1)	197 (58.8)	289 (64.7)	1.3 (1.0-1.6)‡	1.0 (0.7-1.4)	1.5 (1.1-2.0)‡
$P_{interaction}$						0.08	
IGF-1 genotype*,†							
19/19	217 (45.3)	296 (41.0)	138 (44.8)	158 (38.2)	1.0	1.0	1.0
18/18	3 (0.6)	5 (0.7)	2 (0.6)	3 (0.7)	1.3 (0.3-5.7)	0.7 (0.1-8.3)	1.6 (0.3-10.0)
18/19	45 (9.4)	46 (6.4)	15 (4.9)	31 (7.5)	0.8 (0.5-1.2)	0.5 (0.2-1.0)	1.0 (0.6-1.7)
18/20	7 (1.5)	22 (3.0)	8 (2.6)	14 (3.4)	2.4 (1.0-5.7)‡	3.1 (0.4-25.9)	2.2 (0.8-6.0)
18/21	6 (1.3)	10 (1.4)	3 (1.0)	7 (1.7)	1.4 (0.5-3.9)	1.3 (0.1-12.4)	1.4 (0.4-4.7)
19/20	112 (23.4)	198 (27.4)	79 (25.6)	119 (28.7)	1.4 (1.0-1.9)‡	1.1 (0.6-1.8)	1.6 (1.1-2.4)‡
19/21	44 (9.2)	81 (11.2)	38 (12.3)	43 (10.4)	1.3 (0.9-2.0)	1.1 (0.6-2.1)	1.5 (0.9-2.5)
20/20	27 (5.6)	30 (4.2)	13 (4.2)	17 (4.1)	0.8 (0.4-1.3)	0.5 (0.2-1.1)	1.1 (0.5-2.3)
20/21	14 (2.9)	28 (3.9)	10 (3.2)	18 (4.3)	1.7 (0.8-3.3)	2.6 (0.5-12.3)	1.5 (0.7-3.3)
21/21	4 (0.8)	6 (0.8)	2 (0.6)	4 (1.0)	1.0 (0.3-3.8)	0.5 (0.1-3.6)	1.7 (0.3-9.4)
$P_{interaction}$						0.70	
IGFBP-3 genotype§							
CC	182 (36.2)	248 (31.7)	102 (30.4)	146 (32.7)	1.0	1.0	1.0
GC	226 (44.9)	361 (46.2)	157 (46.9)	204 (45.6)	1.2 (0.9-1.5)	1.0 (0.6-1.6)	1.2 (0.9-1.7)
GG	95 (18.9)	173 (22.1)	76 (22.7)	97 (21.7)	1.3 (1.0-1.8)‡	1.5 (0.8-2.6)	1.3 (0.9-1.9)
P_{trend}					0.06	0.23	0.18
$P_{interaction}$						0.62	

*Adjusted for age and postmenopausal hormone use (women).
†n's and %'s between collapsed (19/19 and other) and detailed (19/19, 18/18, etc.) parameterizations of IGF-1 genotype will differ, because less common alleles were included in collapsed parameterization, but excluded in detailed.
‡$P < 0.05$.
§Adjusted for age.

Several recent epidemiologic studies suggest that individual variation in IGF concentrations may be related to risk of colorectal cancer. Analyses of two prospective cohort studies (30, 31) and one case-control study (32) have observed that elevated levels of IGFBP-3 are associated with a significantly increased risk of colorectal cancer, compared with those with lower levels. When adjusted for levels of IGF-1, the association of IGFBP-3 and colorectal cancer was no longer statistically significant, suggesting that the total amount of IGFBP-3 in circulation is the relevant exposure. Data from prospective (25, 26), cross-sectional (27), and case-control (28) studies have suggested that elevated levels IGF-1 and, conversely, low levels of IGFBP-3 are independently associated with an elevated risk of colorectal cancer in both men and women. These results were statistically significant only after adjustment for each other, suggesting that it is the ratio of IGF-1:IGFBP-3 that is relevant in relation to colorectal cancer risk.

Table 3. Association of BMI, physical activity, and postmenopausal hormone use and colorectal cancer risk stratified by IGF-1 genotype

	n Cases (%)		19/19	Other
	19/19	Other	OR (95% CI)	OR (95% CI)
BMI				
Males				
<26.5	54 (39.1)	79 (40.1)	1.0	1.0 (0.5-1.9)
26.5+	84 (60.9)	118 (59.9)	1.9 (1.0-3.7)*	1.6 (0.9-2.8)
$P_{interaction}$			0.63	
Females				
<25.6	65 (41.1)	136 (47.2)	1.0	2.3 (1.5-3.6)*
25.6+	93 (58.9)	152 (52.8)	2.0 (1.2-3.2)*	2.1 (1.4-3.3)*
$P_{interaction}$			0.02	
Vigorous physical activity (h/mo)				
Males				
0	65 (47.1)	99 (50.3)	1.0	1.1 (0.6-2.1)
Low	40 (29.0)	61 (31.0)	1.1 (0.5 2.3)	0.9 (0.4 1.9)
High	33 (23.9)	37 (18.8)	0.8 (0.4 1.8)	0.6 (0.3-1.3)
$P_{interaction}$			0.46	
Females				
0	69 (43.7)	152 (52.6)	1.0	1.8 (1.1-2.9)*
Low	46 (29.1)	71 (24.6)	1.1 (0.6-2.0)	1.2 (0.7-2.1)
High	43 (27.2)	66 (22.8)	0.7 (0.4-1.3)	1.2 (0.7-2.1)
$P_{interaction}$			0.80	
Postmenopausal hormone use†				
Never	65 (47.5)	114 (46.2)	1.0	1.6 (0.9-2.6)
Former	16 (11.7)	26 (10.5)	0.8 (0.3-1.7)	1.9 (0.8-4.2)
Current	56 (40.9)	107 (43.3)	0.9 (0.5-1.5)	1.2 (0.7-2.0)
$P_{interaction}$			0.78	

NOTE: Adjusted for age, race/ethnicity, any sigmoidoscopy, family history of colorectal cancer, smoking status, NSAID use, physical activity, BMI, and postmenopausal hormone use (women).
*$P < 0.05$.
†Among postmenopausal women.

There are several lines of evidence supporting the hypothesis that IGFs are related to colorectal cancer. The mitogenicity of IGF-1 has been well demonstrated. Normal colorectal epithelial cells and cancer cells express IGF-1 receptors (44, 45), which stimulate mitogenesis when activated by IGF-1 *in vitro* (46, 47). IGF-1 exerts its mitogenic effects by increasing DNA synthesis and by stimulating the expression of cyclin D1, an essential cell-cycle protein (48). IGF-1 also inhibits apoptosis by altering expression of Bcl and Bax proteins and blocking initiation of the apoptotic pathway (49-51). IGF-1 action is regulated by interaction with the IGFBPs, mainly IGFBP-3. The role of IGFBP-3 has an inhibitor of IGF-1 activity and as an independent apoptotic agent is well established (8, 9, 52, 53), and IGFBP-3 has been recently recognized to exhibit a number of growth-promoting effects, including the potentiation of IGF-1–induced cell growth (53) and mediation of the growth-stimulatory effects of transforming growth factor-β (54, 55). The consequences of perturbing this metabolic pathway may result in changes in cell proliferation, differentiation, and apoptosis (10).

There are very limited data that have evaluated the association between the IGF variants we studied and colorectal cancer risk. In previous studies, the *IGF-1 CA* microsatellite repeat polymorphism was found to be unrelated to risk of colon or rectal cancer (56) or adenoma (57) and has been inconsistently related to breast cancer risk (58-60), bone density

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Table 4. Association of BMI, physical activity, and postmenopausal hormone use and colorectal cancer risk stratified by IGFBP-3 genotype

	n Cases (%)			CC	CG	GG
	CC	CC	GG	OR (95% CI)	OR (95% CI)	OR (95% CI)
BMI						
Males						
<26.5	41 (40.2)	62 (39.5)	30 (39.5)	1.0	0.6 (0.3-1.2)	0.5 (0.2-1.1)
26.5+	61 (59.8)	95 (60.5)	46 (60.5)	0.8 (0.4-1.6)	1.0 (0.5-2.0)	3.3 (1.1-9.4)*
$P_{interaction}$					<0.01	
Females						
<25.6	70 (48.0)	86 (42.2)	45 (46.9)	1.0	0.9 (0.5-1.5)	0.8 (0.4-1.4)
25.6+	76 (52.1)	118 (57.8)	51 (53.1)	0.9 (0.5-1.4)	1.2 (0.7-1.9)	1.8 (1.0-3.5)*
$P_{interaction}$					0.06	
Vigorous physical activity (h/mo)						
Males						
0	44 (43.1)	86 (54.8)	34 (44.7)	1.0	1.2 (0.5-1.5)	0.7 (0.3-1.6)
Low	35 (34.3)	43 (27.4)	23 (30.3)	0.9 (0.4-2.1)	0.7 (0.3-1.7)	1.6 (0.5-4.7)
High	23 (22.6)	28 (17.8)	19 (25.0)	0.6 (0.2-1.7)	0.4 (0.2-1.0)*	2.5 (0.7-9.3)
$P_{interaction}$					<0.01	
Females						
0	70 (48.0)	106 (52.0)	45 (46.4)	1.0	1.2 (0.7-2.1)	1.2 (0.6-2.3)
Low	39 (26.7)	46 (22.6)	32 (33.0)	0.9 (0.5-1.7)	0.8 (0.4-1.4)	1.4 (0.7-2.8)
High	37 (25.3)	52 (25.5)	20 (20.6)	0.7 (0.4-1.3)	0.9 (0.5-1.6)	0.7 (0.3-1.5)
$P_{interaction}$					0.98	
Postmenopausal hormone use†						
Never	58 (46.0)	77 (42.8)	44 (56.4)	1.0	1.1 (0.6-1.9)	2.1 (1.0-4.4)*
Former	12 (9.5)	18 (10.0)	12 (15.4)	0.9 (0.3-2.4)	1.4 (0.6-3.5)	1.0 (0.4-2.6)
Current	56 (44.4)	85 (47.2)	22 (28.2)	1.1 (0.6-1.9)	1.1 (0.6-2.0)	0.6 (0.3-1.2)
$P_{interaction}$					0.01	

NOTE: Adjusted for age, race/ethnicity, any sigmoidoscopy, family history of colorectal cancer, smoking status, NSAID use, physical activity, BMI, and postmenopausal hormone use.

*$P < 0.05$.

†Among postmenopausal women.

(61-63), body composition (64), non-insulin dependent diabetes mellitus (34, 65, 66), and birth weight (67). There are no previously published reports evaluating the relationship of the *IGFBP-3* G → C single nucleotide polymorphism in exon 1 to colorectal cancer risk, although another variant in the *IGFBP-3* gene (a single nucleotide polymorphism in the promoter region that has been observed to be related to circulating IGFBP-3 levels; refs. 39, 41, 68) was evaluated in relation to both colorectal (56) and breast cancer risk (41) and found to have no independent association. Other studies have reported significant main associations with common variants in other genes involved in IGF physiology, such as *GH1* (69), and *IRS1* and *IRS2* (56), with colorectal cancer risk.

Studies relating the *IGF-1* CA repeat polymorphism to serum or plasma circulating IGF-1 have been inconsistent, and its functional relevance is unclear. Although one study found that homozygosity for the most common allele was associated with statistically significantly lower serum IGF-1 levels than all other genotypes (40), subsequent explorations (57, 70) have failed to find such an association. In a subgroup analysis of this population, we observed significantly elevated levels of circulating IGFBP-3 (although no relationship with circulating IGF-1) among individuals who had a genotype other than the most common (*19/19*), particularly among those with the *19/20* or the *19/21* genotypes.[4] This observation is provocative in light of the results of the current analysis where having an *IGF-1* genotype other than *19/19* was associated with an increased risk of colorectal cancer, particularly among women.

The single nucleotide polymorphism in the *IGFBP-3* gene evaluated in our study is a common G to C transversion in exon 1 at nucleotide 2132 that leads to a Gly → Ala substitution at codon 32 (36), a region that has been shown, in fragment analyses, to contain a high-affinity binding region for IGF-1 (71). Mutational analyses of the IGFBP-3 protein have suggested that substitution of amino acids at key points within the binding pocket can substantially alter affinity (72, 73). Because the half-life of IGFBP-3 in circulation is substantially shorter than that of bound (to IGF-1) IGFBP-3 (8), a polymorphism that affects IGF-1 binding may affect the rate of protein degradation and, hence, the concentration of IGFBP-3 in circulation. Functional assays will be required to definitively characterize and assess the effect of this sequence substitution, but, in our population, we observed a relationship between this polymorphism and circulating IGFBP-3 levels: having the *GG* genotype was associated with significantly elevated circulating IGFBP-3 levels, relative to the *CC* genotype (unpublished data). In our current analysis of colorectal cancer, the *GG* genotype was also related to increased risk of colorectal cancer, parallel to our results for the *IGF-1* polymorphism.

We observed significant interaction between *IGF* genes and lifestyle factors. The relationship between BMI and colorectal cancer risk among women was modified by *IGF-1* genotype, providing evidence that alterations in IGF physiology may be involved in the relationship between BMI and colorectal cancer risk. These results also suggest that heterogeneity in *IGF-1* genotype may be partially responsible for the consistently noted sex differences in the association between obesity and colorectal cancer risk. The presence of statistically significant modification by the *IGFBP-3* genotype further supports a role of IGF-related molecules in mediating the relationship of BMI and postmenopausal hormone use with risk of colorectal cancer. There have been no previous published studies evaluating the interaction between genetic polymorphisms in *IGF* genes and lifestyle risk factors with colorectal cancer. However, in the Physicians' Health Study, investigators found that the inverse association between calcium from dietary milk and risk was strongest among individuals with a high IGF-1:IGFBP-3 ratio (74), supporting the hypothesis the IGFs may mediate the effects of some environmental exposures.

[4] Unpublished data.

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Some limitations should be considered when interpreting results. All covariate data were self-reported and exposure measurement error may have biased our estimates if the epidemiologic data collected were not accurate assessments of an individual's true exposure history. Selection may have biased the main associations of the polymorphisms of interest with colorectal cancer risk if the genotypes of individuals who donated biospecimens were different from those who did not, conditional on disease status. However, selection bias does not affect estimates of interaction ORs, even if participation in our study was jointly affected by exposure, genotype, and disease status (75).

There is plausible biology underlying the hypothesis that IGF physiology is associated with colorectal cancer risk. This hypothesis is supported, and indeed strengthened, by the observed associations between genetic variants in *IGF* genes and colorectal cancer, as well as by the interaction of these variants with BMI, physical activity, and postmenopausal hormone use, important factors in both circulating IGFs and colorectal cancer risk.

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