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Body size, IGF and growth hormone polymorphisms, and colorectal adenomas and hyperplastic polyps

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Abstract

Objective—We examined the risk of colorectal polyps in relation to body size factors and candidate polymorphisms in selected genes of insulin-like growth factor (*IGF1*) (rs5742612), IGF1 receptor (*IGF1R*) (rs2229765), IGF binding protein 3 (*IGFBP3*) (rs2854746) and growth hormone (*GHI*) (rs2665802).

Design—Cases with colorectal adenomas (n=519), hyperplastic polyps (n=691), or both lesions (n=227), and controls (n=772), aged 20–74 years, were recruited from patients who underwent colonoscopy between December 2004 – September 2007 at a large integrated-health plan in Washington state. Subjects participated in a 45-minute telephone interview to ascertain body size and physical activity, and provided a buccal DNA sample for genetic analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable polytomous regression.

Results—Compared to those of normal weight, higher body mass index (BMI) was associated with elevated risk of colorectal adenomas (OR=1.7, 95% CI 1.2–2.3 BMI≥30 kg/m², p-trend=0.002) and both lesions (OR=2.2, 95% CI 1.4–3.2 BMI≥30 kg/m², p-trend=0.003), but there was no relationship with hyperplastic polyps. Obesity at age 18 and a weight gain of ≥21 kg since age 18 were also significantly associated with an increased risk of colorectal adenomas and both lesions, but not hyperplastic polyps. There was a reduced risk of colorectal adenomas (OR=0.6, 95% CI 0.4–0.9) and hyperplastic polyps (OR=0.7, 95% CI 0.5–0.9) associated with the homozygous variant genotype for *GHI*. Few meaningful results were evident for the other polymorphisms.

Conclusions—There is an increased risk of colorectal adenomas and presence of both adenomas and hyperplastic polyps in relation to increasing body size. Some genetic variation in *GHI* might contribute to a reduced risk of colorectal adenomas and hyperplastic polyps.

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Keywords

hyperplastic polyps; colorectal adenomas; insulin-like growth factor (*IGF*); growth hormone (*GHI*); body mass index

INTRODUCTION

Colorectal adenomas are considered to be the precursor lesions to colorectal cancer, but there is some evidence that hyperplastic polyps might also be relevant to the cancer etiology.¹ Large body size and low physical activity are strongly and consistently associated with increased colorectal cancer risk, particularly among men.² Increasing body mass index (BMI) is also associated with increasing risk of colorectal adenomas,^{3–6} but the magnitude appears to be weaker with hyperplastic polyps.⁴ Further, increasing physical activity is associated with a decreased risk of colorectal adenomas.⁷ Few studies have thoroughly evaluated these risk factors in relation to patients with hyperplastic polyps or those with mixed lesions.

The biologic pathway for the influence of body size and BMI on colorectal cancer risk is not well-known, but research evidences suggests that BMI influences hormones in the IGF/GH axis. Higher body mass index increases IGF levels.⁸ Further, some evidence suggests that higher IGF1 serum concentrations or the ratio to levels of IGF binding protein-3 (IGBP3) are related to an increased risk of colorectal neoplasia.⁹ In a recent meta-analysis, increasing IGF1 levels were associated with an increased risk of colorectal cancer.¹⁰ In conditions with increased secretion of GH, such as acromegaly, studies have demonstrated an increased risk of colorectal cancer and hyperplastic polyps.^{11–13} Thus, it is reasonable to consider that polymorphisms which may affect these hormonal concentrations could also be associated with precursor lesions. Two studies study has demonstrated that a genetic polymorphism in *GHI* is associated with a decreased colorectal cancer risk.^{14,15}

We examined the association between colorectal polyp risk with body size factors, including body mass index (BMI) and physical activity, and candidate genetic polymorphisms in insulin-like growth factor (*IGF1*), IGF1 receptor (*IGF1R*), IGF binding protein 3 (*IGFBP3*), and growth hormone (*GHI*). We selected these SNPs based on prior literature which suggested that a potential role in colorectal neoplasia,^{14,16} or through their effect on IGF1 levels^{17,18}.

MATERIALS AND METHODS

Study Participants

Study participants were enrollees of Group Health, a large integrated-health plan in Washington state, aged 20–74 years who underwent colonoscopy for any indication, between December 2004 and September 2007. This exam was considered their index colonoscopy. Eligible cases were patients diagnosed with adenomatous and/or hyperplastic polyps of the colon and/or rectum at this examination. Control subjects had normal findings at their index exam (i.e., no biopsies were performed nor was colorectal disease detected).

Participants were ineligible for study if, based on review of electronic medical records, they had a colonoscopy within 12 months of their index exam; they were enrolled in Group Health for fewer than 3 years; or if they had a prior diagnosis of colorectal cancer, inflammatory bowel disease, familial adenomatous polyposis, or Lynch Syndrome. Participants were further excluded if their index examination was incomplete based on one or more of the following findings: the cecum was not visualized at endoscopy; surgical

excision of lesions found at index examination was recommended; and/or bowel preparation was considered inadequate.

Case subjects were classified on the basis of type and location of polyps found at colonoscopy. For this evaluation, cases were categorized in mutually exclusive categories as: 1) colorectal adenomas (ICD9 211.3); 2) hyperplastic polyps (ICD9 211.4); or 3) both lesions, the presence of both a colorectal adenoma and hyperplastic polyp at index exam (ICD9 211.3 and 211.4).¹⁹ Colorectal adenoma cases were classified according to early and advanced lesions after pathological review. Eligible controls were selected randomly within five-year age categories and calendar year of colonoscopy. Study procedures were approved by the Institutional Review Boards of Group Health and the Fred Hutchinson Cancer Research Center.

Data Collection

Potential study participants were sent an introductory letter for the study about 1–3 months after their index colonoscopy. A study interviewer telephoned within one week of receipt of the letter to discuss the research study and arrange a time for the study interview. The majority of participants were interviewed within 3–4 months of the colonoscopy.

A reference date was established as one year prior to the index colonoscopy date. All study subjects answered questions in regard to exposures, which occurred prior to the reference date. Participants completed a 45-minute telephone interview, using a computer-assisted telephone interview (CATI). This standardized interview covered the following information: patient demographics, current weight and height, weight and height at age 18, medical history, smoking status, lifetime alcohol consumption, first-degree family history of colorectal cancer, previous endoscopy screening, and nonsteroidal anti-inflammatory drug (NSAID) use, and among women, reproductive history, menopausal status, and hormone use. Physical activity was ascertained for moderate or vigorous physical activity, number of days per week, and number of minutes per day.

After the completion of the interview, participants provided consent to review medical records and diagnostic materials. Further, participants were asked to provide a buccal sample for DNA testing. Those who agreed to participate were mailed a buccal cell mouthwash kit, which included detailed instructions for obtaining the buccal sample, based on the protocol by Lum *et al.*²⁰

Eligible participants included 711 with adenomas, 894 with hyperplastic polyps, 310 with both lesions, and 1030 controls. Participation rates in the telephone interview were between 73–77%. Among those interviewed, buccal samples were obtained from approximately 76% of cases and 90% of control participants.

Genotyping

We selected candidate polymorphisms in insulin-like growth factor (*IGF1*) (*IGF1*) (rs5742612: –704T>C), IGF1 receptor (*IGF1R*) (rs2229765: Ex16 –58G>A), IGF binding protein 3 (*IGFBP3*) (rs2854746; Ex1+227 C>G and growth hormone (*GHI*) (rs2665802; T1663A in intron 4). Because our population was primarily Caucasian (90%), we restricted single nucleotide polymorphisms to those that were observed in Caucasian populations with a minor allele frequency of at least 5%.

Genomic DNA was extracted from buccal samples using Qiagen's QIAmp DNA extraction kit (Qiagen, Valencia, CA) and quantified by Picogreen (Invitrogen, Carlsbad, CA). DNA samples were genotyped using ABI pre-developed Taqman Allelic Discrimination Assays (Applied Biosystems, Foster City, CA). Briefly, PCR was performed in 384 well plates with

10ng DNA, 2.5 ul 2X TaqMan Master Mix (Applied Biosystems), 0.25ul 20x assay mix in a total volume of 5ul. Cycling conditions were: 50°C for 2 min, 95°C for 10 min, 40 cycles of 92°C for 15 sec, 60°C for 1min. Plates were read on an ABI 7900HT sequence detection system using SDS 2.3 software. Each plate included positive controls of known genotype obtained from the Coriell Biorepository and negative controls with no DNA added. Assay accuracy was verified by comparing genotypes generated for a panel of Coriell DNA samples to publicly available genotype data for these samples from HapMap (<http://www.hapmap.org/>) and dbSNP (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). For polymorphisms where Coriell sample genotype data were unavailable, assay accuracy was confirmed by genotyping samples by RFLP or sequencing. In addition, 3.5% of samples which were included as duplicates in the study gave 100% concordant genotypes. All SNPs were in Hardy-Weinberg equilibrium in Caucasian controls.

Allele designations used in this manuscript are consistent with the reference allele reported in dbSNP. Of note, the allele designations for rs2665802 in *GHI* used here, with the A allele on the forward strand being the more common allele, are opposite to the allele designations reported in LeMarchand et al.¹⁴ Thus, the homozygous variant genotype, which we describe as the TT genotype, is equivalent to the AA genotype reported in that publication.

Statistical Analysis

We performed multivariable polytomous regression analysis to estimate risk of colorectal adenomas, hyperplastic polyps, and mixed lesions relative to controls utilizing SAS version 9.1 (SAS Institute, Inc, Carey, NC).²¹ BMI was categorized as: <18.5 underweight, 18.5–24.9 kg/m² normal weight, 25–29.9 kg/m² overweight, and ≥30 kg/m² obese.²² Weight gain was calculated as the difference between current weight minus weight at age 18; when this number was negative, these subjects were classified as “lost weight”. The total number of minutes of physical activity were summed and categorized based on the quartiles of minutes within the control group.

Statistical models assessing epidemiologic risk factors were adjusted for the following potential confounding factors: age, sex, race, education, smoking history, alcohol consumption, NSAID use, a first-degree family history of colorectal cancer, and additionally by menopausal status and hormone therapy use in women. BMI and physical activity models were mutually adjusted for each other. Statistical models assessing the genetic polymorphisms were adjusted for sex, age, and race. We also evaluated whether the results differed for men and women. Tests of trend were evaluated by entering an ordinal term of the categorical variable into the regression model. We evaluated the differences in risk stratified by gender and by adenoma lesion type (early and advanced). The results were similar between groups, so we have presented the combined results.

Tests for interaction were performed by including the cross-product term between the gene (*GHI*) and the dichotomous effect modifier (i.e., current BMI, BMI at age 18, and weight gain), adjusting for age, sex, and race.

RESULTS

The final sample for risk factor analysis included 772 controls, 519 with adenomas, 691 with hyperplastic polyps and 227 with both lesions. Participants with available genetic data included 592 controls, 400 with adenomas, 520 with hyperplastic polyps, and 172 with both lesions.

The three case groups and controls were similar in terms of race, education, alcohol consumption, and menopausal status among women (Table 1). Current or former smokers

were more common in the case groups than among controls. More controls were women compared to the case groups.

Risk of colorectal adenomas or both types of lesions was increased in subjects with high current BMI (Table 2). A current BMI ≥ 30 kg/m² was associated with a 1.65-fold increase in risk of adenomas (95% CI 1.22–2.25, p-trend 0.002) and a 2.15-fold increase in risk of both lesions (95% CI 1.43–3.22, p-trend 0.0003) compared those of normal weight. Being obese (BMI ≥ 30 kg/m²) at age 18 was also significantly associated with 4-fold and 3-fold increased risk of adenoma or both lesions, respectively. Further, a weight gain of an additional 21 kg since age 18 was also associated with increased risk of colorectal adenomas and both lesions. There was a suggestion a reduction in risk of adenomas related to any physical activity, but there were no associations detected in relation to physical activity and any of the other lesions.

In the candidate polymorphism analysis, we observed a 43% reduction in risk of hyperplastic polyps associated with the G allele compared to homozygous AA for *IGF-1* (Table 3), but no association with either colorectal adenomas or both lesions. The TT genotype for the candidate SNP in *GHI* was associated with a decrease in risk of colorectal adenomas and hyperplastic polyps, but not with both lesions. Candidate SNPs in *IGF1* and *IGFBP3* were unrelated to risk of any colorectal lesions (Table 3).

In a stratified analysis by men and women, the risks did not vary (data not shown). Both men and women showed elevated risks of colorectal adenomas and both type lesions associated with increasing BMI. Further, tests for interaction between *GHI* and current BMI, BMI at age 18, and weight gain did not reveal any differences between strata. There were similar increased associations with advanced adenomas as with all adenomas combined (data not shown).

DISCUSSION

Our results suggest that body size factors associated with colorectal adenomas are also associated with an increased risk of both lesion types or the development of an adenoma in the presence of a hyperplastic polyp. Genetic variation in *GHI* might contribute to a reduced risk of colorectal adenomas and hyperplastic polyps.

Our results confirm prior research observations of obesity and adult weight gain as independently associated with incident colorectal adenomas,^{3,5,6} but not with hyperplastic polyps.⁴ In stratified analyses, we detected an increased risk of colorectal adenomas and both lesions in men as well as women. Morimoto et al. observed an increased risk of hyperplastic polyps, adenomatous polyps and both types of polyps associated with increasing BMI among men, but not among women.¹⁹ The relationship between BMI and colorectal cancer has also not been as strong by gender. A recent meta-analysis of obesity and colorectal cancer has summarized this association as 1.41 in men (95% CI 1.30–1.54) and 1.08 in women (95% CI 0.98–1.18).²³ These findings are clinically important, as increasing body size has also been associated with growth of adenomas²⁴ and recurrence of colorectal adenomas.²⁵

There is consistent evidence that weight gain in adulthood has been associated with colorectal adenomas.^{5,6} Our findings confirm that obesity at an earlier age and weight change of 21 kg or more since age 18 increases the risk of colorectal adenomas and both lesions, but not hyperplastic polyps.

We did not observe any association for any of the polyp types and physical activity. Increasing physical activity has been associated with a reduction of sporadic colorectal

adenomas,⁷ but not with hyperplastic polyps.⁴ It has long been hypothesized that energy balance, physical activity, and obesity act cohesively to modify polyp formation.²⁶ In our analysis BMI and changes in weight were more important risk factors than other measures of energy balance (i.e., physical activity).

We observed a reduction in risk of colorectal adenomas and hyperplastic polyps associated with the TT genotype of *GH1*. Our results with *GH1* are supported by two previous reports^{14 15}. Le Marchand et al. initially suggested a reduction in risk of colorectal cancer with the homozygous variant genotype¹⁴, and results from Gao and colleagues also report a reduced risk of colorectal cancer associated with this same *GH1* genetic variant¹⁵. It has been reported that growth hormone tends to be upregulated in colorectal adenomas and adenocarcinoma, but less so in normal tissue or hyperplastic polyps.²⁷ We did not detect a significant reduction in participants with both lesion types, but there was a suggestion of a reduced risk. We detected no significant interactions between our strongest genetic polymorphism in *GH1* and measures of body weight (i.e., current BMI, BMI at age 18, and weight gain).

The association with the candidate SNP in *IGF1* is a new finding. Prior reports have focused on the 19-repeat allele in *IGF1*.¹⁶ Our analysis selected a different SNP in the *IGF1* gene which indicated that those who carry a single copy of A allele are at reduced risk for colorectal adenomas and both lesions. Further research should confirm these initial findings.

We did not detect any association between the candidate SNPs for *IGFBP3* or *IGF1R*. Other studies have also not detected an association between the SNP in *IGFBP3* and colorectal cancer.^{28–30} No studies have specifically evaluated polymorphisms in *IGF1R* and colorectal polyps. High levels of *IGF1R* expression have been demonstrated in colorectal cancer tissue³¹ and have been associated with increased free IGF-1 levels.^{17,18} Because we did not have complete coverage of the variation of this gene, further studies should continue to evaluate more comprehensively variation in this gene.

Those with both lesions are inherently different from those with only adenomas or hyperplastic polyps because these subjects have at least two lesions, whereas the exclusive lesion type might only have one lesion detected on colonoscopy. When we evaluated our results based on the number of lesions (1 vs. >1), we found no meaningful differences between the results (data not shown).

This is among the largest study of these three types of colorectal lesions, and we collected complete epidemiologic and histopathologic data. Similar to the population within the state, there is little racial diversity among this population, and further investigations should demonstrate whether similar patterns are seen among different racial and ethnic populations. Our analysis is not without its limitations. The genetic analysis presented is limited by both complete gene coverage and statistical power. Better understanding of the genetic variation is warranted.

These findings suggest that risk factors for colorectal adenomas were similar to those subjects who had both colorectal adenomas and hyperplastic polyps. This suggests that subjects with both lesions have similar risk factors to colorectal adenomas. Further, the development of hyperplastic polyps involves different risk factors than those lesions which contain colorectal adenoma.

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TABLE 1

Selected characteristics of population-based controls and cases with adenomas, hyperplastic polyps or both types of lesions, both men and women, Group Health, Seattle, Washington.

Characteristics	TOTAL			
	Controls (n=772)	Adenomas (n=519)	Hyperplastic (n=691)	Both (n=227)
	N (%)	N (%)	N (%)	N%
Age at colonoscopy (years)				
<50	50 (6%)	29 (6%)	45 (7%)	12 (5%)
50–54	146 (19%)	80 (15%)	146 (21%)	37 (16%)
55–59	172 (22%)	123 (24%)	183 (26%)	52 (23%)
60–64	160 (21%)	109 (21%)	149 (22%)	54 (24%)
65–69	136 (18%)	96 (18%)	84 (12%)	34 (15%)
70+	108 (14%)	82 (16%)	84 (12%)	38 (17%)
Sex				
Men	309 (40.0)	259 (49.9)	304 (44.0)	133 (58.6)
Women	463 (60.0)	260 (50.1)	387 (56.0)	94 (42.4)
Race				
Caucasian	661 (86%)	431 (83%)	592 (86%)	193 (85%)
Other	111 (14%)	88 (17%)	99 (14%)	34 (15%)
Education (years)				
< 12	10 (1%)	9 (2%)	5 (1%)	1 (<1%)
12	84 (11%)	46 (9%)	47 (7%)	21 (9%)
13–15	214 (28%)	147 (28%)	222 (32%)	86 (38%)
≥16	464 (60%)	317 (61%)	416 (60%)	116 (52%)
Family history of colorectal cancer				
No	642 (83%)	434 (84%)	542 (78%)	185 (81%)
Yes	130 (17%)	85 (16%)	149 (22%)	42 (19%)
Smoking status				
Never	459 (60%)	277 (53%)	353 (51%)	105 (46%)
Current	280 (36%)	211 (41%)	274 (40%)	90 (40%)
Former	32 (4%)	31 (6%)	64 (9%)	32 (14%)
Alcohol consumption (drinks/week)				
<7	374 (49%)	247 (48%)	332 (49%)	97 (44%)
≥7	395 (51%)	268 (52%)	352 (51%)	125 (56%)
Menopausal status [‡]				
Premenopausal	68 (15%)	33 (13%)	67 (17%)	16 (17%)
Postmenopausal	395 (85%)	226 (87%)	320 (83%)	78 (83%)
Hormone therapy use [‡]				
Never	214 (46%)	117 (45%)	193 (50%)	47 (50%)
Current	68 (15%)	27 (10%)	55 (14%)	10 (11%)
Former	179 (39%)	116 (45%)	138 (36%)	37 (39%)

* Cells might not add to the total due to missing data

[‡] Among women only.

Odds ratios and 95% confidence intervals between body weight and physical activity on colorectal adenomas, hyperplastic polyps, and both lesions.

TABLE 2

Characteristic	Controls		Adenomas		Hyperplastic Polyps		Both	
	N (%)	N (%)	N (%)	OR (95% CI)*	N (%)	OR (95% CI)*	N (%)	OR (95% CI)*
Current BMI (kg/m ²) [‡]								
18.5–24.9	319 (41%)	170 (33%)	1.00 (Referent)		277 (40%)	1.00 (Referent)	68 (30%)	1.00 (Referent)
25–29.9	293 (38%)	202 (39%)	1.21 (0.92–1.58)		263 (38%)	1.02 (0.80–1.31)	82 (36%)	1.08 (0.74–1.59)
≥30	158 (21%)	143 (28%)	1.65 (1.22–2.25)		148 (22%)	1.09 (0.81–1.45)	76 (34%)	2.15 (1.43–3.22)
<i>p-trend</i>			0.002			0.6		0.0003
BMI (kg/m ²) age 18 [‡]								
<18.5	87 (11%)	62 (12%)	1.23 (0.86–1.77)		73 (11%)	0.95 (0.67–1.35)	18 (8%)	0.84 (0.47–1.50)
18.5–24.9	603 (79%)	377 (73%)	1.00 (Referent)		536 (78%)	1.00 (Referent)	160 (71%)	1.00 (Referent)
25–29.9	72 (9%)	58 (11%)	1.21 (0.83–1.77)		69 (10%)	1.05 (0.73–1.50)	43 (19%)	1.99 (1.28–3.09)
≥30	6 (1%)	16 (3%)	4.02 (1.55–10.50)		8 (1%)	1.35 (0.46–3.97)	5 (2%)	3.02 (0.89–10.28)
<i>p-trend</i>			0.2			0.6		0.002
Weight Gain from age 18 [‡]								
Weight Loss	51 (7%)	28 (5%)	1.03 (0.60–1.78)		46 (7%)	1.26 (0.78–2.03)	10 (4%)	1.22 (0.54–2.74)
0–5 kg	150 (20%)	80 (16%)	1.00 (Referent)		108 (16%)	1.00 (Referent)	25 (11%)	1.00 (Referent)
6–10	124 (16%)	86 (17%)	1.23 (0.83–1.82)		123 (18%)	1.37 (0.96–1.96)	32 (14%)	1.34 (0.74–2.44)
11–20	245 (32%)	165 (32%)	1.18 (0.84–1.66)		229 (33%)	1.28 (0.94–1.75)	85 (38%)	1.90 (1.15–3.14)
21+	196 (26%)	153 (30%)	1.41 (0.99–2.02)		178 (26%)	1.29 (0.93–1.80)	73 (32%)	2.16 (1.28–3.63)
Physical activity [¶]								
Never	476 (62%)	352 (68%)	1.00 (Referent)		424 (61%)	1.00 (Referent)	152 (67%)	1.00 (Referent)
Ever	296 (38%)	167 (32%)	0.78 (0.61–1.00)		267 (39%)	1.02 (0.81–1.27)	75 (33%)	0.88 (0.63–1.24)
Total minutes of exercise (per week) [¶]								
No exercise	476 (62%)	352 (68%)	1.00 (Referent)		424 (61%)	1.00 (Referent)	152 (67%)	1.00 (Referent)
<45	67 (9%)	36 (7%)	0.73 (0.47–1.13)		55 (8%)	0.89 (0.60–1.32)	18 (8%)	0.84 (0.47–1.50)
45–89	79 (10%)	51 (10%)	0.90 (0.61–1.33)		78 (11%)	1.11 (0.78–1.57)	16 (7%)	0.64 (0.35–1.19)
90–119	56 (7%)	26 (5%)	0.66 (0.40–1.09)		46 (7%)	0.94 (0.62–1.44)	15 (7%)	1.12 (0.60–2.09)
≥120	94 (12%)	54 (10%)	0.79 (0.55–1.15)		87 (13%)	1.07 (0.77–1.49)	26 (11%)	0.99 (0.60–1.63)

* Adjusted for age, sex, race, education, smoking, alcohol, NSAID use, and family history of colorectal cancer, and menopausal status and hormone use in women

† Additional adjusted for physical activity

‡ Additionally adjusted for body mass index and diabetes

TABLE 3

Odds ratios and 95% confidence intervals between genotypes of IGF-1 and receptor, IGFBP-3, and growth hormone with colorectal adenomas, hyperplastic polyps and both lesions.

Characteristic	Controls		Adenomas		Hyperplastic Polyps		Both	
	N (%)	N (%)	N (%)	OR (95% CI) *	N (%)	OR (95% CI) *	N (%)	OR (95% CI) *
Total								
<i>IGF-1</i> (rs5742612)								
AA	523 (88%)	363 (91%)	1.00 (Referent)		483 (93%)	1.00 (Referent)	155 (90%)	1.00 (Referent)
GA/GG	69 (12%)	37 (9%)	0.78 (0.50–1.19)		37 (7%)	0.57 (0.37–0.87)	17 (10%)	0.85 (0.48–1.51)
<i>IGF-1 receptor</i> (rs2229765)								
GG	197 (33%)	132 (33%)	1.00 (Referent)		160 (31%)	1.00 (Referent)	55(32%)	1.00 (Referent)
GA	286 (49%)	183 (46%)	0.99 (0.74–1.32)		260 (50%)	1.15 (0.88–1.51)	75(44%)	0.99 (0.66–1.47)
AA	106 (18%)	80 (20%)	1.17 (0.81–1.69)		101 (19%)	1.21 (0.86–1.71)	40(24%)	1.42 (0.88–2.30)
<i>IGFBP3</i> (rs2854746)								
GG	193 (32%)	143 (36%)	1.00 (Referent)		203 (39%)	1.00 (Referent)	62(36%)	1.00 (Referent)
CG	308 (52%)	197 (49%)	0.87 (0.66–1.15)		234 (44%)	0.73 (0.56–0.94)	85(49%)	0.87 (0.60–1.26)
CC	93 (16%)	58 (15%)	0.83 (0.56–1.23)		89 (17%)	0.91 (0.64–1.29)	25(15%)	0.82 (0.48–1.40)
<i>Growth hormone</i> (rs2665802)								
AA	195 (34%)	150 (38%)	1.00 (Referent)		200 (39%)	1.00 (Referent)	69(41%)	1.00 (Referent)
AT	280 (48%)	191 (49%)	0.89 (0.67–1.18)		244 (47%)	0.85 (0.65–1.10)	72(42%)	0.73 (0.50–1.07)
TT	106 (18%)	51 (13%)	0.63 (0.42–0.94)		74 (14%)	0.68 (0.48–0.98)	29(17%)	0.79 (0.48–1.29)

* Adjusted for age, sex, and race