

Null Results in Brief**Dinucleotide Repeat in the Insulin-like Growth Factor-I Gene Is Not Related to Risk of Colorectal Adenoma¹****Edward Giovannucci,² Christopher A. Haiman,
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Introduction

IGF-I³ may be associated with bone mineral density in mice (1) and in men with IOM (2). Rosen *et al.* (3) examined a polymorphic microsatellite composed of variable length CA repeats 1-kb upstream from the transcription start site of *IGF-I* among 25 men with IOM. Men with IOM had a significant excess of homozygosity for the most common allele (CA19), and the CA19/19 genotype was associated with lower serum IGF-I compared with other genotypes (129 *versus* 154 ng/ml; $P = 0.03$) in normal controls. IGF-I level may also increase risk of colorectal cancer. In the NHS, high plasma IGF-I and low IGFBP-3 concentrations were associated with an elevated risk of colorectal cancer and adenoma (4). We examined whether this CA repeat predicted risk of colorectal adenoma and plasma IGF-I levels.

Materials and Methods

Cases of colorectal adenoma and controls were drawn from participants in the NHS, a prospective study of United States female registered nurses (4). From 1989 to 1990, 32,826 NHS participants provided a blood specimen, which was processed and frozen. Among these women, the follow-up response rate through 1994 was 98%. Self-reported diagnoses of colorectal adenoma on questionnaires were confirmed through histopathologic reports.

To be eligible for selection as a case or control, a woman must have supplied a blood sample, must have subsequently undergone sigmoidoscopy or colonoscopy by 1994, and must not have had a prior cancer or adenoma diagnosis. One control was matched to each case on birth year, month of blood draw, fasting status, year of endoscopy, family history of colorectal cancer, and indication(s) for endoscopy. A total of 249 matched

pairs were identified. For 202 of the matched pairs, we previously had assayed plasma concentrations of IGF-I and IGFBP-3 using ELISAs with reagents from Diagnostic Systems Laboratory Inc. (Webster, TX; Ref. 4).

The methods for DNA extraction and amplification have been described previously (5). The oligonucleotide primers used for PCR were: 5'-GCTAGCCAGCTGGTGTATT-3' and 5'-ACCACTCTGGGAGAAGGGTA-3', as described previously (3). Rapid fragment length detection was performed using the ABI 377 DNA Sequencer (PE Corp.). Representative homozygotes (19/19 and 20/20) were sequenced to confirm (CA)_n repeat number. Amplified products were determined relative to Gene Scan-500 size standard using Genescan and Genotyper Analysis software (PE Corp.). Concordance for blinded quality control samples was 100%.

We computed ORs and 95% CIs using conditional logistic regression (SAS version 6.12; SAS Institute, Cary, NC). We compared mean concentrations of plasma IGF-I and IGFBP-3, by genotype. Differences in means were tested using *t* tests. The study had 80% power (two-sided test; $\alpha = 0.05$) to detect an OR of 0.59 for all of the other genotypes *versus* the CA19/29 genotype assuming a CA19/19 prevalence of 0.40.

Results

Frequency of CA alleles did not differ appreciably between cases and controls (Table 1). For cases and controls combined, the most common alleles were CA19 (63%) and CA20 (24%). None of the other alleles exceeded a frequency of 5%.

Comparing the CA19/19 genotype (106 cases and 100 controls) *versus* all of the other genotypes combined (133 cases and 149 controls), the OR was 1.10 (95% CI, 0.78–1.55) for total colorectal adenomas, 0.90 (95% CI, 0.53–1.52) for large or tubulovillous/villous adenomas, and 1.34 (95% CI, 0.87–2.08) for small/tubular adenomas. Relative to women with the CA19/20 genotype (73 cases and 73 controls), women with genotype CA19/19 (106 cases and 100 controls) did not have a lower adenoma risk (OR = 1.02; 95% CI, 0.67–1.55). None of the other genotypes was related to either an increased or decreased risk of colorectal adenoma relative to the CA19/20 genotype.

In the study by Rosen *et al.* (3), men with the CA19/20 genotype appeared to have the highest serum IGF-I concentrations. No significant difference was noted for plasma IGF-I concentrations between women possessing the CA19/19 genotype (mean = 168.6 ng/ml; $n = 171$) compared with all others (mean = 167.7 ng/ml; $n = 233$; *t* test; $P = 0.88$) or to women with the CA19/20 genotype (166.4 ng/ml; $n = 117$; $P = 0.76$). Plasma IGFBP-3 also did not differ by genotype. These results were similar for controls and cases.

Discussion

Unlike a previous study (3), we did not find lower circulating IGF-I concentrations in individuals with the CA19/19 genotype,

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³ The abbreviations used are: IGF, insulin-like growth factor; IGFBP-3, IGF binding protein-3; IOM, idiopathic osteoporosis; CA, cytosine-adenosine; NHS, Nurses' Health Study; OR, odds ratio; CI, confidence interval.

Table 1 Frequencies of IGF-I CA repeat alleles in colorectal adenoma cases and controls in the NHS (1989–94)

CA allele	Cases	(%)	Controls	(%)
11	1	(0.2)	3	(0.6)
14	1	(0.2)	0	(0)
16	1	(0.2)	0	(0)
17	8	(1.6)	6	(1.2)
18	25	(5.0)	20	(4.0)
19	322	(64.7)	308	(61.8)
20	112	(22.5)	128	(25.7)
21	20	(4.0)	25	(5.0)
22	8	(1.6)	8	(1.6)

despite a 4-fold greater sample size. In addition, total adenoma and large or villous adenoma were not associated with the CA genotype. Our study could not rule out moderate size. However, if this polymorphism acts by influencing circulating IGF-I levels, an important sized effect would be unlikely, because IGF-I concentrations did not vary among the genotypes.

In conclusion, this study does not support the hypothesis that a CA microsatellite region 1-kb upstream from the *IGF-I* gene is an important predictor of either circulating IGF-I or IGFBP-3 concentrations, or of risk of colorectal adenoma.

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