Cancer Causes Control
DOI 10.1007/s10552-009-9438-4

ORIGINAL PAPER

Association of IGF1 and IGFBP3 polymorphisms with colorectal polyps and colorectal cancer risk

Elisabeth Feik · Andreas Baierl · Barbara Hieger · Gerhard Führlinger · Astrid Pentz · Stefan Stättner · Werner Weiss · Thomas Pulgram · Gernot Leeb · Karl Mach · Michael Micksche · Andrea Gsur

Received: 16 January 2009 / Accepted: 14 September 2009

Abstract
Purpose Insulin-like growth factor 1 (IGF1) is a peptide growth factor that promotes cell proliferation and inhibits apoptosis. The bioavailability of IGF1 is regulated by the insulin-like growth factor binding protein 3 (IGFBP3). The purpose of this study was to examine the association of genetic variants in IGF1 (rs6214, rs6220, and rs35767) and IGFBP3 (rs2854744 and rs2854746) with risk of colorectal polyps and colorectal cancer.
Methods In this ongoing colorectal cancer study of Austria (CORSA), a total of 3,360 Caucasian participants, consisting of 178 colorectal cancer patients, 328 patients with high risk polyps, 1,059 patients with low risk colorectal polyps, and 1,795 colonoscopy-negative controls, were recruited within a large colorectal screening project in the province Burgenland and from three hospitals in Vienna. Multiple logistic regression was applied to compare individuals of the control group against three different risk groups, namely, colorectal cancer group, high risk polyp group, and low risk polyp group.
Results Carriers of the homozygous polymorphic genotype of the SNP rs6214 were associated with an increased colorectal risk (OR = 1.79, 95% CI 1.04–1.90) compared to the colonoscopy-negative controls; this was also found when combining colorectal cancer cases and high risk polyp group (OR = 1.39, 95% CI 1.01–1.90).
Conclusion Our results suggest that the SNP rs6214 of IGF1 could have an impact on developing colorectal cancer and colorectal polyps with villous elements.

Keywords Colorectal cancer · Colorectal polyps · IGF1 · IGFBP3 · Molecular epidemiology · Polymorphism

Abbreviations

CRC	Colorectal cancer
CORSA	Colorectal cancer study of Austria
IGF1	Insulin-like growth factor 1
IGFBP3	Insulin-like growth factor binding protein 3
SNP	Single nucleotide polymorphism

Introduction

Colorectal cancer is the second most common cancer and is responsible for 20% of all cancer deaths in developed countries. In Austria, the incidence of colorectal cancer is in the top third within the European Union and the second most common cancer-related death in men and women nationwide. There is a remarkable decrease in colorectal

The study was approved by the institutional review boards at the Medical University of Vienna and Burgenland.

E. Feik · B. Hieger · G. Führlinger · A. Pentz · M. Micksche · A. Gsur (✉)
Department of Medicine I, Institute of Cancer Research, Medical University of Vienna, Borschkegasse 8a, 1090 Vienna, Austria
e-mail: andrea.gsur@meduniwien.ac.at

A. Baierl
Department of Statistics and Decision Support Systems, University of Vienna, Vienna, Austria

S. Stättner
Department of Surgery, SMZ Süd, Vienna, Austria

W. Weiss · T. Pulgram
Department of Gastroenterology, Rudolfstiftung, Vienna, Austria

G. Leeb · K. Mach
Hospital Oberpullendorf, Burgenland, Austria

Published online: 26 September 2009

cancer rates from east to west in Austria, with the highest incidence rates in the province Burgenland, followed by Vienna [1].

Members of the insulin-like growth factor pathway are important regulators of cell proliferation, differentiation, and apoptosis [2, 3]. Insulin-like growth factor 1 (IGF1) is a peptide growth factor that promotes cell proliferation and inhibits apoptosis. Its proliferative activity is mainly regulated by the mitogen-activated protein kinase signaling pathway and its antiapoptotic activity by the PI-3 kinase pathway [4]. IGF1 spans 85 kb of 12q22-24.1 and is not in strong linkage disequilibrium with neighboring genes [5]. Most of the circulating IGF1 are bound to an acid-labile subunit and to one of six insulin-like growth factor binding proteins (IGFBPs), among which the most important is insulin-like growth factor binding protein 3 (IGFBP3) [6]. This complex regulates the bioavailability of IGF1 to the target tissues. IGFBP3 is located on chromosome 7p13 and contains five exons. This complex regulates the bioavailability of IGF1 to the target tissues.

Studies have found increased expression of IGF1 in several malignancies including that of the gastrointestinal tract [7]. Some epidemiological studies suggested that high levels of circulating IGF1 and/or low levels of IGFBP3 are associated with an elevated risk of colorectal carcinoma [8, 9]. While nutrition is an important determinant of circulating IGF1 levels [10, 11], twin studies have shown that a large part of the interindividual variability in circulating IGF1 levels is due to genetic variation [12, 13].

The colorectal cancer study of Austria (CORSA) is nested within a large screening program of the province Burgenland, which includes 3,360 subjects. The purpose of this study was to examine the association between genetic polymorphisms and haplotypes in IGF1 (rs6214, rs6220, and rs35767) and IGFBP3 (rs2854744 and rs2854746) with risk of colorectal polyps and colorectal cancer.

Materials and methods

Study population

In this ongoing molecular epidemiology colorectal cancer study in Austria (CORSA), 3,360 Caucasian participants were recruited since May 2002 within a large colorectal screening project in the province Burgenland, Austria. In this "Screening project Burgenland against colorectal cancer," which uses fecal occult blood tests of 120,000 participants, aged between 40 and 80, whereof 2,500–3,000 participants per year have a positive fecal occult blood testing and receive further diagnostic workup such as colonoscopies. These persons were asked to participate in our molecular epidemiology study and after their written informed consent, a short questionnaire on diet and smoking habits was obtained from all participants. The study was approved by the institutional review boards.

Table 1 Classification of polyps in high risk and low risk group

High risk group	Low risk group
Adenomatous tubulovillous polyps	
Adenomatous villous polyps	Hyperplastic polyps
Adenomatous tubular and tubulovillous polyps	Adenomatous tubular polyps

Cases were newly diagnosed within this screening project, previously untreated, and histologically confirmed colorectal cancer patients. Due to the expected low number of cases diagnosed in this screening study, further colorectal cases were recruited from three hospitals in Vienna (Division of Oncology, Medical University of Vienna; Department of Surgery, SMZ Süd; and Department of Gastroenterology, KH Rudolfstiftung).

The polyp group consists of 882 patients with adenomatous, 232 with hyperplastic, and 67 with adenomatous/hyperplastic polyps. For statistical analysis, a classification in high risk and low risk group (Table 1) was performed, depending on the villous elements. The control group consists of participants without pathological findings that means free of polyps and colorectal cancer at the time of colonoscopy. Based on the colonoscopy and in the case of a pathological finding on histological confirmation, the participants were assigned to four groups: colorectal cancer patients, high risk polyp group, low risk polyp group, and controls.

Genotyping

Blood samples (5 ml) from each participant were stored in the hospitals in Burgenland and transported from there on dry ice to the Institute of Cancer Research in Vienna. DNA was extracted by standard protocols (Qiagen) from peripheral blood. Genotyping was performed with ABI Prism 7500 Sequence Detection System (Applied Biosystems) using the fluorogenic 5′ nuclease assay with TaqMan Minor Groove Binder (MGB) probes. The reaction contained 20 ng genomic DNA, TaqMan 2× PCR Master Mix, forward and reverse primers and probes for the wild type and the mutant allele in a total volume of 10 µl. Sequences and concentrations of primers and TaqMan-MGB probes used for each polymorphism analyzed are summarized in Table 2. Universal reaction conditions were 2 min at 50°C, 10 min at 95°C, 40 cycles with 15 s at 92°C, and annealing/extension at 60°C for 1 min. Allelic discrimination was carried out by measurement of fluorescence yields of the two different dyes at 60°C. Genotyping was done blinded

Table 2 Primers and TaqMan-MGB probes for genotyping IGF1 and IGFBP3 polymorphisms using fluorogenic 5′ nuclease assay

Polymorphism	Primers and probes[a]	Concentration (nM)
rs6214 (IGF1)	F: 5′-AAT TAT TCC CTC TCA ACA AAA CTT TAT AGG-3′	900
	R: 5′-TGA AGG AAA TAA GTC ATA GAC ACT CTT AGA A-3′	900
	Wild type: CTG CAG ACT TAA C**G**T GT (VIC labeled)	200
	Mutated: CTG CAG ACT TAA C**A**T GT (FAM labeled)	200
rs6220 (IGF1)	F: 5′-AAC AAA GAG ATT TCT ACC AGT GAA AGG-3′	900
	R: 5′-GCC TAG AAA AGA AGG AAT CAT TGT G-3′	900
	Wild type: AGT AAA ACC T**T**G TTT AAT AC (VIC labeled)	100
	Mutated: AGT AAA ACC T**C**G TTT AAT A (FAM labeled)	100
rs35767 (IGF1)	F: 5′-AGA GTA GGA TTT CAA GCA GAA CTG TGT-3′	900
	R: 5′-TGG AAA TAA CCT GGA CCT TGA ATT-3′	900
	Wild type: CTG AGA GTC ATG **C**GG A (VIC labeled)	200
	Mutated: CTG AGA GTC ATG **T**GG AA (FAM labeled)	200
rs2854744 (IGFBP-3)	F: 5′-CAC CTT GGT TCT TGT AGA CGA CAA-3′	900
	R: 5′-GGC GTG CAG CTC GAG ACT-3′	900
	Wild type: CTC GTG C**G**C ACG C (VIC labeled)	200
	Mutated: CTC GTG C**T**C ACG CC (FAM labeled)	100
rs2854746 (IGFBP-3)	F: 5′-GCC GCT GCG CTG ACT CT-3′	900
	R: 5′-GCT CGC AGC GCA CCA C-3′	900
	Wild type: AAG CCC **G**CC GAG C (VIC labeled)	200
	Mutated: AGC CC**C** CCG AGC T (FAM labeled)	200

[a] Variable nucleotides in bold letters

to case–control status, and 10% of samples were randomly repeated for quality control, with complete congruence.

Selection of SNPs focused on those within exons, promoter, or regulatory regions and with a relatively high minor allele frequency (MAF) in Caucasians. SNPs were selected from publicly available databases such as the SNP 500 cancer database (http://snp500cancer.nci.nih.gov/) and the NCBI SNP database (http://www.ncbi.nlm.nih.gov/).

Statistical analysis

Genotypic counts of controls were tested for Hardy–Weinberg equilibrium using a χ^2 test. Haplotype estimates were determined and the frequencies of the most common haplotypes for gene IGF1 and IGFBP3, respectively, were derived using the program FASTPHASE [14]. Linkage disequilibrium (LD) statistics were computed using Haploview 4.0 [15].

Multiple logistic regression was applied to compare individuals of the control group against three different risk groups defined in Table 1.

Separate models were estimated where each of the five polymorphisms described in Table 4 was included as three-level factor (homozygous wild type, heterozygous, homozygous polymorphic), and each haplotype was included as explanatory variable. Age, sex, and body mass index were used as confounders. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated for each polymorphism and haplotype; reference categories were wild type and the most frequent haplotype, respectively.

Gene–gene interactions were investigated by estimating models with two polymorphisms, one of each of the two genes. Because of high LD between the polymorphisms on IGFBP3, only polymorphism rs2854744 was chosen. Likelihood ratio tests were conducted to compare a model with interaction effect between the two polymorphisms to a model without interaction term.

Analysis of the data was performed using the software R Ver 2.6.2. All P values are two-sided; P values <0.05 were considered to be statistically significant.

Results

Characteristics of study subjects are given in Table 3. A total of 3,360 participants were included in the CORSA study. The study population consists of 178 patients with colorectal cancer, 328 patients with high risk polyps, 1,059 patients with low risk polyps, and 1,794 colonoscopy-negative controls, respectively. Overall, 1,854 study participants were male and 1,506 were female. No differences in the age distribution were found between cases and controls except for the age group 70 and older where colorectal cancer patients tend to be older than controls.

The genotype distribution in controls was in Hardy–Weinberg equilibrium for the SNPs rs6214, rs35767,

Table 3 Selected characteristics of the study population

	CRC patients $n = 178$ (5.3%)	High risk group $n = 328$ (9.8%)	Low risk group $n = 1{,}059$ (31.5%)	Controls $n = 1{,}794$ (53.4%)
Age (years)				
≤50	14 (7.9)	44 (13.5)	142 (13.4)	349 (19.4)
>50–≤60	37 (20.8)	68 (20.8)	240 (22.7)	437 (24.4)
>60–≤70	51 (28.6)	125 (38.2)	391 (36.9)	577 (32.2)
>70–≤80	58 (32.6)	86 (26.3)	271 (25.6)	410 (22.8)
>80	18 (10.1)	4 (1.2)	15 (1.4)	21 (1.2)
Sex				
Male	106 (59.6)	216 (65.9)	694 (65.5)	838 (46.7)
Female	72 (40.4)	112 (34.1)	365 (34.5)	957 (53.3)
Body mass index (kg/m^2)				
≤19	2 (1.7)	2 (0.6)	8 (0.8)	9 (0.5)
>19–≤25	31 (25.6)	59 (18.6)	207 (19.8)	381 (21.9)
>25–≤30	48 (39.7)	157 (49.4)	474 (45.4)	747 (42.9)
>30	40 (33.1)	100 (31.4)	355 (34.0)	605 (34.7)
Missing	57	10	15	52
Smoking				
Current	28 (15.9)	61 (19.1)	211 (20.3)	240 (13.7)
Former	71 (40.3)	103 (32.3)	331 (31.9)	488 (27.9)
Never	77 (43.8)	155 (48.6)	496 (47.8)	1,024 (58.4)

rs2854744, and rs2854746. For SNP rs6220, a P value of 0.03 was observed indicating deviation from Hardy–Weinberg equilibrium. The MAF frequencies of the three IGF1 SNPs ranged from 0.38 to 0.17. The MAF of the IGFBP3 SNP rs2854744 and rs2854746 was 0.46 and 0.42, respectively.

Multiple logistic regression was applied to compare individuals of the control group against three different groups: colorectal cancer group; high risk group in combination with colorectal cancer; and low risk group in combination with high risk and colorectal cancer (Table 4). Carriers of the homozygous polymorphic genotype of the SNP rs6214 were associated with an increased risk for colorectal cancer compared to the colonoscopy-negative controls with an OR of 1.79 (95% CI 1.04–3.08). Furthermore, an increased risk was found when comparing colorectal cancer cases and high risk group versus the controls with an OR of 1.39 (95% CI 1.01–1.90). The other investigated SNPs in IGF1 as well as in IGFBP3 were not found to be associated with colorectal cancer risk.

In a haplotype analysis (Table 5) comparing colorectal cancer patients versus the controls, the rare TCT haplotype for IGF1 had an OR of 5.61 (95% CI 1.78–17.75). The "at risk" haplotype is defined by the rs6214 T allele, rs6220 C allele, and rs35767 T allele.

Furthermore, we investigated the interaction of the IGF1 and IGFBP3 SNPs with a likelihood ratio test (data not shown), confounders were age, sex, and BMI. The combination of IGF1 rs35767 and IGFBP3 rs2854744 showed a substantially significant difference with a P value of 0.014 when comparing the carcinoma and high and low risk group versus controls with an OR of 1.5 (95% CI 1.09–1.69).

Discussion

We have performed a large case–control study (CORSA) to assess the role of five genetic variants in IGF1 (rs6214, rs6220, and rs35767) and IGFBP3 (rs2854744 and rs2854746) on colorectal cancer and polyp risk. We found a statistically significant association with increased colorectal cancer risk for the SNP rs6214 and high risk polyps. The functional consequence of this SNP, located in the 3′ region of IGF1, is yet unknown. In the CORSA study, none of the other investigated SNPs of IGF1 nor IGFBP3 showed a significant association with colorectal cancer risk, except one rare haplotype in IGF1, which was associated with a more than fivefold risk of developing colorectal cancer. However, this finding must be considered with caution because of the small number of carriers with this haplotype and the wide OR.

Colorectal polyps are classified as either neoplastic (adenomatous polyps) or non-neoplastic (hyperplastic polyps). Adenomatous polyps are classified histologically as tubular, tubulovillous, or villous. Only a small proportion of adenomatous polyps will develop into cancer, and the chance is greater in polyps with a villous histology

Table 4 Genotype distribution of the SNPs in IGF1 and IGFBP3

Gene	SNP	Genotype	Controls	CRC		*P* value	CRC and high risk group		*P* value	CRC, high and low risk group		*P* value
				Cases	OR (95% CI)		Cases	OR (95% CI)		Cases	OR (95% CI)	
IGF1	rs6214	CC	648	37	1		161	1		571	1	
		CT	837	60	1.27 (0.83–1.95)	0.28	199	0.98 (0.77–1.24)	0.85	677	0.94 (0.81–1.10)	0.46
		TT	245	24	**1.79 (1.04–3.08)**	**0.04**	79	**1.39 (1.01–1.90)**	**0.04**	229	1.11 (0.89–1.38)	0.33
	rs6220	TT	912	60	1		222	1		759	1	
		TC	666	53	1.22 (0.83–1.80)	0.32	179	1.11 (0.88–1.38)	0.38	588	1.07 (0.92–1.25)	0.37
		CC	152	8	0.93 (0.43–2.00)	0.84	38	1.08 (0.73–1.61)	0.69	130	1.06 (0.82–1.38)	0.66
	rs35767	CC	1,208	79	1		310	1		1,023	1	
		CT	470	40	1.26 (0.85–1.89)	0.25	119	0.97 (0.76–1.24)	0.83	416	1.05 (0.89–1.23)	0.59
		TT	52	2	0.58 (0.14–2.45)	0.46	10	0.77 (0.38–1.54)	0.45	38	0.90 (0.58–1.39)	0.63
IGFBP3	rs2854744	AA	504	37	1		129	1		430	1	
		AC	845	59	1.00 (0.65–1.54)	0.99	214	1.04 (0.80–1.33)	0.77	735	1.06 (0.90–1.26)	0.46
		CC	381	25	0.98 (0.57–1.66)	0.93	96	1.05 (0.78–1.42)	0.74	312	1.02 (0.83–1.25)	0.85
	rs2854746	CC	588	42	1		149	1		487	1	
		CG	822	55	0.98 (0.64–1.49)	0.91	211	1.05 (0.83–1.34)	0.68	726	1.11 (0.95–1.30)	0.19
		GG	320	24	1.16 (0.69–1.97)	0.57	79	1.03 (0.75–1.41)	0.86	264	1.04 (0.85–1.28)	0.69

Confounder: age, sex, and body mass index

Significant values are given in bold letters

Table 5 Haplotype distribution of the SNPs in IGF1 and IGFBP3

Gene	Haplotype	Controls	CRC		*P* value	CRC and high risk group		*P* value	CRC and high and low risk group		*P* value
			Cases	OR (95% CI)		Cases	OR (95% CI)		Cases	OR (95% CI)	
IGF1	CTC	1,558	102	1	0	381	1	0	1,317	1	0
	TTC	672	54	1.26 (0.84–1.79)	0.19	180	1.14 (0.93–1.40)	0.21	561	1.03 (0.90–1.18)	0.65
	TCC	407	34	1.31 (0.87–1.98)	0.19	117	1.20 (0.95–1.53)	0.13	362	1.07 (0.91–1.26)	0.41
	CTT	296	23	1.17 (0.73–1.88)	0.52	69	0.95 (0.71–1.27)	0.72	250	1.02 (0.85–1.24)	0.81
	CTC	249	8	0.57 (0.27–1.20)	0.14	61	1.06 (0.78–1.44)	0.72	222	1.10 (0.90–1.34)	0.32
	TTT	230	16	1.06 (0.61–1.58)	0.83	52	0.94 (0.68–1.31)	0.73	198	1.04 (0.84–1.28)	0.74
	CTT	30	1	0.45 (0.06–3.42)	0.44	10	1.27 (0.60–2.66)	0.53	30	1.17 (0.69–1.97)	0.56
	TCT	18	4	**5.61 (1.78–17.75)**	**0.003**	8	**2.44 (1.03–5.79)**	**0.04**	14	1.07 (0.52–2.20)	0.86
IGFBP3	AC	1,849	133	1	0	472	1	0	1,593	1	0
	CG	1,458	103	1.03 (0.79–1.35)	0.81	369	1.03 (0.88–1.20)	0.75	1,252	1.03 (0.93–1.14)	0.62
	CC	149	6	0.56 (0.24–1.30)	0.18	37	1.02 (0.70–1.50)	0.91	107	0.87 (0.67–1.14)	0.31
	AG	4	0	0		0			2		

Confounder: age, sex, and body mass index

Significant values are given in bold letters

[16]. The St. Marks Hospital study demonstrated that 4.8% of tubular, 22.5% of tubulovillous, and 40.7% of villous adenomas were malignant [17]. Therefore, for the statistical analysis, we divided our polyp group into a high risk and low risk group, based on the villous element. Patients with villous histology are at greater risk to develop colorectal cancer and are therefore assigned to the high risk group.

The strength of the CORSA study is that controls were known to be polyp-free and free of colorectal cancer at the time of colonoscopy and blood sampling. Using a control group, which did not undergo colonoscopy, could include some undiagnosed participants with colorectal polyps or colorectal cancer because in this age group these conditions are relatively common. Furthermore, this molecular epidemiology study consists of a large sample size, although, as expected in a screening program, there are predominantly patients with colorectal polyps and polyp-free persons.

A limitation of this study is that there is not enough power to investigate gene–gene interactions, especially for cancer patients.

The genotype distribution in controls for SNP rs6220 was not found to be in Hardy–Weinberg equilibrium for unknown reasons. However, we can exclude a genotyping error because in each run, a self-designed wild type probe and homozygous polymorphic probe were included as controls, and 10% of samples were randomly repeated.

We are aware that by genotyping three SNPs in IGF1 and two SNPs in IGFBP3 we have not covered the whole genes. But a haplotype tagging SNP approach, genotyping all tagging SNPs of IGF1 and IGFBP3, was not the scope of this study. The recent progress through the application of genome-wide association studies will bring new insights in colorectal cancer etiology. Recently, genome-wide association studies have identified colorectal cancer susceptibility loci at 8q24 and 18q21 [18, 19].

Our criteria for selecting the SNPs were relatively high MAF in Caucasians, location in exons or regulatory regions and therefore a possible influence on circulating plasma levels of IGF1 and IGFBP1. Some of the genotyped SNPs in the CORSA study have been found to be associated with differences in circulating IGF1 and IGFBP3 plasma levels in previous studies.

The three IGF1 and one of the IGFBP3 SNPs (rs2854744) genotyped in our study were also investigated in a Caucasian breast cancer study by Canzian et al. [20]. For none of the investigated IGF1 SNPs, a strong association on circulating IGF1 levels was found; only a modest effect on mean circulating IGF1 levels was found for IGF1 SNP rs6220 and rs35767. In accordance, Palles et al. [21] reported for the IGF1 SNP rs35767 a borderline significant association of higher IGF1 levels. However, Al-Zahrani et al. [22] found in their Caucasian breast cancer study, a statistically significant association of the polymorphic allele of IGF1 SNP rs6220 with plasma levels of IGF1 in females but not in males. The IGF1 SNP rs6214 was not associated with IGF1 plasma levels in this study [22].

Some studies show influence of the IGFBP3 SNP rs2854744 on plasma IGFPB3 levels. Canzian et al. [20] observed a strong association between increased IGFBP3 plasma levels and SNPs in the 5′ region of the IGFBP3 gene belonging to the same haplotype, raising the question, which of these SNPs causes the association with IGFBP3 levels? An in vitro study by Deal et al. [23] confirmed that

the polymorphic allele of the IGFBP3 SNP rs2854744 affects the IGFBP3 transcription. Al-Zahrani et al. [22] confirmed this finding as they found the polymorphic allele of the IGFBP3 SNP rs2854744 also associated with an increase in IGFBP3 plasma levels.

Recently, a German group investigated also the SNPs rs2854744 and rs2854746 of IGFBP3 and their association with colorectal cancer in a case–control study consisting of 661 colorectal cases and 607 matched controls, randomly selected from a list of residents. In accordance with our study, they found no significant association with colorectal cancer risk for these two SNPs [24]. The MAF of SNP rs2854746, located in exon 1 of IGFBP3, was in controls of our CORSA study in accordance with the findings of the German study and the MAF for Caucasians in the SNP 500 cancer database. The MAF for the IGFBP3 SNP rs2854744, located in exon 1, was in our CORSA study also in accordance with the data in the SNP 500 cancer database but somewhat higher in the German study.

In summary, our results suggest that the SNP rs6214 of IGF1 could have an impact on developing colorectal cancer and high risk colorectal polyps. However, this finding needs to be replicated in further studies.

Acknowledgments We thank Marlies Pusman for excellent recruitment of patients and Martin Preyer for genotyping. Furthermore, we thank all physicians involved in this study for data management and blood sampling. This study was supported by a grant from "Österreichische Krebshilfe."

References

1. Vutuc C, Waldhoer T, Haidinger G, Ahmad F, Micksche M (1999) The burden of cancer in Austria. Eur J Cancer Prev 8(1):49–55
2. Bustin SA, Jenkins PJ (2001) The growth hormone-insulin-like growth factor-I axis and colorectal cancer. Trends Mol Med 7(10):447–454
3. Stewart CE, Rotwein P (1996) Growth, differentiation, and survival: multiple physiological functions for insulin-like growth factors. Physiol Rev 76(4):1005–1026
4. Jenkins PJ, Mukherjee A, Shalet SM (2006) Does growth hormone cause cancer? Clin Endocrinol (Oxf) 64(2):115–121
5. Rodriguez S, Gaunt TR, Day IN (2007) Molecular genetics of human growth hormone, insulin-like growth factors and their pathways in common disease. Hum Genet 122(1):1–21
6. Baxter RC (1994) Insulin-like growth factor binding proteins in the human circulation: a review. Horm Res 42(4–5):140–144
7. Samani AA, Brodt P (2001) The receptor for the type I insulin-like growth factor and its ligands regulate multiple cellular functions that impact on metastasis. Surg Oncol Clin N Am 10(2):289–312, viii
8. Probst-Hensch NM, Yuan JM, Stanczyk FZ et al (2001) IGF-1, IGF-2 and IGFBP-3 in prediagnostic serum: association with colorectal cancer in a cohort of Chinese men in Shanghai. Br J Cancer 85(11):1695–1699
9. Ma J, Pollak MN, Giovannucci E et al (1999) Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. J Natl Cancer Inst 91(7):620–625
10. Thissen JP, Ketelslegers JM, Underwood LE (1994) Nutritional regulation of the insulin-like growth factors. Endocr Rev 15(1):80–101
11. Kaaks R, Lukanova A (2001) Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 60(1):91–106
12. Hong Y, Pedersen NL, Brismar K, Hall K, de Faire U (1996) Quantitative genetic analyses of insulin-like growth factor I (IGF-I), IGF-binding protein-1, and insulin levels in middle-aged and elderly twins. J Clin Endocrinol Metab 81(5):1791–1797
13. Harrela M, Koistinen H, Kaprio J et al (1996) Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. J Clin Invest 98(11):2612–2615
14. Scheet P, Stephens M (2006) A fast and flexible statistical model for large-scale population genotype data: applications to inferring missing genotypes and haplotypic phase. Am J Hum Genet 78(4):629–644
15. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21(2):263–265
16. Winawer SJ, Zauber AG, Fletcher RH et al (2006) Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin 56(3):143–159 quiz 184–185
17. Markowitz AJ, Winawer SJ (1997) Management of colorectal polyps. CA Cancer J Clin 47(2):93–112
18. Tomlinson I, Webb E, Carvajal-Carmona L et al (2007) A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. Nat Genet 39(8):984–988
19. Tenesa A, Dunlop MG (2009) New insights into the aetiology of colorectal cancer from genome-wide association studies. Nat Rev Genet 10:353–358
20. Canzian F, McKay JD, Cleveland RJ et al (2006) Polymorphisms of genes coding for insulin-like growth factor 1 and its major binding proteins, circulating levels of IGF-I and IGFBP-3 and breast cancer risk: results from the EPIC study. Br J Cancer 94(2):299–307
21. Palles C, Johnson N, Coupland B et al (2008) Identification of genetic variants that influence circulating IGF1 levels: a targeted search strategy. Hum Mol Genet 17(10):1457–1464
22. Al-Zahrani A, Sandhu MS, Luben RN et al (2006) IGF1 and IGFBP3 tagging polymorphisms are associated with circulating levels of IGF1, IGFBP3 and risk of breast cancer. Hum Mol Genet 15(1):1–10
23. Deal C, Ma J, Wilkin F et al (2001) Novel promoter polymorphism in insulin-like growth factor-binding protein-3: correlation with serum levels and interaction with known regulators. J Clin Endocrinol Metab 86(3):1274–1280
24. Pechlivanis S, Wagner K, Chang-Claude J et al (2007) Polymorphisms in the insulin like growth factor 1 and IGF binding protein 3 genes and risk of colorectal cancer. Cancer Detect Prev 31(5):408–416