Mol Biol Rep (2014) 41:8099–8106
DOI 10.1007/s11033-014-3708-2

Association of insulin-like growth factor-I receptor polymorphism with colorectal cancer development

Noyko S. Stanilov · Iliya A. Karakolev · Tashko S. Deliysky · Jovcho P. Jovchev · Spaska A. Stanilova

Received: 18 January 2013 / Accepted: 26 August 2014 / Published online: 5 September 2014

Abstract The insulin-like growth factor (IGF) system plays a prominent role in the cancer development. The IGF-1 receptor (IGF-1R) and its associated signalling pathway is an important growth regulatory pathway that has been implicated in colorectal carcinogenesis. This study was designed to compare +3179G/A *IGF1R* (rs 2229765) genotype distribution in 110 colorectal cancer (CRC) patients to a group of 143 healthy controls (HCs). We also investigated serum IGF-1 levels in CRC patients and HCs in an association to genotype. IGF-1 serum levels were measured by enzyme-linked immunosorbent assay and genotyping for the +3179G/A polymorphism was performed by restriction fragment length polymorphisms–polymerase chain reaction assay. Although the genotype frequencies were comparable in both groups, higher frequency of dominant genotypes [AA/AG; 71 vs. 62 %; odds ratio (OR) = 1.52] and lower frequency of GG genotype (29 vs. 38 %) was seen in cases versus controls. When CRC patient's group was divided into stages of disease by tumor–node–metastasis classification we observed the significantly highest frequency of AA genotype in III stage compared to controls: 22.5 versus 15 %; OR = 3.37, $p = 0.026$. There was a significant association between IGF-1R rs2229765 polymorphism and advanced CRC (AA/AG vs. GG: OR = 3.06, $p = 0.004$). The frequency of A-allele in advanced CRC was significantly higher then early CRC (52 vs. 37.7, OR = 1.78). According to genotype serum IGF-1 levels was significantly decreased in patients with GG genotype then patients with dominant genotypes. Our results showed a relationship between the +3179G>A polymorphism of the IGF-1R and serum IGF-1 with the progression of colorectal carcinoma. A dominant genetic model was established for IGF-1R rs2229765 polymorphism and CRC progression.

Keywords Insulin-like growth factor · IGF-1R · rs 2229765 · Colorectal cancer · Polymorphism

Introduction

The insulin-like growth factor (IGF) system is comprised of ligands (IGF-I and IGF-II), receptors (IGF-1R and IGF-2R), and a family of six binding proteins. The IGF pathway plays an important role in growth and development and in the maintenance of tissue homeostasis through regulation of cell cycle progression [1]. Both IGF-1 and IGF-2 exert their biological effects through activation of IGF type 1 receptor (IGF-1R). IGFs binding activate intrinsic tyrosine kinase activity, resulting in receptor autophosphorylation and stimulation of signaling cascades that include the RAS/RAF/MEK/ERK and PI3K/AKT/TOR pathways. Activation of the receptor and transduction of the intracellular signaling kinase cascades culminates in cell proliferation, differentiation and anti-apoptotic effects [2].

N. S. Stanilov · J. P. Jovchev
Department of Neurosurgery, Surgery and Urology, 2nd Surgery Clinic, University Hospital, Stara Zagora, Bulgaria

N. S. Stanilov
BMI Healthcare, Winterbourne Hospital, Dorchester, Dorset, UK

I. A. Karakolev · S. A. Stanilova (✉)
Department of Molecular Biology, Immunology and Medical Genetics, Medical Faculty, Trakia University, Aremiska 11 street, Stara Zagora, Bulgaria
e-mail: stanilova@mf.uni-sz.bg; spaska.stanilova@abv.bg

T. S. Deliysky
Oncology Center, University School of Medicine, Pleven, Bulgaria

The signaling pathway of IGF-1R is an important growth regulatory pathway that plays a crucial role in cancer development [3, 4]. Increased levels of IGF ligands and over-expression of IGF-1R have been observed in many cancers and have been shown to affect proliferation, differentiation, migration and apoptosis of cancer cells. In tumors, such as colorectal, which may drive their own growth and survival through over-expression of autocrine IGF-II, the role of IGF-1R is especially critical [4, 5].

Two meta-analysis studies support a significant elevated risk for breast, prostate and colorectal cancer (CRC) among individuals with the highest IGF-1 and IGF-binding protein-3 (IGFBP3) levels compared with individuals with the lowest concentrations [6, 7].

A lot of studies investigated the association of IGF-1 related gene polymorphisms with serum levels and CRC susceptibility. The most investigated polymorphism in IGF-1 gene a cytosine–adenosine dinucleotide repeat sequence (CA15–22) that resides in the promoter region has been associated with serum levels and with CRC risk in some studies [8–13] but not in all [14]. More recently, polymorphic variants such as single nucleotide polymorphisms (SNPs) located in regulatory regions of IGF-1 and IGFBP3 have been reported to be associated with risk of CRC [7, 15, 16]. In contrast to IGF-1 and IGFBP gene polymorphisms, only one paper reported data for association of IGF-1R polymorphisms and colorectal neoplasia [17]. LeRoy et al. examined the association between the *IGF1R* rs7166348 and IGF-1 levels with colorectal neoplasia. They showed the probability of colorectal neoplasia was greatest (71.8 %) among carriers of any A allele for rs7166348 of IGF1R [17]. Recently, SNP located in exon 16 (rs2229765) of *IGF1R* gene was found associated with levels of free IGF-I and human longevity [18, 19].

To expand our knowledge for IGF-1R related SNPs implication in CRC risk we assessed the role of G>A transition in exon 16, codon 1013 (rs 2229765) at *IGF1R* as risk factors for CRC development.

Materials and methods

Subjects

A group of 110 Bulgarian patients (Caucasian) with CRC were included in the study of distribution of the IGF-1R polymorphism. Cases with new diagnosis of CRC attending the Trakia University Hospital and St Ivan Rilski Hospital in Stara Zagora as well as the Oncology Center in Pleven, Bulgaria were selected. All patients had no previous history of inflammatory bowel disease or any of the known hereditary cancer syndromes. The histopathological result confirmed the diagnosis of cancer. The patients group was composed of 67 (61 %) male and 43 (39 %) female. The mean age at diagnosis of male versus female among the cases was 64 ± 10.8 versus 66.8 ± 10.1 years ($p = 0.34$; t test). The mean age of total group of CRC patients was 65.4 ± 10.7 years. Tumor grading and staging was performed according to the tumor–node–metastasis (TNM) classification [20]. Patients did not receive chemotherapy or radiation therapy before surgery. Demographic data and disease status of 110 CRC patients are presented in Table 1.

Randomly selected 143 ages and sex matched healthy donors living in the same regions of Bulgaria served as control group. They were without any previous cancer diagnosis. All patients and controls are from the Bulgarian Caucasian ethnic subgroup.

Blood specimens from the patients before surgery and healthy donors were collected in tripotassium EDTA sterile tubes for DNA isolation. For quantitative determination of IGF-1, plasma samples were separated from venous blood and stored at −70 °C until use.

Informed consent was obtained from all subjects and authorization was given by the Ethics Review Board of the Faculty of Medicine, Trakia University, Stara Zagora.

DNA extraction and genotyping for the +3179G/A polymorphism (rs 2229765) by restriction fragment length polymorphism (RFLP)-PCR

Genomic DNA (gDNA) from blood samples was extracted using a column-based blood gDNA purification kit (Amersham Biosciences, Buckinghamshire, UK). The concentration of resulting DNA was measured spectrophotometrically at 260 nm by using NanoVuetm Spectrophotometer 9GE Healthcare, Buckinghamshire, UK. The ratio of absorptions at 260 versus 280 nm was used to assess the purity of DNA samples and stored at −70 °C until use.

To assess the rs2229765 genotype, a gDNA aliquot (about 30–50 ng/μl) was amplified by polymerase chain reaction (PCR) using the following primers: forward 5′-tcttctccagtgtacgttcc-3′ and reverse 5′-ggaactttctctttaccacatg-3′. The cycling parameters for IGF-IR G/A SNP in +3179 were as follows: initial incubation step of 2 min at 95 °C; 35 cycles: 30 s at 94 °C, 30 s at 58 °C, and 30 s at 72 °C and a final extension step of 7 min at 72 °C completed the reaction. The resulting PCR product of 255 bp containing the polymorphic site were digested using 2.5 units of restriction endonuclease *Mnl*I (Fermentas, Latvia) per reaction for 3 h at 37 °C. The rs2229765 genotype was examined after loading the corresponding enzymatic digestions on an agarose gel electrophoresis unit with standard 50 bp DNA marker ladder (Fermentas, Latvia) for instrumental lining-up. In each PCR run, heterozygous control template was used to ensure accuracy. For

Table 1 Demographic data and disease status of CRC patients at the time of diagnosis

	I stage	II stage	III stage	IV stage	Total
Number of patients (%)	15 (13.6)	42 (38.2)	40 (36.4)	13 (11.8)	110 (100)
Male (%)	9 (13.5)	25 (37.3)	22 (32.8)	11 (16.4)	67 (61)
Female (%)	6 (14)	17 (39)	18 (42)	2 (5)	43 (39)
Age (mean ± SD)	58.5 ± 21.5	63.4 ± 10.3	65.3 ± 9.8	63.1 ± 6.9	65.4 ± 10.7

quality control, 10 % of randomly selected samples were analyzed for the second time without finding any discrepancies. PCR amplification was performed in a GeneAmp PCR System 9700 (Applied Biosystems). Kits for PCR reactions were supplied by Fermentas, Latvia.

IGF-1 determination

Enzyme-linked immunosorbent assay (ELISA) was used for measuring IGF-1 in patients and healthy donors. The amounts of IGF-1 were determined in plasma using commercially available Quantikine® Human IGF-1 ELISA kits purchased from R&D Systems (USA) following the manufacturer's instructions. Color reaction developed was measured in OD units at 450 nm on an ELISA reader (Multiskan® EX, Thermo ELECTRON CORPORATION, Finland). The concentration of IGF-1 was determined by using standard curve constructed with kit's standards over the range of 0–6 ng/ml and multiplied by the dilution factor 100. The minimum detectable dose of Quantikine® Human IGF-1 ELISA kit is 0.02 ng/ml.

Statistical analysis

Allele and genotype frequencies were calculated by direct counting. Using an interactive Online Software Package at http://statpages.org/index.html, the statistical significance of the difference was calculated by 2 × 2 table test and Hardy–Weinberg equilibrium was tested for with a goodness of fit χ^2-test with one degree of freedom to compare the observed genotype frequencies among the subjects with the expected genotype frequencies. Comparison of expected frequencies with the values observed was performed using χ^2-test goodness-of-fit test. The odds ratios (OR) and 95 % confidence intervals (CIs) were calculated to assess the relative risk and severity conferred by a particular allele and genotype.

Results

Association of IGF-1R +3179G/A polymorphism with CRC susceptibility and severity

PCR products and restriction fragments were visualized on a 4 % agarose gel stained with ethidium bromide (0.5 mg/ml). The +3179G allele yields four fragments: 132, 80, 23, and 20 bp, respectively; the +3179A allele yields three fragments: 132, 100, and 20 bp (Fig. 1). The genotype distribution and allele frequencies of +3179G/A SNP in IGF-1R gene among CRC patients with respect to disease severity and healthy donors are presented in Table 2. The genotype distribution for IGF-1R +3179G/A polymorphism was in agreement with Hardy–Weinberg equilibrium among cases and controls ($\chi^2 = 1.47$; $p = 0.479$).

Using the OR method was studied the strength of the association between the rs2229765 IGF-1R polymorphism and predisposition to the disease. In the table were represented the assembly ORs for the patient group, relative to the control age and gender matched group of healthy volunteers, that were calculated for the homozygous (GG vs. AA), heterozygous (AG vs. GG) and dominant (GG vs. AG/AA) genetics model of comparison.

It was calculated following genotype frequencies in healthy control (HC) group: GG, 38 %; AG, 47 %; AA, 15 % and respectively in patients with CRC: GG, 29 %; AG, 53 %; AA, 18 %. Although there was no significant association between the *IGF1R* genotypes and susceptibility to CRC in the investigated Bulgarian population it was a trend of higher frequency of dominant AA/AG genotypes (71 %) among cases compared to controls (62 %) with OR = 1.52 but without statistical significance ($p = 0.120$). Further, we investigated the association of +3179 A/G *IGF1R* polymorphisms and progression of CRC. After grading and staging the cases according to TNM classification, we established that dominant genotypes of *IGF1R* polymorphisms was more frequent in patients with stages III and IV (82.5 and 84.6 %, respectively) than patients with I and II stage (47 and 64 %). Moreover the frequency of AA and AG genotypes in the third stage determine the risk of approximately three-fold higher for progression of the disease (OR = 3.37 and 2.81, $p < 0.05$, respectively) compared to homozygous genotype GG. The frequency of A-allele was also significantly higher in CRC stages III versus controls. Next the patient's group was divided to early and advanced stages as follow: I and II stages—early; III and IV stages—advanced. It was confirmed that the presence of A-allele in homo and heterozygous genotypes of patients was significantly associated with advanced stages (OR = 3.12 for AA; OR = 3.37 for AG, $p < 0.05$) compared to early CRC. Moreover,

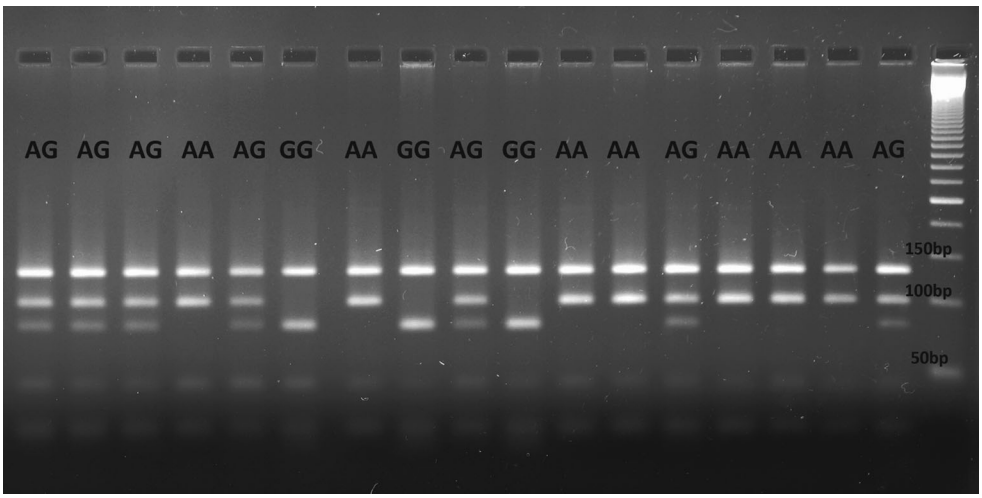

Fig. 1 Genotyping of IGF-1R polymorphism rs2229765 (+3179G>A) on a 4 % agarose gel electrophoresis. The +3179G allele yields four fragments: 132, 80, 23, and 20 bp, respectively the +3179A allele yields three fragments: 132, 100, and 20 bp

differences of A-allele frequencies between advanced and early CRC was also statistically significant (OR = 1.78, $p = 0.035$).

IGF-1R +3179G/A polymorphism and IGF-1 serum levels

Serum IGF-1 levels in groups of CRC patients and controls, distributed by genotype were shown in Fig. 2. The mean of IGF-1 serum level in group of CRC was significantly lower to those in healthy donors (55.31 vs. 68.67; $p = 0.031$). When mean value of serum IGF-1 level of HC was compared to CRC stratified by genotype a significant differences was established for GG genotype alone (44.8 vs. 71.1; $p = 0.007$). The presence of G allele was associated with decreasing IGF-1 levels in both investigated groups, more pronounced in patients' group.

In Fig. 3 are presented data of serum level of IGF-1 of CRC patients in early and advanced stages for each genotype. Decreased level of IGF-1 in CRC patients with GG genotype compared to AG and AA genotypes in CRC group was significant. The lowest level of IGF-1 was detected for genotype GG in both early and advanced CRC and the differences were significant. For patients with AA and AG genotypes were detected approximately the same values for IGF-1 in serum.

Discussion

In this paper we demonstrated that IGF-1R +3179 polymorphism, a synonymous G–A for glutamic acid at aminoacid 1043 (rs2229765), play a role in progression of CRC. This polymorphism has also a functional effect on IGF-1 plasma level in patients with CRC. In particular, patients bearing at least one allele A at the IGF-1 A/G at +3179 site have higher plasma IGF-1 levels and higher risk of developed advanced stages of CRC.

Both epidemiological population-based studies, which showed a correlation between circulating IGF-1 levels and cancer risk, and laboratory-based research performed by a number of investigators, which showed that IGFs can promote the growth of cancer cells provided validation for the relevance of IGF signaling in colorectal carcinogenesis [21]. The central components of the IGF system and the main subject of this paper are the IGF-1R, a type 2 tyrosine kinase receptor that is synthesized as a single-chain 1367-amino acid pre-propeptide from IGF-1R gene, which is located on chromosome 15q26.3 [22]. Activation of IGF-1/IGF-1R signaling pathway has been shown to affect proliferation, differentiation, migration and apoptosis of cancer cells. This suggests an important role in CRC development and validates this pathway as a potential therapeutic target [5, 23, 24]. Overexpression of the IGF1-R has been identified as a hallmark of CRC progression by means of Northern blotting, immunohistochemistry and real time PCR [25, 26].

To evaluate the role of IGF pathway-related genes in CRC most studies investigated genetic variation within the IGF1 and the IGFBPs genes for CRC risk. Morimoto et al. examined the relationship of two common genetic polymorphisms in IGF-1 (a cytosine–adenosine dinucleotide repeat) and IGFBP-3 (a G → C SNP) with CRC risk [10]. There was evidence that IGF-1 genotype modified the relationship between body-mass index BMI and CRC among women, in such way that high BMI increased risk of CRC only among those with the 19/19 genotype. In the

Table 2 Genotype, allele distribution and odd ratio (OR) of the IGF-1R gene polymorphism SNP+3179G/A (rs2229765) in CRC patients and healthy controls (HC)

		AA	AG	AA/AG	GG	A	G
Early CRC (stage I–II)	57 (51.8 %)	9 (15.8 %)	25 (43.8 %)	34 (59.6 %)	23 (40.4 %)	43 (37.7 %)	71 (62.3 %)
OR (95 % CI)	–	1.02 (0.37–2.81)	0.89 (0.43–1.84)	0.92 (0.47–1.81)	1.0 (reference)	0.98 (0.61–1.58)	1.0 (reference)
p value	–	*0.958*	*0.738*	*0.805*		*0.942*	
						$^{F}p = 1.000$	
Advanced CRC (stage III–IV)	53 (48.2 %)	11 (20.7 %)	33 (62.3 %)	44 (83 %)	9 (17 %)	55 (52 %)	51 (48 %)
OR (95 % CI)	–	**3.20 (1.04–9.97)**	**3.01 (1.25–7.44)**	**3.06 (1.31–7.32)**	1.0 (reference)	**1.75 (1.09–2.82)**	1.0 (reference)
p value	–	***0.021***	***0.007***	***0.004***		***0.014***	
						$^{F}p = 0.015$	
CRC	**110 (100 %)**	**20 (18 %)**	**58 (53 %)**	**78 (71 %)**	**32 (29 %)**	**98 (45 %)**	**122 (55 %)**
OR (95 % CI)	–	**1.63 (0.72–3.72)**	**1.48 (0.82–2.71)**	**1.52 (0.86–2.68)**	**1.0 (reference)**	**1.3 (0.89–1.89)**	**1.0 (reference)**
p value	–	***0.197***	***0.163***	***0.120***		***0.145***	
						$^{F}p = 0.146$	
Healthy controls	**143 (100 %)**	**21 (15 %)**	**67 (47 %)**	**88 (62 %)**	**55 (38 %)**	**109 (38 %)**	**177 (62 %)**
Early versus advanced		**0.32 (0.08–1.19)**	**0.29 (0.10–0.82)**	**0.30 (0.11–0.80)**	1.0 (reference)	**0.56 (0.32–0.99)**	1.0 (reference)
		p = 0.053	***p = 0.009***	***p = 0.007***		***p = 0.035***	
						$^{F}p = 0.041$	
Advanced versus early		**3.12 (0.84–12.01)**	**3.37 (1.21–9.54)**	**3.31 (1.25–8.91)**	1.0 (reference)	**1.78 (1.01–3.16)**	1.0 (reference)
		p = 0.053	***p = 0.009***	***p = 0.007***		***p = 0.035***	
						$^{F}p = 0.041$	
Early versus CRC		0.63 (0.22–1.79)	0.60 (0.28–1.30)	0.61 (0.30–1.25)	1.0 (reference)	0.75 (0.46–1.23)	1.0 (reference)
		p = 0.333	*p = 0.158*	*p = 0.142*		*p = 0.231*	
						$^{F}p = 0.244$	
Advanced versus CRC		1.95 (0.61–6.32)	2.02 (0.80–5.21)	2.01 (0.82–4.99)	1.0 (reference)	1.34 (0.82–2.20)	1.0 (reference)
		p = 0.204	*p = 0.102*	*p = 0.095*		*p = 0.213*	
						$^{F}p = 0.236$	

The significant value of OR and 95 % CI is indicated in bold

$p < 0.05$ is indicated in italics

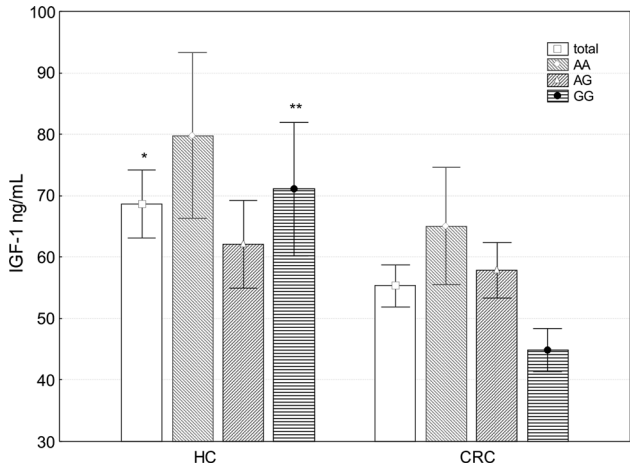

Fig. 2 Serum IGF-1 levels in groups of CRC patients and age-matched healthy donors (HC), distributed by genotype of +3179G>A IGF-1R polymorphism. The results are presented as mean value ± SE. $^{*}p < 0.05$; $^{**}p < 0.001$

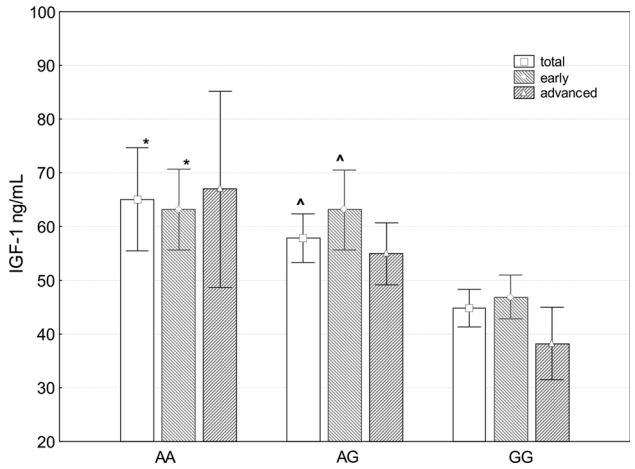

Fig. 3 Serum IGF-1 levels in groups of CRC patients according to +3179G>A IGF-1R genotypes and disease activity: early stages (I + II) and advanced stages (III + IV) of CRC. The results are presented as mean value ± SE. $^{*}p < 0.05$ AA versus GG; $^{\wedge}p < 0.05$ AG versus GG

same direction are studies of Wong et al. which have examined polymorphisms in the *IGF-I* and *IGFBP3* genes in relation to plasma levels of the respective gene products and in relation to CRC risk in a case–control study nested within a prospective cohort of 63,257 Singapore Chinese [9, 13]. Zecevic et al. indicated a statistically significant association between shorter IGF1 CA-repeat lengths and increased risk for CRC in hereditary non-polyposis CRC [11]. In contrast Pechlivanis et al. did not find any association between the CA repeat length of the two SNPs in the IGF1 (rs35767 and rs7136446) and four SNPs in the IGFBP3 genes and the risk of CRC [14].

Compared to the large number of genetic association studies for polymorphisms of IGF1 and the IGFBPs genes data on IGF1R polymorphisms are scarce. Le Roy et al. investigated 521 SNPs in 18 IGF pathway related genes including 2 SNP in IGF1R (rs7166348 and rs496601) [17]. Their analysis indicates that one SNP in IGF1R (rs7166348) was the optimal first split, and probability of colorectal neoplasia was greatest among carriers of any A allele for rs7166348 in IGF-1R. Our finding that another SNP in IGF1R gene (rs2229765) is implicated in CRC development confirms a pivotal role of IGF-1R signaling in CRC. The IGF1R has also been reported to form heterodimers with the HER2/ERBB2/NEU tyrosine kinase and to contribute to the development of resistance to HER2 inhibition with the monoclonal antibody trastuzumab [27, 28]. Recently published data demonstrates that IGF1R polymorphisms are potential predictive and prognostic molecular markers for cetuximab efficacy in wt KRAS mCRC patients [29, 30].

Our result showed that IGF1-R +3179A/G polymorphism is associated with circulating IGF-1 in CRC patients where dominant genotypes (AA homozygous and heterozygous) exhibit significantly higher quantity of plasma IGF-1 compared to GG genotype. Simultaneously the probability of advanced CRC was greatest among carriers of any A allele for rs2229765. We are not the first ones to hypothesize that genetic variation in IGF1R influences plasma IGF-1 levels. Bonafe et al. reported that healthy elderly subjects who carried AA genotype of the +3179 A/G in IGF1-R, had lower levels of free plasma IGF-1 and are more represented among long-lived people [18]. Few years later, Albani et al. confirmed the importance of the +3179 A allele in IGF1-R for male longevity and plasma IGF-1 level, which dropped significantly after 85 years of age [19].

Two meta-analysis studies support a significant elevated risk for CRC (approximately 30 %) among individuals with the highest IGF-1 levels compared with individuals with the lowest concentrations [6, 7]. Our results are in accordance with these observations and contribute to a better understanding of the role of IGF-1 in CRC development. They have demonstrated that enhanced plasma IGF-1 supports the progression of CRC from early to advanced stages. Previous studies reveal that at an early stage certain tumor cells exhibit growth factor dependence progression [3, 4]. For example strong and statistically significant upregulated IGF-1R mRNA expression was found only for the group of early stages of CRC [25, 26]. At these early stages, IGF-I activates the MAP kinase pathway, which triggers proliferation, and the PI3 kinase pathway, which promotes cell survival and stabilization of β-catenin [1–6, 29, 30]. In summary IGF1 is a potent mitogenic activator via the Ras/Raf/mitogen-activated protein kinase signaling pathway and a powerful

antiapoptotic molecule through the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and thus favors tumor progression. Our results for enhanced level of IGF-1 in CRC patients with dominant genotype (AA and AG) and significant association of progression to advanced stages are in the same direction. Moreover IGF-I may also contribute to higher invasive and metastatic potential of colon cancer cells due to its effects on cell motility, migration and VEGF expression [31–34].

Some limitations of the present study should be addressed. The number of patients is relatively small notably when they were divided into stages thus, caution should be adopted when explaining our results. For this reason we divided patient groups into two (early and advanced cancer) instead to four groups for final discussion. Further investigations are necessary in order to confirm the significance of the +3179 A/G in IGF1R in CRC progression and applications of data for clinical practice.

In conclusion the results of this study support the role of genetic polymorphism in the IGF pathway genes, particularly the +3179 A/G in IGF1R in CRC development. Data included in this paper suggest that investigated functional polymorphism of the IGF1R gene (rs2229765) participates in the maintenance of CRC progression rather than in its initial development. This effect is mediated partly by plasma level of IGF-1.

Acknowledgments This work was supported by Grant N: 4/2012 from the Fund for Scientific and Mobile project from Faculty of Medicine at the Trakia University, Stara Zagora, Bulgaria.

References

1. Dupont J, Pierre A, Froment P, Moreau C (2003) The insulin-like growth factor axis in cell cycle progression. Horm Metab Res 35:740–750
2. Baserga R, Hongo A, Rubini M, Prisco M, Valentinis B (1997) The IGF-I receptor in cell growth, transformation and apoptosis. Biochim Biophys Acta 1332:F105–F126
3. Baserga R, Peruzzi F, Reiss K (2003) The IGF-1 Receptor in cancer biology. Int J Cancer 107:873–877
4. LeRoith D, Roberts CT (2003) The insulin-like growth factor system and cancer. Cancer Lett 195:127–137
5. Durai R, Yang W, Gupta S, Seifalian AM, Winslet MC (2005) The role of the insulin-like growth factor system in colorectal cancer: review of current knowledge. Int J Colorectal Dis 20:203–220
6. Morris JK, George LM, Wu T, Wald NJ (2006) Insulin-like growth factors and cancer: no role in screening. Evidence from the BUPA study and meta-analysis of prospective epidemiological studies. Br J Cancer 95:112–117
7. Chen W, Wang S, Tian T, Bai J, Hu Z, Xu Y, Dong J, Chen F, Wang X, Shen H (2009) Phenotypes and genotypes of insulin-like growth factor 1, IGF-binding protein-3 and cancer risk: evidence from 96 studies. Eur J Hum Genet 17:1668–1675
8. Slattery ML, Murtaugh M, Caan B, Ma KN, Neuhausen S, Samowitz W (2005) Energy balance, insulin-related genes and risk of colon and rectal cancer. Int J Cancer 115:148–154
9. Wong HL, Delellis K, Probst-Hensch N, Koh WP, van den Berg D, Lee HP, Yu MC, Ingles SA (2005) A new single nucleotide polymorphism in the insulin-like growth factor I regulatory region associates with colorectal cancer risk in Singapore Chinese. Cancer Epidemiol Biomarkers Prev 14:144–151
10. Morimoto LM, Newcomb PA, White E, Bigler J, Potter JD (2005) Insulin-like growth factor polymorphisms and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 14:1204–1211
11. Zecevic M, Amos CI, Gu X, Campos IM, Jones JS, Lynch PM, Rodriguez-Bigas MA, Frazier ML (2006) IGF1 gene polymorphism and risk for hereditary nonpolyposis colorectal cancer. J Natl Cancer Inst 98:139–143
12. Reeves SG, Rich D, Meldrum CJ, Colyvas K, Kurzawski G, Suchy J, Lubinsky J, Scott RJ (2008) IGF1 is a modifier of disease risk in hereditary non-polyposis colorectal cancer. Int J Cancer 123:1339–1443
13. Wong HL, Koh WP, Probst-Hensch NM, van den Berg D, Yu MC, Ingles SA (2008) Insulin-like growth factor-1 promoter polymorphisms and colorectal cancer: a functional genomics approach. Gut 57:1090–1096
14. Pechlivanis S, Wagner K, Chang-Claude J, Hoffmeister M, Brenner H, Försti A (2007) Polymorphisms in the insulin like growth factor 1 and IGF binding protein 3 genes and risk of colorectal cancer. Cancer Detect Prev 31:408–416
15. Feik E, Baierl A, Hieger B, Fuhrlinger G, Pentz A, Stattner S, Weiss W, Pulgram T, Leeb G, Mach K, Micksche M, Gsur A (2010) Association of IGF1 and IGFBP3 polymorphisms with colorectal polyps and colorectal cancer risk. Cancer Causes Control 21:91–97
16. Ollberding NJ, Cheng I, Wilkens LR, Henderson BE, Pollak MN, Kolonel LN, Marchand L (2012) Genetic variants, prediagnostic circulating levels of insulin-like growth factors, insulin, and glucose and the risk of colorectal cancer: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev 21:810–820
17. LeRoy EC, Moore JH, Hu C, Martinez ML, Lance P, Duggan D, Thompson PA (2011) Genes in the insulin and insulin-like growth factor pathway and odds of metachronous colorectal neoplasia. Hum Genet 129:503–512
18. Bonafe M, Barbieri M, Marchegiani F, Olivieri F, Ragno E, Glampieri C et al (2003) Polymorphic variants of insulin-growth factor I receptor (IGF-IR) and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: cues for evolutionary conserved mechanism of life span control. J Clin Endocrinol Metab 88:3299–3304
19. Albani D, Batelli S, Polito L, Vittori A, Pesaresi M, Gajo GB (2009) A polymorphic variant of the insulin-like growth factor 1 (IGF-1) receptor correlates with male longevity in the Italian population: a genetic study and evaluation of circulating IGF-1 from the "Treviso Longeva (TRELONG)" study. BMC Geriatr 9:19–26
20. Jessup JM, Gunderson LL, Greene FL et al (2002) Colon and rectum. In: Greene FL, Page AL, Fleming ID et al (eds) AJCC cancer staging manual, 6th edn, pp 113–124. Springer, New York
21. Donovan EA, Kummar S (2008) Role of insulin-like growth factor-1R system in colorectal carcinogenesis. Crit Rev Oncol/Hematol 66:91–98
22. Abbott AM, Bueno R, Pedrini MT, Murray JM, Smith RJ (1992) Insulin-like growth factor I receptor gene structure. J Biol Chem 267:10759–10763
23. Baserga R (2005) The insulin-like growth factor-I receptor as a target for cancer therapy. Expert Opin Ther Targets 9:753–768
24. Tao Y, Pinzi V, Bourhis J, Deutsch E (2007) Mechanisms of disease: signaling of the insulin-like growth factor 1 receptor pathway—therapeutic perspectives in cancer. Nat Clin Pract Oncol 4:591–602
25. Allison AS, McIntyre MA, McArdle C, Habib FK (2007) The insulin-like growth factor type 1 receptor and colorectal neoplasia: insights into invasion. Hum Pathol 38:1590–1602

26. Karakolev I, Stanilov N, Miteva L, Jovchev J, Dobreva Z, Stanilova S (2012) Expression of IGF-1R mRNA in colorectal carcinoma patients. Biotechnol Biotechnol Equipment 26:89–95
27. Lu Y, Zi X, Zhao Y, Mascarenhas D, Pollak M (2001) Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). J Natl Cancer Inst 93:1852–1857
28. Nahta R (2012) Deciphering the role of Insulin-like growth factor-I receptor in transtuzumab resistance. Chemother Res Pract. doi: 10.1155/2012/648965
29. Winder T, Zhang W, Yang D, Ning Y, Bohanes P, Gerger A, Wilson PM, Pohl A, Mauro DJ, Langer C, Rowinsky EK, Lenz HJ (2010) Germline polymorphisms in genes involved in the IGF1 predict efficacy of cetuximab in wild-type KRAS mCRC patients pathway. Clin Cancer Res 16:5591–5602
30. Li R, Pourpak A, Morris S (2009) Inhibition of the insulin-like growth factor-1 receptor (IGF1R) tyrosine kinase as a novel cancer therapy approach. J Med Chem 52:4981–5004
31. Andre F, Rigot V, Thimonier J, Montixi C, Parat F, Pommier G, Marvaldi J, Luis J (1999) Integrins and E-cadherin cooperate with IGF-I to induce migration of epithelial colonic cells. Int J Cancer 83:497–505
32. Akagi Y, Liu W, Zebrowski B, Xie K, Ellis LM (1998) Regulation of vascular endothelial growth factor expression in human colon cancer by insulin-like growth factor-I. Cancer Res 58:4008–4014
33. Bauer TW, Fan F, Liu W, Johnson M, Parikh N, Parry G et al (2005) Insulin like growth factor-I-mediated migration and invasion of human colon carcinoma cells requires activation of c-Met and urokinase plasminogen activator receptor. Ann Surg 241:748–758
34. Chang C-H, Wang Y, Trisal P, Li R, Rossi DL, Nair A et al (2012) Evaluation of a novel hexavalent humanized anti-IGF-1R antibody and its bivalent parental IgG in diverse cancer cell lines. PLoS ONE 7(8):e44235. doi:10.1371/journal.pone.0044235