J Hum Genet (2008) 53:227–238
DOI 10.1007/s10038-007-0241-3

ORIGINAL ARTICLE

IGF-I (CA) repeat polymorphisms and risk of cancer: a meta-analysis

Xin Chen · Jianming Guan · Yuting Song · Peilin Chen · Hongxia Zheng · Cheng Tang · Qihan Wu

Received: 23 August 2007 / Accepted: 13 December 2007 / Published online: 10 January 2008

Abstract Insulin-like growth factor-I modulates cell growth and survival, and is thought to be important in tumor development. A (CA)19 repeat polymorphism in the promoter region of *IGF-I* gene that may affect transcription activity has been implicated as a risk factor for cancer, but individual studies have been inconclusive or controversial. Therefore, we performed a meta-analysis of 17 studies with IGF-I (CA)19 repeat genotyping on 8,799 patients and 13,901 controls. There were seven studies with prostate cancer (2,307 cases; 2,622 controls), seven studies with breast cancer (3,533 cases; 7,771 controls), and three studies with colorectal cancer (2,959 cases; 3,508 controls). Overall, the random effects odds ratio (OR) for the (CA)19 versus non-(CA)19 allele was 1.03 [95% confidence interval (CI), 0.95–1.11], with some between-study heterogeneity ($P < 0.0001$). There was no suggestion of an overall effect either in recessive or dominant modeling of (CA)19 allele effects, and the comparison of (CA)19 homozygosity versus non-(CA)19 homozygosity also showed no differential susceptibility to cancer (OR, 0.99; 95% CI, 0.84–1.16). No effect of (CA)19 was seen in subjects of breast cancer (seven comparisons, OR = 1.03; 95% CI, 0.90–1.17, $P = 0.005$ for heterogeneity), prostate cancer (seven comparisons, OR = 1.08; 95% CI, 0.88–1.27; $P = 0.0002$ for heterogeneity) and colorectal cancer (three comparisons, OR = 0.96; 95% CI, 0.89–1.03, $P = 0.36$, no significant between-study heterogeneity). There was also no evidence that the (CA)19 allele associated with the risk of cancer in Caucasians and Asians. The meta-analysis shows that this (CA)19 repeat polymorphism is unlikely to be a major determinant of susceptibility to cancer on a wide population basis. However, a larger single study is required to further evaluate the association IGF-I (CA)19 polymorphisms and the cancer risk in a specific population.

Keywords IGF-I · Cancer · Polymorphism · Meta-analysis

X. Chen · P. Chen · H. Zheng · C. Tang · Q. Wu (✉)
Laboratory of Gene Function, School of Life Science, East China Normal University, 200062 Shanghai, People′s Republic of China
e-mail: qhwu@bio.ecnu.edu.cn

J. Guan
Department of Urology, Shanghai Minghang District Central Hospital, Shanghai, People′s Republic of China

Y. Song
School of Life Science, Fudan University, Shanghai, People's Republic of China

Introduction

Tumor is one of deadly diseases of mankind. Up to now, the detailed mechanisms of cancer remain largely unknown. As cellular proliferation is central to the carcinogenic process, pathways that regulate and control cell growth are undoubtedly important to the etiology of cancer (Neuhausen et al. 2005). The insulin-like growth factor signaling pathway is one such pathway. At the same time, there are many articles that report that genetic polymorphism was associated with susceptibility to cancer. Genetic polymorphisms are natural variations in the genomic DNA sequence present in more than 1% of the population (Yang and Roden 2003). Also, some genetic polymorphisms have been proved to play important roles in susceptibility to cancer.

Insulin-like growth factor I (IGF-I) is a member of the large family of insulin-related peptides that includes insulin, IGF-I and IGF-II, and is one of the most well-characterized growth factors (Daughaday and Rotwein

1989; LeRoith and Raizada 1993). It is primarily produced by the liver and plays an important role in the regulation of cell proliferation, differentiation, and apoptosis with a recognized effect on tumor growth (Pollak 2000a, b; Parrizas and LeRoith 1997). Epidemiological studies have offered hints that high levels of IGF-I might be a risk factor for cancer. Results of early studies on the risk of prostate (Chan et al. 1998), breast (Hankinson et al. 1998), colorectal (Ma et al. 1999), lung (Yu et al. 1999), and cervical (Schaffer et al. 2007) cancer suggest that high circulating IGF-I concentrations are associated with an increased risk of cancer. Recent meta-analyses, done separately by cancer site and comparing uppermost versus lowermost categories, show that *IGF-I* is associated with increased risk of prostate cancer, colorectal cancer, and premenopausal breast cancer, but not with postmenopausal breast cancer or lung cancer (Renehan et al. 2004). Despite the number of factors that can influence IGF-I levels, it has been estimated that up to 60% of the variability has a genetic basis (Harrela et al. 1996; Hong et al. 1996).

A known genetic cytosine-adenine (CA) repeat polymorphism in the human *IGF-I* gene has been the focus of many recent studies because it is proximate to the promoter, at 1 kb upstream from the transcription start site (Rotwein et al. 1986; Weber et al. 1989). This polymorphism might be associated with circulating IGF-I levels. But several clinical studies have not revealed consistent evidence for the association between the (CA) repeat polymorphism and circulating IGF-I levels (Rosen et al. 1998; Jernstrom et al. 2001a, b; Vaessen et al. 2001; Missmer et al. 2002; Allen et al. 2002; Frayling et al. 2002). Some studies have shown an association between high serum IGF-I levels and the most common *IGF-I* allele that had a length of (CA)19 repeats (Vaessen et al. 2001; Rietveld et al. 2003), while other studies report the reverse results (Jernstrom et al. 2001a, b; Rosen et al. 1998).

Some studies were conducted to investigate the association between the (CA) repeat polymorphism of *IGF-I* and the susceptibility to prostate, breast, and colorectal cancer (Missmer et al. 2002; Yu et al. 2001; Wen et al. 2005; DeLellis et al. 2003; Wagner et al. 2005; Cleveland et al. 2006; Figer et al. 2002; González-Zuloeta et al. 2007; Tsuchiya et al. 2005; Li et al. 2004; Friedrichsen et al. 2005; Neuhausen et al. 2005; Schildkraut et al. 2005; Chen et al. 2006; Nam et al. 2003; Morimoto et al. 2005; Wong et al. 2005; Slattery et al. 2004, 2005). Like the association between the (CA) repeat polymorphism and circulating IGF-I levels, results from these studies have been inconsistent, and the reasons underlying heterogeneous results, including study populations, and designs and assay characteristics need to be further investigated.

Here, we performed a meta-analysis from all eligible case-control studies to address the association of *IGF-I* (CA)19 polymorphisms to cancer. We also performed meta-analysis in detailed cancer and different populations.

Materials and methods

Identification and eligibility of relevant studies

To identify all articles that examined the association of *IGF-I* (CA) repeat polymorphism with cancer, we conducted a literature search of the PubMed database using the following keywords and subject terms: "prostate," "colorectal," "lung," "breast," "cervical," "cancer," "polymorphism*," and "insulin-like growth factor-I." References to retrieved articles were screened. Abstracts, case reports, editorials, and review articles were excluded. Studies included in the current meta-analysis had to meet all the following criteria: (1) use a case-control design and (2) the genotype distribution of the control population must be in Hardy–Weinberg equilibrium (HWE).

Data extraction

Data were independently abstracted in duplicate by two investigators using a standard protocol and data-collection form. Data were collected on the genotype according to different kinds of cancers. Characteristics abstracted from the studies included the name of the first author, location of the study, year of publication, ethnicity of the study population, and characteristics of cases and control selection criteria.

Statistical analysis

The meta-analysis examined the overall association of the *IGF-I* allele (CA)19 with the risk of prostate, breast, and colorectal cancer, the contrast of homozygote(CA)19 versus non-(CA)19, the recessive ((CA)19/(CA)19 versus (CA)19/non-(CA)19 + non(CA)19/non-(CA)19) and dominant ((CA)19/(CA)19+(CA)19/non-(CA)19 versus non-(CA)19/-non(CA)19)) models to allele (CA)19.

Odds ratios (OR) corresponding to 95% confidence interval (CI) was applied to assess the strength of association of *IGF-I* with prostate, breast, and colorectal cancer since case-control studies were used, and OR was calculated according to the method of Woolf (Woolf 1955). A chi-square based Q statistic test was performed to assess the between-study heterogeneity (Lau et al. 1997). Heterogeneity was considered significant for $P < 0.10$ because of the low power of the statistic. A fixed-effect model using the Mantel–Haenszel method and a random-effects model

using the DerSimonian and Laird method were used to pool the results (Petitti 1994). In the absence of between-study heterogeneity, the two methods provide similar results. Random effects are more appropriate when heterogeneity is present. The significance of the pooled OR was determined by the Z test; a P value of <0.05 was considered significant. For each genetic contrast, *IGF-I* subgroup analysis according to ethnicity was only considered for Caucasian and Asian populations to estimate ethnic-specific OR and had at least three independent studies.

Publication bias was investigated by funnel plot, in which the standard error of log (OR) of each study was plotted against its OR. An asymmetric plot suggested possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR (Egger et al. 1997). The significance of the intercept was determined by the t test as suggested by Egger, and a P value of <0.05 was considered significant.

Hardy–Weinberg equilibrium was tested by the chi-square test for goodness of fit using a web-based program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Analyses were performed using the software Stata version 9, ReviewManage 4.2. All P values were two-sided.

Result

Eligible studies

Nineteen articles were retrieved based on the searching criteria for cancer susceptibility related to *IGF-I* (CA) repeat polymorphisms (Missmer et al. 2002; Yu et al. 2001; Wen et al. 2005; DeLellis et al. 2003; Wagner et al. 2005; Cleveland et al. 2006; Figer et al. 2002; González-Zuloeta et al. 2007; Tsuchiya et al. 2005; Li et al. 2004; Friedrichsen et al. 2005; Neuhausen et al. 2005; Schildkraut et al. 2005; Chen et al. 2006; Nam et al. 2003; Morimoto et al. 2005; Wong et al. 2005; Slattery et al. 2004, 2005), and 17 met our inclusion criteria. One article was not included because the genotype distribution in the control population significantly deviates from HWE (Missmer et al. 2002). One article was replaced with its updated study (Slattery et al. 2004). Seven of the 17 eligible articles investigated prostate cancer (Tsuchiya et al. 2005; Li et al. 2004; Friedrichsen et al. 2005; Neuhausen et al. 2005; Schildkraut et al. 2005; Chen et al. 2006; Nam et al. 2003), seven studies investigated breast cancer (Yu et al. 2001; Wen et al. 2005; DeLellis et al. 2003; Wagner et al. 2005; Cleveland et al. 2006; Figer et al. 2002; González-Zuloeta et al. 2007), and three studies investigated colorectal cancer (Morimoto et al. 2005; Wong et al. 2005; Slattery et al. 2005). No detailed genotype data were available in the 3 of the 17 eligible articles (Yu et al. 2001; Figer et al. 2002; Li et al. 2004). All eligible studies that evaluated *IGF-I* (CA) repeat polymorphisms to cancer susceptibility were on the basis of (CA)19 allele versus non-(CA)19 allele. In addition, some of these eligible studies not only reported the distribution of the number of (CA) repeat, but also analyzed (CA)17 or (CA)21 allele to cancer susceptibility (Wen et al. 2005; Wong et al. 2005). Overall, *IGF-I* (CA)19 allele was the most prevalent allele in both the patients and the controls. Therefore, we performed a meta-analysis about the association of *IGF-I* (CA)19 polymorphisms to cancer. There was a considerable diversity of ethnic groups. Nine of the 17 eligible articles represent studies with a Caucasian population (Wagner et al. 2005; Cleveland et al. 2006; Figer et al. 2002; Li et al. 2004; Friedrichsen et al. 2005; Neuhausen et al. 2005; Schildkraut et al. 2005; Chen et al. 2006; Nam et al. 2003), and 5 of the 9 show detailed allele information (Wagner et al. 2005; Cleveland et al. 2006; Figer et al. 2002; Schildkraut et al. 2005; Chen et al. 2006). In study populations with Asians, detailed allele information was available in three eligible articles (Wen et al. 2005; Tsuchiya et al. 2005; Wong et al. 2005). Hence, we also performed meta-analysis in Caucasian and Asian populations, respectively. Among the 17 eligible articles included, 82% (14/17) stated that the age and sex status were matched between case and control populations. Studies provided genotyping data of mixed population indicated as "unknown" ethnic (Table 1). Two studies were different from the others because they used a related case-control design (Wagner et al. 2005; Li et al. 2004). We excluded the two studies when doing sensitivity analysis. But the overall effect of the (CA)19 on the cancer risk did not change.

Meta-analysis database

The eligible studies included a total of 8,799 patients and 13,901 controls of whom 8,038 and 13,225, respectively, had genotype data. A total of 3,533 patients and 7,771 controls for breast cancer, 2,307 patients and 2,622 controls for prostate cancer, and 2,959 patients and 3,508 controls for colorectal cancer were investigated. Table 2 shows both genotype and allele frequencies of cancer patients and controls in the eligible studies. Overall, the prevalence of (CA)19 allele was 56.9 and 57.4% in all patients and controls. The prevalence rate of (CA)19 allele across the controls of Caucasian and Asian descent were 65.5 and 33.3%, respectively. The result indicated that the distribution of (CA)19 allele frequency had a significant difference in Caucasian and Asian populations. The (CA)19 allele was more highly represented among the cases of colorectal cancer (60.2%) than in the

Table 1 Characteristics of studies included in the meta-analysis

First author(year)	Country	Selection/characteristics of cases	Selection/characteristics of controls	Cases	Controls
Prostate cancer					
Chen (2006)	USA	Cases had either a registry-confirmed diagnosis of prostate cancer or had documentation of prostate cancer by both self-report and a hospital discharge diagnosis code in CHS records	Controls were individually matched to cases on race, year of entry, age at enrollment (within 4 years), and clinic. No documentation of prostate cancer	213	213
Friedrichsen (2005)	USA	Histologically confirmed adenocarcinoma of the prostate diagnosed	Controls with respect to age, race, family history of prostate cancer matched cases	591	538
Neuhausen (2005)	USA	Prostatectomy-documented cancer	Race, age-matched (within 5 years of birth year) with no previous history of prostate cancer	199	267
Schildkraut (2005)	USA	Newly diagnosed prostate cancer cases by searching DVAMC electronic surgical pathology records	Controls were frequency matched to the cases based on 5-year age groups and race	100	93
Tsuchiya (2005)	Japan	Patients with BPH, total PSA levels (>4.0 ng/ml by the tandem-R assay)	Normal serum PSA levels, race matched, without any apparent voiding symptoms	303	262
Nam (2003)	Canada	Either a PSA value >4.0 ng/ml or an abnormal DRE. No patient had a history of prostate cancer before prostate biopsy	No evidence of cancer	483	804
Li (2004)	USA	From 414 discordant families, sibling sets consisted of probands with CaP diagnosed at age 73 or younger and at least one brother without CaP	From 414 discordant families	440	480
Breast cancer					
Wen (2005)	China	Cases were identified through a rapid case-ascertainment system	Randomly selected from the general female population in Shanghai and frequency-matched to cases on age (5-year interval)	1,041	1,086
Wagner (2005)	Poland, Finland	Familial breast cancer cases	Randomly matched controls	787	900
Cleveland (2006)	USA	Cases were confirmed by the physician and medical records, and diagnosed invasive breast cancer	Frequency matched by 5-year age group to the expected age distribution of cases, under 65 years of age	1,028	1,086
Figer (2002)	Israel	With histopathologically proven breast cancer	No information regarding family history of cancer, randomly sampled subjects	268	144
Yu (2001)	USA	Patients had a histologically confirmed diagnosis	The controls were matched to the cases at a 1:1 ratio on age (±5 years) and race	53	53
DeLellis (2003)	Hawaii	Case ascertainment was completed through the surveillance, epidemiology and end results (SEER) cancer registries in Hawaii and Los Angeles	Randomly selected from a large multiethnic cohort study in in Hawaii and Los Angeles	220	373
González-Zuloeta (2007)	The Netherlands	Only identified cases that had also been pathologically confirmed were considered valid	Randomly selected from a suburb of Rotterdam aged 55 or older	203	3,978

Table 1 continued

First author(year)	Country	Selection/characteristics of cases	Selection/characteristics of controls	Cases	Controls
Colorectal cancer					
Slattery (2005)	USA	No previous history of colorectal cancer, no known familial adenomatous polyposis, ulcerative colitis, or Crohn's disease, between ages 30 and 79 years	Controls were matched to cases by sex and by 5-year age groups, colon cancer and rectal cancer	1,947	2,156
Wong (2005)	China	Histologic information on each colorectal cancer diagnosis was confirmed by reviewing the pathology report	Randomly sampled subjects	290	873
Morimoto (2005)	USA	Cases included all male and female residents ages 20–74 years diagnosed with incident invasive colon or rectal cancer	Randomly sampled subjects	722	479

Table 2 Distribution of (CA)19 genotype and allele among breast, prostate, colorectal cancer cases and controls included in the meta-analysis

First author(year)	Racial descent	Genotype						Allele			
		(CA)19 homozygosity		(CA)19 heterozygosity		Non-(CA)19 homozygosity		(CA)19		Non-(CA)19	
		Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Breast cancer											
Wen (2005)	Chinese	142	133	510	497	389	456	794	763	1,288	1,409
Wagner (2005)	Polish, Finnish	231	440	312	517	101	138	774	1,397	514	793
Cleveland (2006)	Caucasian	405	449	456	464	143	129	1,266	1,362	742	722
Figer (2002)	Jewish	NA[a]	NA	NA	NA	NA	NA	373	186	163	102
Yu (2001)	Unknown	NA	NA	NA	NA	NA	NA	33	23	73	83
DeLellis (2003)	Hawaii/Los Angeles multi-ethnic	97	98	153	180	70	95	347	376	293	370
González-Zuloeta (2007)	Unknown	86	1,744	69	1,404	48	830	241	4,892	165	3,064
Prostate cancer											
Chen (2006)	Caucasian, African American.	79	75	96	97	38	41	254	247	172	179
Friedrichsen (2005)	Caucasia, African American.	219	219	289	237	73	64	727	675	435	365
Neuhausen (2005)	Non-Hispanic Caucasian	78	107	86	124	29	32	242	338	144	188
Tsuchiya (2005)	Blacks, whites	18	6	130	82	155	174	166	94	440	430
Schildkraut (2005)	Japanese	20	28	39	33	35	20	79	89	109	73
Nam (2003)	Caucasian, black, Asian	189	275	230	373	64	156	608	923	358	685
Li (2004)	African-American, Hispanic, Asian-American, Caucasian	NA	NA	NA	NA	NA	NA	548	586	332	372
Colorectal cancer											
Slattery (2005)	Unknown	760	878	915	983	272	295	2,435	2,739	1,459	1,573
Wong (2005)	Chinese	35	121	145	378	110	374	215	620	365	1,126
Morimoto (2005)	Unknown	296	217	325	201	101	61	917	635	527	323

NA not available

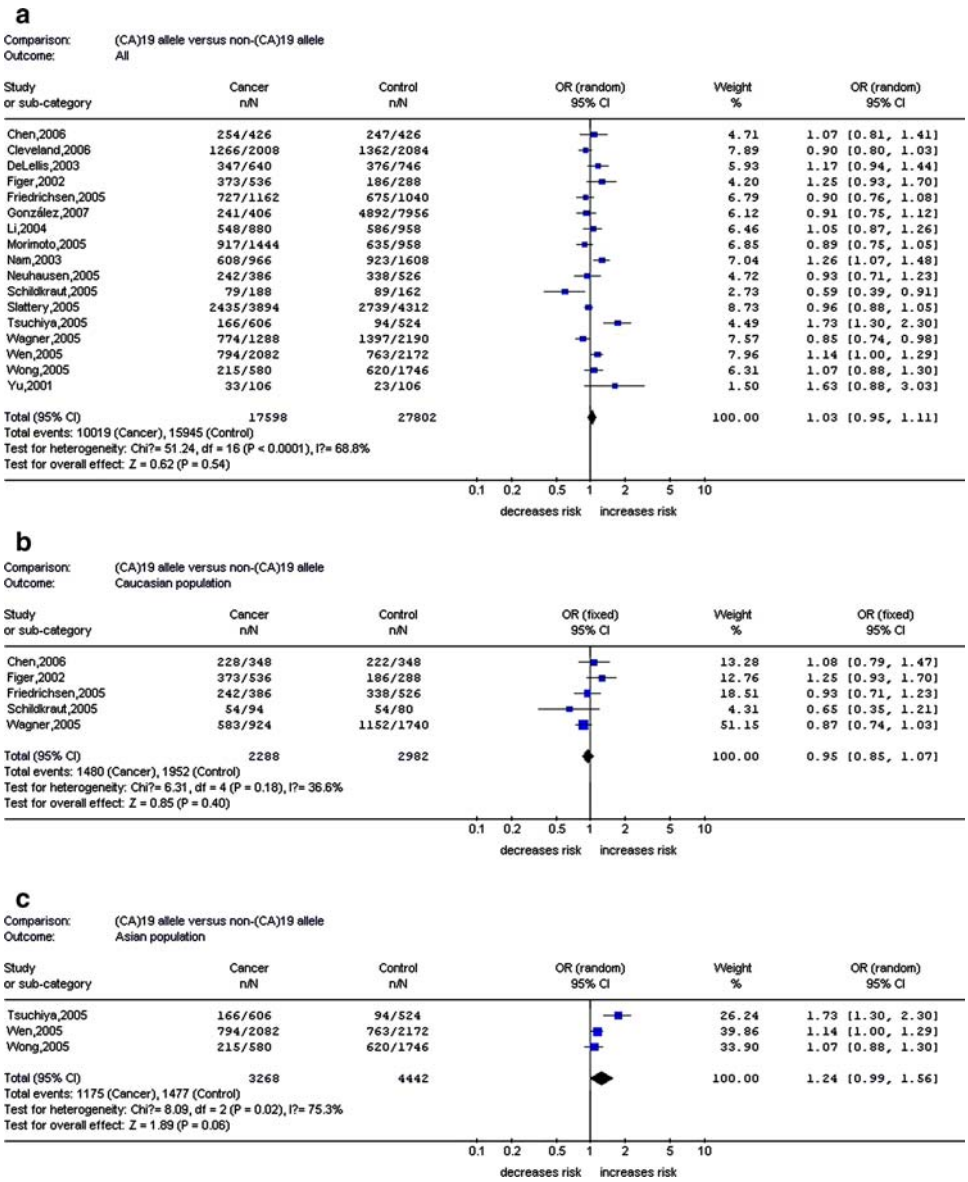

Fig. 1 Overall meta-analysis for *IGF-I* (CA)19 polymorphism [(CA)19 vs. non-(CA)19 allele] in cancers. Each comparison was presented by the name of the first author and the year of publication. The study was shown by a point estimate of the OR and the accompanying 95% CI. *n* indicates the total number of (CA)19 alleles; *N* indicates the total number of (CA)19 alleles plus non-(CA)19 alleles. **a** Analyzed the comparison in cancers. **b** Analyzed the comparison in Asian population under a random-effects model. **c** Analyzed the comparison in Caucasian population under a fixed-effects model

corresponding controls (56.9%). The (CA)19 allele had a lower representation among patients with breast cancer (54.2%) than in controls (57.9%). The (CA)19 allele was represented almost the same among cases of prostate cancer (56.9%) and corresponding controls (56.3%) (Table 2).

Overall effects for alleles

We performed a meta-analysis from all eligible case-control studies to compare *IGF-I* (CA)19 versus non-(CA)19 allele. Since significant heterogeneity existed between the 17 studies, the random effects model was used to pool the results (Fig. 1a). There was no evidence that the (CA)19 allele associated with the risk of cancer in a worldwide population and the summary OR = 1.03, 95% CI (0.95–1.11), $P = 0.54$, $P_{\text{heterogeneity}} < 0.0001$). According to the different kinds of cancer, we also performed three meta-analyses with prostate, breast, and colorectal cancer (Fig. 2a, b, c). In the subgroup analyses of three different kinds of cancer, no heterogeneity existed in colorectal cancer, while significant heterogeneity existed in prostate and breast cancer. We also found no association between the (CA)19 polymorphism and the risk of breast, prostate, and colorectal cancer, respectively. Last, we performed two meta-analyses in Caucasians with five studies and in Asian populations with three studies (Fig. 1b, c), We also found that no heterogeneity existed in the Caucasian population, which might decrease the cancer risk for (CA)19 carriers (OR = 0.95; 95% CI, 0.85–1.07), while heterogeneity existed in the Asian population, which might increase the cancer risk for (CA)19 carriers(OR = 1.24; 95% CI,

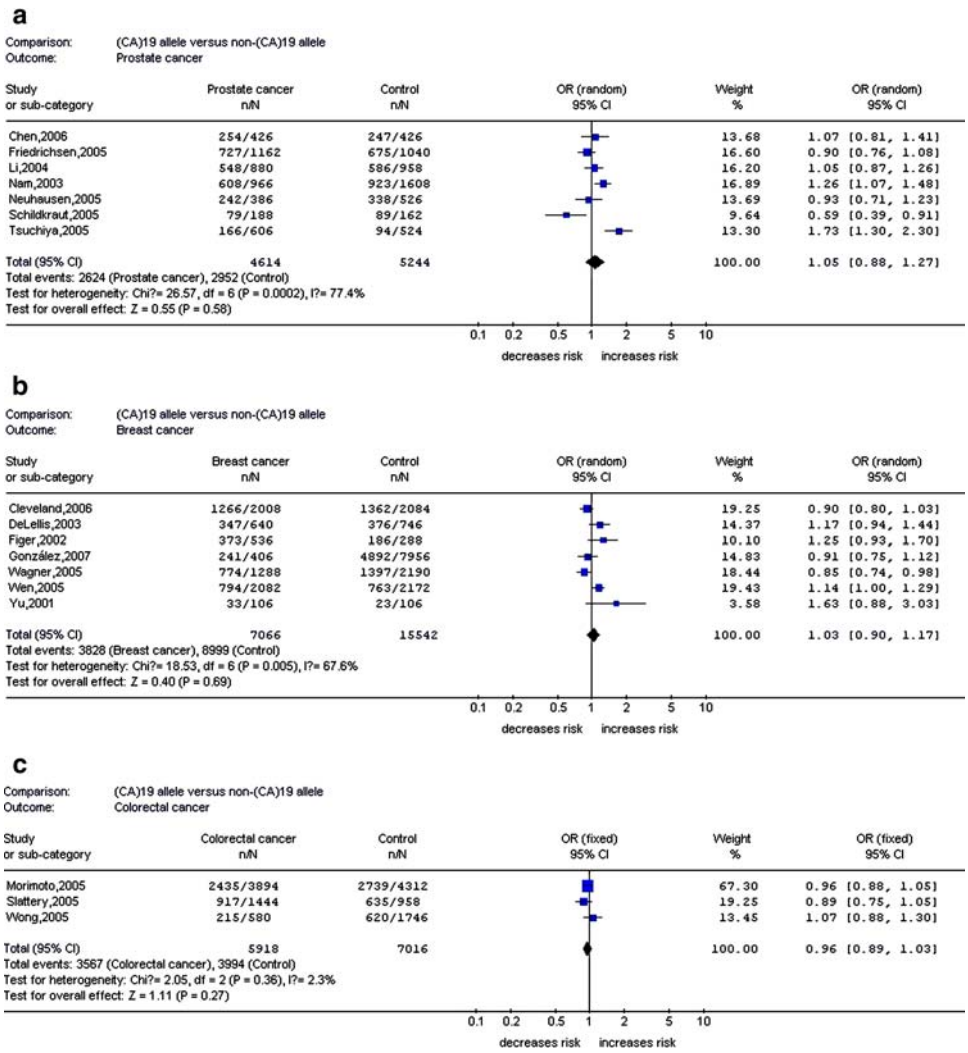

Fig. 2 Three meta-analyses for *IGF-I* (CA)19 polymorphism [(CA)19 vs. non-(CA)19 allele] in prostate, breast, and colorectal cancer. Each comparison was presented by the name of the first author and the year of publication. The study was shown by a point estimate of the OR and the accompanying 95% CI. *n* indicates the total number of (CA)19 alleles; *N* indicates the total number of (CA)19 alleles plus non-(CA)19 alleles. **a** Analyzed the comparison in prostate cancer. **b** Analyzed the comparison in breast cancer under a random-effects model. **c** Analyzed the comparison in colorectal cancer under a fixed-effects model

0.99–1.56). However, no heterogeneity existed in the Caucasian population, while significant heterogeneity existed in the Asian population.

Other genetic contrasts

In 3 of the 17 eligible articles no detailed genotype data were available (Yu et al. 2001; Figer et al. 2002; Li et al. 2004). Therefore, 14 articles were available when doing the meta-analysis under other genetic contrasts. The results further suggested that (CA)19 showed no association to cancer risk in an additive genetic model, the summary [OR = 0.99, 95% CI (0.84–1.16), $P = 0.87$, $p_{\text{heterogeneity}} = 0.001$], as well as in recessive [OR = 0.96, 95% CI (0.87–1.05), $P = 0.36$, $P_{\text{heterogeneity}} = 0.05$] and dominant genetic models [OR = 1.05, 95% CI (0.91–1.20), $P = 0.53$, $P_{\text{heterogeneity}} = 0.0004$]. Five of the 14 eligible articles investigated prostate cancer, 6 studies investigated breast cancer, and 3 studies investigated colorectal cancer. In the three kinds of cancer, we also performed meta-analysis in other different genetic models. No evidence of association between (CA)19 polymorphism and prostate, breast, and colorectal cancer was discerned, respectively (Table 3).

Sensitivity analysis

Sensitivity analysis was performed by sequential omission of individual studies under various contrasts, as well as in prostate cancer, breast cancer, and colorectal cancer subgroups. In the meta-analysis of the Asian population, after exclusion of Tsuchiya et al. (2005), the heterogeneity no longer existed, and the estimate of the overall effect changed [OR = 1.12, 95% CI (1.01–1.24), $P = 0.04$, $P_{\text{heterogeneity}} = 0.60$]. In fact, the result of Tsuchiya et al.'s (2005) study was that the 19-allele of *IGF-I* appears to increase the risk of prostate cancer in the Japanese population, which did not conflict with the results of the other two studies involved in meta-analysis of the Asian population. In the prostate cancer subgroup analysis, the between-study heterogeneity remained after exclusion the study of Schildkraut et al.

Table 3 Summary of odds ratios (ORs) and 95% CIs for various comparisons

Contrast	Comparison (number of studies)	Random-effects OR (95%CI)	Fixed-effects OR (95%CI)	*P* for heterogeneity	*P* value (fixed)	*P* value (random)
All cancer						
(CA)19 allele versus non-(CA)19 allele	All (17)	1.03 (0.95–1.11)	1.00 (0.96–1.05)	0.0001	0.54	0.84
(CA)19 allele versus non-(CA)19 allele	Caucasians (5)	0.97 (0.82–1.14)	0.95 (0.85–1.07)	0.18	0.7	0.4
(CA)19 allele versus non-(CA)19 allele	Asian (3)	1.24 (0.99–1.56)	1.18 (1.07–1.30)	0.02	0.06	0.001
(CA)19 homozygosity versus non-(CA)19 homozygosity	All (14)	0.99 (0.84–1.16)	0.95 (0.85–1.09)	0.001	0.87	0.65
(CA)19 homozygosity versus (CA)19 heterozygosity + non-(CA) 19 homozygosity	All (14)	0.96 (0.87–1.05)	0.95 (0.89–1.01)	0.05	0.36	0.1
(CA)19 homozygosity + (CA)19 heterozygosity versus non-(CA)19 homozygosity	All (14)	1.05 (0.91–1.20)	1.06 (0.98–1.15)	0.0004	0.53	0.12
Breast cancer						
(CA)19 allele versus non-(CA)19 allele	All (7)	1.03 (0.90–1.17)	1.00 (0.93–1.06)	0.05	0.69	0.94
(CA)19 homozygosity versus non-(CA)19 homozygosity	All (5)	1.18 (0.78–1.76)	1.12 (0.98–1.29)	0.00001	0.43	0.11
(CA)19 homozygosity versus (CA)19 heterozygosity + non-(CA)19 homozygosity	All (5)	0.97 (0.85–1.10)	0.95 (0.85–1.05)	0.18	0.63	0.35
(CA)19 homozygosity + (CA)19 heterozygosity versus non-(CA)19 homozygosity	All (5)	0.97 (0.79–1.19)	0.95 (0.85–1.17)	0.02	0.77	0.85
Prostate cancer						
(CA)19 allele versus non-(CA)19 allele	All (7)	1.05 (0.88–1.27)	1.08 (0.99–1.17)	0.0002	0.58	0.01
(CA)19 homozygosity versus non-(CA)19 homozygosity	All (6)	1.09 (0.70–1.68)	1.15 (0.94–1.21)	0.002	0.71	0.16
(CA)19 homozygosity versus (CA) 19 heterozygosity + non-(CA)19 homozygosity	All (6)	1.01 (0.78–1.31)	1.02 (0.89–1.17)	0.02	0.92	0.79
(CA)19 homozygosity + (CA)19 heterozygosity versus non-(CA)19 homozygosity	All (6)	1.12 (0.80–1.56)	1.25 (1.06–1.47)	0.002	0.51	0.008
Colorectal cancer						
(CA)19 allele versus non-(CA)19 allele	All (3)	0.96 (0.89–1.03)	0.96 (0.89–1.03)	0.36	0.28	0.27
(CA)19 homozygosity versus non-(CA)19 homozygosity	All (3)	0.92 (0.79–1.08)	0.92 (0.79–1.08)	0.78	0.31	0.31
(CA)19 homozygosity versus (CA)19 heterozygosity + non-(CA)19 homozygosity	All (3)	0.91 (0.81–1.01)	0.91 (0.81–1.01)	0.7	0.07	0.07
(CA)19 homozygosity + (CA)19 heterozygosity versus non-(CA)19 homozygosity	All (3)	1.02 (0.87–1.20)	1.02 (0.89–1.17)	0.28	0.77	0.77

CI confidence interval

(2005). Further exclusion of Tsuchiya et al. (2005) makes the between-study heterogeneity no longer exist, but the overall effect of the (CA)19 to the prostate cancer risk did not change. In the breast cancer subgroup analysis, the between-study heterogeneity remained after exclusion of the study of Wagner et al. (2005); further exclusion of Cleveland et al. (2006) makes the between-study heterogeneity no longer exist, and the overall effect of the (CA)19 to breast cancer risk changed [OR = 1.11, 95% CI (1.02–1.22), $P = 0.02$, $P_{\text{heterogeneity}} = 0.20$].

Publication bias

Begg's funnel plot for the comparison of (CA)19 allele vs. non-(CA)19 allele in the OR analysis and Egger's test

provided no evidence for funnel plot asymmetry in overall cancer ($t = 1.05$, $P = 0.309$), breast cancer ($t = 1.22$, $P = 0.276$), prostate cancer ($t = -0.51$, $P = 0.631$), and colorectal cancer ($t = 0.18$, $P = 0.886$).

Discussion

Many studies report that high circulating IGF-I concentrations are associated with an increased risk of cancer including prostate (Chan et al. 1998), breast (Hankinson et al. 1998), colorectal (Ma et al. 1999), lung (Yu et al. 1999), and cervical (Schaffer et al. 2007) cancer. However, some articles report *IGF-I* (CA) repeat polymorphisms were associated with susceptibility to cancers including prostate, breast, and colorectal cancer. In this study, we performed meta-analysis of the three kinds of cancer. The summary OR indicated that *IGF-I* (CA)19 polymorphisms are not associated with cancer risk in all different comparisons.

Three studies of meta-analyses in the Asian population researched the relationship between *IGF-I* (CA)19 polymorphisms and prostate (Tsuchiya et al. 2005), breast (Wen et al. 2005), and colorectal (Wong et al. 2005) cancer, respectively, while five articles of meta-analyses in the Caucasian population just researched the relationship between IGF-I (CA)19 polymorphisms and prostate (Schildkraut et al. 2005; Chen et al. 2006) and breast cancer (Wagner et al. 2005; Cleveland et al. 2006; Figer et al. 2002). We found that no heterogeneity existed in the Caucasian population, and it might decrease the cancer risk for (CA)19 carriers, while heterogeneity existed in the Asian population and might increase cancer risk for (CA)19 carriers. A sensitivity analysis was performed in the Asian population with three articles. Two out of three articles observed that *IGF-I* genotypes containing the (CA)19 were consistently associated with increased risk of prostate and breast cancer (Wen et al. 2005; Tsuchiya et al. 2005). After exclusion of Tsuchiya et al. (2005), the heterogeneity no longer existed, and the estimated overall effect changed [OR = 1.12, 95% CI (1.01–1.24), $P = 0.04$, $p_{\text{heterogeneity}} = 0.60$]. The study of Tsuchiya et al. (2005) is the origin of the heterogeneity. The reason is not that the study reported no relationship between (CA)19 allele and cancer risk, but it indicated a more strong positive association between *IGF-I* (CA)19 polymorphism and increased prostate cancer risk. This information indicated that (CA)19 allele carriers might have increased risk of cancer in the Asian population. In addition, the prevalence rate of (CA)19 allele across the controls of Caucasian and Asian descent were 65.5 and 33.3%, respectively. The result indicated that the distribution of (CA)19 allele frequency has a significant difference in Caucasian and Asian populations, and the physiological function of (CA)19 allele might differentiate in different population. Overall, the association of *IGF-I* (CA)19 polymorphisms to susceptibility to cancer might be different in different populations. However, the study population of our meta-analysis was composed of different races. The ethnic composition of the study populations might be the main reason why the results of our study yielded a non-statistically significant decreased or increased risk for (CA)19 carriers. We suggested that investigators should stratify analyses by racial/ethnic group in the future.

Two of the 17 eligible articles were different from the others (Wagner et al. 2005; Li et al. 2004), because they used a related case-control design. The result of Li et al.'s (2004) study was that no association existed between genetic polymorphisms in *IGF-I* and prostate cancer. Wagner et al. (2005) detected an increased breast cancer risk with a borderline significance in the Polish familial cases homozygous for the non-(CA)19 alleles (OR = 1.51, 0.96–2.39, $P = 0.07$). We excluded the two studies when doing sensitivity analysis. But the overall effect of the (CA)19 to the cancer risk did not change.

Prostate cancer is the most commonly diagnosed non-cutaneous malignancy among men and the second leading cause of cancer-related deaths in men in Western countries (Landis et al. 1999). Several previous studies have shown that the (CA)19 allele may be associated with increased risk of prostate cancer (Tsuchiya et al. 2005; Schildkraut et al. 2005). Other studies, however, reported a decreased risk of prostate cancer subjects with the (CA)19 allele (Friedrichsen et al. 2005) or no association (Li et al. 2004; Neuhausen et al. 2005; Schildkraut et al. 2005; Chen et al. 2006; Nam et al. 2003). Molecular epidemiological studies have presented seemingly contradictory results concerning a potential role of the *IGF-I* (CA)19 polymorphisms in prostate cancer susceptibility. In our meta-analysis in the prostate cancer subgroup, seven articles were retrieved based on the searching criteria for prostate cancer susceptibility related to *IGF-I* (CA)19 polymorphisms. We aimed to obtain summary estimates for the strength of the postulated genetic association, as well as to quantify and explain the potential between-study heterogeneity. No evidence of association between (CA)19 allele and prostate cancer risk [$P = 0.41$, OR = 1.08, 95% CI (0.89–1.31), $P_{\text{heterogeneity}} < 0.0001$] was found. The between-study heterogeneity remained after exclusion the study of Schildkraut et al. (2005). Further exclusion of Tsuchiya et al. (2005) makes the between-study heterogeneity no longer exist, but the overall effect of the (CA)19 to the cancer risk did not change. The main study population of six out of seven articles was from Caucasians. This might mean that our conclusion on prostate cancer was more representative in the Caucasian population than in others

and was not directly applicable to the Asian population. Therefore, further research is warranted to reveal whether prostate cancer susceptibility related to *IGF-I* (CA)19 polymorphisms or not in Asian population.

Breast cancer is the most common malignancy in women worldwide (Parkin et al. 2001, 2002). There are two meta-analyses for breast cancer that yielded conflicting results (Wen et al. 2005; González-Zuloeta et al. 2007). We updated the analysis by including new available published data. The results of our meta-analysis yielded a non-statistically significant increased cancer risk for (CA)19 carriers. The result of the first meta-analysis indicated that *IGF-I* genotypes containing the (CA)19 were consistently associated with increased risk of breast cancer across four studies (overall OR = 1.22, 95% CI: 1.06–1.41, *P* for heterogeneity test = 0.524, 1,331 breast cancer cases; 1,478 controls) (Wen et al. 2005). The findings supported the hypothesis that *IGF-I* gene polymorphisms might be a significant genetic factor for breast cancer susceptibility, in contrast to the results found in our study. However, the second meta-analysis results indicated that the *IGF-I* (CA)19 polymorphism was not likely to predict the risk of breast cancer across six studies in postmenopausal women. The meta-analysis yielded a pooled OR = 1.05 (95% CI = 0.95–1.17) for (CA)19 heterozygous carriers versus (CA)19 homozygous carriers, and OR = 1.26 (95% CI = 0.87–1.82) for (CA)19 non-carriers versus (CA)19 homozygous carriers(González-Zuloeta et al. 2007), the same results found in our study. In our study, the articles on the relation between the *IGF-I* (CA)19 polymorphism and breast cancer risk till now retrieved eight studies. The study of Missmer et al. was not included in our meta-analysis because the genotype distribution in the control population significantly deviates from HWE. But this study was used in two previous meta-analyses papers, which might cause misleading results in those two previous meta-analyses. A sensitivity analysis was performed in the breast cancer subgroup. After exclusion of two studies by Wagner et al. (2005) and Cleveland et al. (2006), the between-study heterogeneity no longer existe,d and the overall effect of the (CA)19 to the cancer risk changed, yielding a positive result that *IGF-I* (CA)19 carriers had significantly increased breast cancer risk. However, to date, the relationship between *IGF-I* (CA)19 polymorphisms and breast cancer susceptibility was not sure, and further study is needed.

Four out of 17 articles researched the association *IGF-I* (CA) repeat polymorphisms to susceptibility of colorectal cancer. One article was replaced with its updated study. No significant heterogeneity existed among the three studies when comparing (CA)19 allele in colorectal cancer. But the number of studies on colorectal cancer was so small that we could not come to definite results. Therefore, the results need to be verified in a larger study.

Many studies have found that *IGF-I* (CA) repeat polymorphism had many kinds of polymorphic forms. It has been reported that the *IGF-I* polymorphic (CA) repeat ranges from 11 to 23 units (Wen et al. 2005; Cleveland et al. 2006). The (CA)19 allele was reportedly most frequently observed in Caucasians (Cleveland et al. 2006), and some studies showed that (CA)19 alleles are also most commonly found in Asians (Wen et al. 2005; Tsuchiya et al. 2005). The distribution of (CA)19 allele varies in different populations. It indicated that future work in this area should be stratified according to race and ethnicity. Since the (CA) repeat region in the *IGF-I* gene is located near the promoter, 1 kb upstream from the transcription initiation site, some studies have suggested that the polymorphic (CA) repeats affected transcription activity of the gene (Tae et al. 1994). Several previous studies have shown that the (CA)19 allele might be associated with an elevated level of plasma IGF-I (Vaessen et al. 2001; Rietveld et al. 2003), while other studies reported a reduced level of plasma IGF-I subjects with the (CA)19 allele (Jernstrom et al. 2001a, b; Rosen et al. 1998) or no association (Wen et al. 2005; Chen et al. 2006; Friedrichsen et al. 2005; Allen et al. 2002; Kato et al. 2003). Five of the 17 eligible articles investigated the association of *IGF-I* genotype not only with phenotype, but also with cancer risk (Wen et al. 2005; Chen et al. 2006; Friedrichsen et al. 2005; Yu et al. 2001; DeLellis et al. 2003). But the definite relationships among them are still unclear. In addition, the relationship between the (CA)17, (CA)21 allele and level of plasma IGF-I has been reported in some studies (Wen et al. 2005; Wong et al. 2005).Furthermore, Gebhardt et al. (1999) reported that the length of the repeats was inversely correlated with the transcription activity of the gene. Therefore, if the association *IGF-I* (CA) repeat polymorphism to circulating IGF-I concentrations is exists, the more reasonable explanation should be the length of (CA) repeats is proportional or inversely proportional to circulating IGF-I concentrations. Cleveland et al. (2006) reported that IGF-I genotypes that include alleles with fewer than (CA)19 repeats appear to be associated with an increased risk of breast cancer, particularly among premenopausal women. One study has also found a reverse association of breast cancer risk with the (CA)17 allele (Wen et al. 2005). Previous investigations of the *IGF-I* promoter (CA) repeat polymorphism have generally categorized *IGF-I* genotype with respect to whether a subject carried a (CA)19 repeat allele or not. Therefore, it is possible that the association between *IGF-I* (CA) repeat polymorphisms and cancer risk might be modified by the number of (CA) repeats. However, no sufficient studies are available to be included that do meta-analysis so far. More careful stratification analyses according to the length of (CA) repeats and cancer types are needed. For example, the number of (CA) repeats should below 19 or above 19.

Although our meta-analysis yielded a negative association between *IGF-I* (CA) repeat polymorphisms and cancer risk, some potential analytic issues should also be considered. First, some nondifferential misclassification bias is possible. Most studies could not exclude latent cancer cases in the control group. Second, we could not address whether these *IGF-I* polymorphisms might have an effect on the clinical behavior of cancer or other clinicopathologic attributes. The meta-analysis cannot exclude the possibility that other polymorphisms in *IGF-I* may still be useful to pursue. Moreover, we could not address gene-gene and gene-environmental interactions. The latter may be important for genes that code proteins with detoxifying function, but would require detailed information on exposures to various potential carcinogens and individual-level data (Ioannidis et al. 2002) and would be most meaningful only for common exposures that are found to be strong risk factors for the disease.

A very large number of subjects is needed to establish or refute a genetic association of modest magnitude (Ioannidis et al. 2001), and even larger numbers are needed to validate subgroup differences, let alone more subtle associations such as gene-gene and gene-environment interactions. Given the large number of potential genetic risk factors that may be probed, several initial observations may not be validated by subsequent evidence.

In conclusion, our meta-analysis suggests that the *IGF-I* (CA)19 polymorphism had no association to cancer risk in a worldwide population. Further stratification to ethnicity (Caucasians and Asians) and cancer types (prostate, breast, and colorectal cancer) did not reveal the significant association of the polymorphism to cancer risk. However, a significant difference of distribution of genotypes of *IGF-I* (CA)19 polymorphism did exist in Caucasians and Asians. Whether the *IGF-I* (CA)19 polymorphism has association to different kinds of cancer risk needs further investigation. More studies or large case-control studies, especially in Asian populations, should be performed to clarify possible roles of *IGF-I* (CA) repeat polymorphism in cancer. In addition, future studies for the length of (CA) repeats focus not only on (CA)19 versus non-(CA)19, but also on the comparison of other alleles selected from the group.

Acknowledgments We thank Dr. Jianfeng Dai (Yale University) and Dr. Yan Huang (Fudan University) for their expert assistance.

References

Allen NE, Davey GK, Key TJ, Zhang S, Narod SA (2002) Serum insulin-like growth factor I (IGF-I) concentration in men is not associated with the cytosine-adenosine repeat polymorphism of the IGF-I gene. Cancer Epidemiol Biomarkers Prev 11:319–320

Cleveland RJ, Gammon MD, Edmiston SN, Teitelbaum SL, Britton JA, Terry MB, Eng SM, Neugut AI, Santella RM, Conway K (2006) IGF1 CA repeat polymorphisms, lifestyle factors and breast cancer risk in the Long Island Breast Cancer Study Project. Carcinogenesis 27:758–765

Chen C, Freeman R, Voigt LF, Fitzpatrick A, Plymate SR, Weiss NS (2006) Prostate cancer risk in relation to selected genetic polymorphisms in insulin-like growth factor-I, insulin-like growth factor binding protein-3, and insulin-like growth factor-I receptor. Cancer Epidemiol Biomarkers Prev 15(12):2461–2466

Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M (1998) Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 279:563–566

DeLellis K, Ingles S, Kolonel L, McKean-Cowdin R, Henderson B, Stanczyk F, Probst-Hensch NM (2003) IGF1 genotype, mean plasma level and breast cancer risk in the Hawaii/Los Angeles multiethnic cohort. Br J Cancer 88:277–282

Daughaday WH, Rotwein P (1989) Insulin-like growth factors I and II. Peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. Endocr Rev 10:68–91

Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634

Frayling TM, Hattersley AT, McCarthy A, Holly J, Mitchell SM, Gloyn AL, Owen K, Davies D, Smith GD Ben-Shlomo Y (2002) A putative functional polymorphism in the IGF-I gene: association studies with type 2 diabetes, adult height, glucose tolerance and fetal growth in UK populations. Diabetes 51:2313–2316

Friedrichsen DM, Hawley S, Shu J, Humphrey M, Sabacan L, Iwasaki L, Etzioni R, Ostrander EA, Stanford JL (2005) IGF-I and IGFBP-3 polymorphisms and risk of prostate cancer. Prostate 65:44–51

Figer A, Karasik YP, Baruch RG, Chetrit A, Papa MZ, Sade RB, Rizel S, Friedman E (2002) Insulin-like growth factor I polymorphism and breast cancer risk in Jewish women. Isr Med Assoc J 4:759–762

González-Zuloeta Ladd AM, Liu F, Houben MP, Arias Vasquez A, Siemes C, Janssens AC, Coebergh JW, Hofman A, Janssen JA, Stricker BH, van Duijn CM. (2007) IGF-1 CA repeat variant and breast cancer risk in postmenopausal women. Eur J Cancer doi: 10.1016/j.ejca.2007.04.026

Gebhardt F, Zanker KS, Brandt B (1999) Modulation of epidermal growth factor receptor gene transcription by a polymorphic dinucleotide repeat in intron 1. J Biol Chem 274:13176–13180

Harrela M, Koistinen H, Kaprio J, Lehtovirta M, Tuomilehto J, Eriksson J, Toivanen L, Koskenvuo M, Leinonen P, Koistinen R, Seppälä M (1996) Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. J Clin Invest 98:2612–2615

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 81:1791–1797

Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351:1393–1396

Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG (2001) Replication validity of genetic association studies. Nat Genet 29:306–309

Ioannidis JP, Rosenberg PS, Goedert JJ, O'Brien TR (2002) Commentary: metaanalysis of individual participants' data in genetic epidemiology. Am J Epidemiol 156:204–210

Jernstrom H, Chu W, Vesprini D, Vesprini D, Tao Y, Majeed N, Deal C, Pollak M, Narod SA (2001a) Genetic factors related to racial variation in plasma levels of insulin-like growth factor-1: implications for premenopausal breast cancer risk. Mol Genet Metab 72:144–154

Jernstrom H, Deal C, Wilkin F, Chu W, Tao Y, Majeed N, Hudson T, Narod SA, Pollak M (2001b) Genetic and non-genetic factors associated with variation of plasma levels of insulin-like growth factor-I and insulin-like growth factor-binding protein-3 in healthy premenopausal women. Cancer Epidemiol Biomarkers Prev 10:377–384

Kato I, Eastham J, Li B, Smith M, Yu H (2003) Genotype–phenotype analysis for the polymorphic CA repeat in the insulin-like growth factor-I (IGF-I) gene. Eur J Epidemiol 18(3):203–209

Li L, Cicek MS, Casey G, Witte JS (2004) No association between genetic polymorphisms in IGF-I and IGFBP-3 and prostate cancer. Cancer Epidemiol Biomarkers Prev 13:497–498

Lau J, Ioannidis JP, Schmid CH (1997) Quantitative synthesis in systematic reviews. Ann Intern Med 127:820–826

Landis SH, Murray T, Bolden S, Wingo PA (1999) Cancer statistics, 1999. CA Cancer J Clin 49:8–31, 1

LeRoith D, Raizada MK (ed) (1993) Proceedings of the 4th international symposium on insulin, IGFs, and their receptors, vol 343. Adv Exp Med Biol, 20–23 April 1993 Woods Hole, Massachusetts, pp 1–417

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(5):1204–1211

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 91:620–625

Missmer SA, Haiman CA, Hunter DJ, Willett WC, Colditz GA, Speizer FE, Pollak MN, Hankinson SE (2002) A sequence repeat in the insulin-like growth factor-1 gene and risk of breast cancer. Int J Cancer 100:332–336

Nam RK, Zhang WW, Trachtenberg J, Jewett MA, Emami M, Vesprini D, Chu W, Ho M, Sweet J, Evans A, Toi A, Pollak M, Narod SA (2003) Comprehensive assessment of candidate genes and serological markers for the detection of prostate cancer. Cancer Epidemiol Biomarkers Prev 12:1429–1437

Neuhausen SL, Slattery ML, Garner CP et al. (2005) Prostate cancer risk and IRS1, IRS2, IGF1, and INS polymorphisms: strong association of IRS1 G972R variant and cancer risk. Prostate 64:168–174

Pollak M (2000a) Insulin-like growth factor physiology and neoplasia. Growth Horm IGF Res 10:S6–S7

Pollak M (2000b) Insulin-like growth factor physiology and cancer risk. Eur J Cancer 36:1224–1228

Parkin DM, Bray FI, Devesa SS (2001) Cancer burden in the year 2000. The global picture. Eur J Cancer 37(Suppl 8):S4–S66

Parrizas M, LeRoith D (1997) Insulin-like growth factor-1 inhibition of apoptosis is associated with increased expression of the bcl-xL gene product. Endocrinology 138:1355–1358

Petitti D (1994) Meta-analysis, decision analysis, and cost effectiveness analysis. Oxford University Press, New York

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (eds) (2002) Cancer incidence in five continents, vol VIII. IARC Sci Publ 155:1–781

Rietveld I, Janssen JA, Hofman A, Pols HA, van Duijn CM, Lamberts SW (2003) A polymorphism in the IGF-I gene influences the age-related decline in circulating total IGF-I levels. Eur J Endocrinol 148:171–175

Rosen CJ, Kurland ES, Vereault D, Adler RA, Rackoff PJ, Craig WY, Witte S, Rogers J, Bilezikian JP (1998) Association between serum insulin growth factor-I (IGF-I) and a simple sequence repeat in IGF-I gene: implications for genetic studies of bone mineral density. J Clin Endocrinol Metab 83:2286–2290

Rotwein P, Pollock KM, Didier DK, Krivi GG (1986) Organization and sequence of the human insulin-like growth factor I gene.Alternative RNA processing produces two insulin-like growth factor I precursor peptides. J Biol Chem 261:4828–4832

Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M (2004) Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 363:1346–1353

Schildkraut JM, Demark-Wahnefried W, Wenham RM, Grubber J, Jeffreys AS, Grambow SC, Marks JR, Moorman PG, Hoyo C, Ali S, Walther PJ (2005) IGF1 (CA)19 repeat and IGFBP3-202 A/C genotypes and the risk of prostate cancer in black and white men. Cancer Epidemiol Biomarkers Prev 14:403–408

Schaffer A, Koushik A, Trottier H, Duarte-Franco E, Mansour N, Arseneau J, Provencher D, Gilbert L, Gotlieb W, Ferenczy A, Coutlée F, Pollak MN, Franco EL; Biomarkers of cervical cancer risk study team (2007) Insulin-like growth factor-i and risk of high-grade cervical intraepithelial. Cancer Epidemiol Biomarkers Prev 16(4):716–722

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

Slattery ML, Samowitz W, Curtin K, Ma KN, Hoffman M, Caan B, Neuhausen S (2004) Associations among IRS1, IRS2, IGF1, and IGFBP-3 genetic polymorphisms and colorectal cancer. Cancer Epidemiol Biomarkers Prev 13(7):1206–1214

Tae HJ, Luo X, Kim KH (1994) Roles of CCAAT/enhancer-binding protein and its binding site on repression and derepression of acetyl-CoA carboxylase gene. J Biol Chem 269:10475–10484

Tsuchiya N, Wang L, Horikawa Y, Inouse T, Kakinuma H, Matsuura S, Sato K, Ogawa O, Kato T, Habuchi T (2005) CA repeat polymorphism in the insulin-like growth factor-I gene is associated with increased risk of prostate cancer and benign prostatic hyperplasia. Int J Oncol 26:225–231

Vaessen N, Heutink P, Janssen JA, Witteman JC, Testers L, Hofman A, Lamberts SW, Oostra BA, Pols HA, van Duijn CM (2001) A polymorphism in the gene for IGF-I: functional properties and risk for type 2 diabetes and myocardial infarction. Diabetes 50:637–642

Woolf B (1955) On estimating the relation between blood group and disease. Ann Hum Genet 19:251–253

Wen W, Gao YT, Shu XO, Yu H, Cai Q, Smith JR, Zheng W (2005) Insulinlike growth factor-I gene polymorphism and breast cancer risk in Chinese women. Int J Cancer 113:307–311

Wong H-L, DeLellis K, Nicole P-H, Woon-Puay K, David Van Den B, Hin-Peng L, Mimi CY, Sue AI (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(1):144–150

Wagner K, Hemminki K, Israelsson E, Grzybowska E, Söderberg M, Pamula J, Pekala W, Zientek H, Mielzynska D, Siwinska E, Försti A (2005) Polymorphisms in the IGF-1 and IGFBP 3 promoter and the risk of breast cancer. Breast Cancer Res Treat 92:133–140

Weber JL, May PE (1989) Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. Am J Hum Genet 44:388–396

Yang RC, Roden RBS (2003) Genetic polymorphism and tumor immunotherapy. Curr Pharmacogenom 1:37–57

Yu H, Li BD, Smith M, Shi R, Berkel HJ, Kato I (2001) Polymorphic CA repeats in the IGF-I gene and breast cancer. Breast Cancer Res Treat 70:117–122

Yu H, Spitz MR, Mistry J, Gu J, Hong WK, Wu X (1999) Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. J Natl Cancer Inst 91:151–156