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The association between IGF1 Gene 3'-UTR polymorphisms and cancer risk

A Meta-analysis

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Abstract

Background and Objective: Insulin-like growth factor 1 (*IGF1*) gene three prime untranslated region (3'-UTR) polymorphisms have been reported to be associated with cancer risk. However, the conclusions of the relevant studies are not consistent. The present meta-analysis evaluates the relationship between *IGF1* gene 3'-UTR polymorphisms (rs5742714, rs6214, and rs6220) and cancer risk.

Methods: Articles regarding the relationship between *IGF1* rs5742714, rs6214, and rs6220 polymorphisms and cancer risk were selected by searching the PubMed, Embase, and Web of Science databases before April 30, 2018. Altogether, we obtained 34 case-controlled studies from 20 articles, including 21,568 cases and 31,199 controls. The strength of associations was quantified using odds ratios (ORs) and the corresponding 95% confidence intervals (CIs).

Results: In the present meta-analysis, no significant associations were detected between rs5742714, rs6214, and rs6220 and overall cancer risk. Thus, in stratified analyses, we found that rs6214 was associated with a significantly reduced risk of breast cancer under the allele, heterozygote, and dominant models (A vs G: OR, 0.94, 95% CI,0.88–1.00, $P = .044$; GA vs GG: OR, 0.88, 95% CI, 0.80–0.97, $P = .012$; AA + GA vs GG: OR, 0.89, 95% CI, 0.81–0.97, $P = .011$), as well as pancreatic cancer under the recessive model (AA vs GA + GG: OR, 0.68, 95% CI,0.53–0.87, $P = .003$). Also, rs6220 was associated with a significantly increased risk of breast cancer under the homozygote model (GG vs AA: OR, 1.23, 95% CI, 1.02–1.48, $P = .031$). In addition, rs6220 was found to increase overall cancer risk among Caucasians under the allele model (G vs A: OR, 1.06, 95% CI, 1.00–1.13, $P = .043$).

Conclusions: In this meta-analysis, we investigated and reviewed the relationship between *IGF1* gene 3'-UTR polymorphisms (rs5742714, rs6214, and rs6220) and cancer risk based on present epidemiological studies. Further studies are needed to draw more precise conclusions in the future.

Abbreviations: 3'-UTR = three prime untranslated region, ALL = acute lymphoblastic leukemia, BMI = body mass index, CI = confidence interval, IGF1 = insulin-like growth factor 1, OR = odds ratio, RCC = renal cell carcinoma, SNP = single nucleotide polymorphism, TGCT = testicular germ cell tumors.

Keywords: 3'-UTR, cancer, IGF1, meta-analysis, polymorphism

1. Introduction

Insulin-like growth factor 1 (IGF1) plays an important role in regulating cellular proliferation and apoptosis.[1] Most circulating IGF1 is bound to insulin-like growth factor binding protein 3 (IGFBP3), which can extend the half-life of IGF1.[2] IGF1 has been implicated in cancer development due to its key role in cell proliferation, differentiation, and apoptosis.[3] Many prospective studies have suggested that elevated IGF1 levels in the circulation can increase cancer risk.[4,5]

While nutrition is a key factor that influences IGF1 levels in the circulation, studies of twins have indicated that 40% to 60% of the variation in IGF1 levels in the circulation depends on hereditary factors.[6–9] Several *IGF1* polymorphisms have been identified as risk factors for cancers in genome-wide association studies (GWAS).[10]

Three prime untranslated region (3'-UTR) contains important sequences that regulate mRNA transcription, stability, cellular localization, and microRNA binding.[11] Many studies have shown a relationship between *IGF1* 3'-UTR single nucleotide polymorphisms (SNPs) and cancer susceptibility, but these results are not consistent.[12–31] For example, Jiang et al report that the rs5742714 can increase the risk of gastric cancer,[25] while Ennishi et al maintain that there is no obvious association between rs5742714 and gastric cancer risk.[20] Dong et al report that *IGF1* rs6214 can reduce the risk of pancreatic cancer,[31] while Nakao et al's overall analysis indicates that rs6214 does not affect pancreatic cancer risk, but that the polymorphism could increase the risk of pancreatic cancer among patients with body

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mass indexes (BMIs) of 25 or greater at the age of 20.[21] The inconclusive nature of these results necessitated the present meta-analysis, which will provide a more accurate evaluation of the association between the *IGF1* 3'-UTR polymorphisms rs5742714, rs6214, and rs6220 and cancer risk.

2. Methods

2.1. Ethics statement

As all analyses were based on previously published studies, no ethical approval or patient consent was required.

2.2. Search strategy

We performed a literature search for all available articles concerning the association between *IGF1* 3'-UTR polymorphisms and cancer risk in PubMed, Embase, and Web of Science databases (before April 30, 2018). The following keywords were used: "IGF1 or IGF-1 or insulin-like growth factor 1," "polymorphism or SNP or mutation or variant," and "cancer or carcinoma or tumor." We also identified relevant studies via checking reference lists.

2.3. Inclusion and exclusion criteria

The included studies met the following criteria:

(1) addressing the relationship between *IGF1* polymorphisms and cancer risk,
(2) having a case-control or cohort study design,
(3) having been published in English, and
(4) containing sufficient genotype data.

The exclusion criteria were as follows:

(1) not having a case-controlled or cohort study design,
(2) being meta-analyses or reviews, and
(3) not having sufficient genotype data.

2.4. Data extraction and quality score

The 2 authors worked independently to extract information and evaluate the quality of the studies. The following information was extracted: name of first author, publication year, country, ethnicity, type of cancer, genotyping methods, control source, and alleles or genotypes frequency. The quality of the studies was assessed using a quality score form [32] (Supplementary Table 1, http://links.lww.com/MD/C721). Quality scores ranged from 0 to 15. Any disagreement was resolved via discussion.

2.5. Statistical analysis

All statistical analyses were performed with the STATA software (Version 12.0, Stata Corporation, College Station, TX). The strength of each association was estimated using ORs and 95% CIs in 5 genetic models: the allele, homozygote, heterozygote, dominant, and recessive models. P values $<.05$ were considered statistically significant. A Q test and I^2 statistic were used to assess heterogeneity.[33] If the heterogeneity test was $P > .1$, this would indicate that the heterogeneity was not significant, a fixed-effect model was used to synthesis the OR and 95% CI.[34] Otherwise, the random-effects model was applied.[35] Hardy–Weinberg equilibrium (HWE) for control was calculated via a Chi-squared test. Stratified analyses were conducted by ethnicity, cancer type, control source, and quality score. Sensitivity analyses were

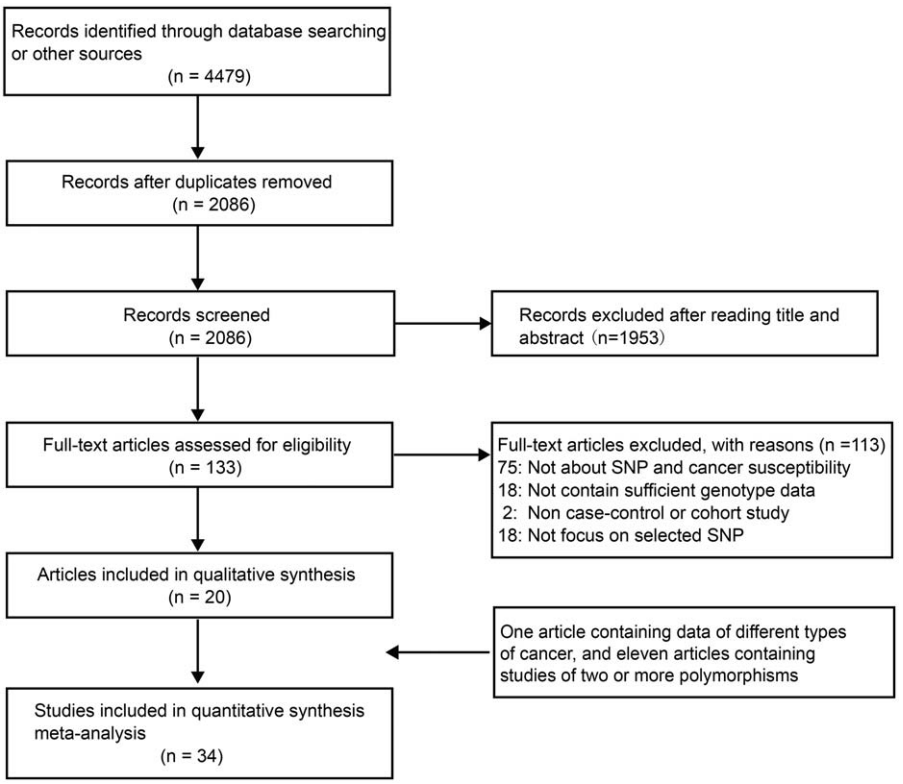

Figure 1. The flow diagram of included/excluded studies.

carried out to evaluate the stability of the results by omitting a single study each time. Begg test and Egger test were applied to detect potential publication bias.[36,37]

3. Results

3.1. Characteristics of the studies

The selection for eligible articles for inclusion in this meta-analysis is shown in Figure 1. Initially, 4479 articles were retrieved via a database search and references browsing. After removing duplicates, 2086 articles remained. After screening the titles and abstracts, 133 articles were retained for full-text review. Ultimately, we included 20 articles in this meta-analysis.[12–31] There is 1 article containing data for different types of cancer,[23] and there are 11 articles that contain studies of various *IGF1* polymorphisms.[12,13,15,17,19–21,24,26,27,30] In total, we identify 34 case-controlled studies from 20 articles in this meta-analysis, including 21,568 cases and 31,199 controls. The important characteristics of the selected articles are listed systematically in Table 1. We assessed the quality of these studies using a quality score form (Supplementary Table 1, http://links.lww.com/MD/C721). We provide the genotype distributions and allele frequencies in Table 2.

3.2. Meta-analysis

The associations between *IGF1* rs5742714, rs6214, and rs6220 polymorphisms and cancer risk were evaluated using odds ratios (ORs) and their 95% confidence intervals (CIs) under the following 5 genetic models: the allele homozygote, heterozygote, dominant, and recessive models. We also conducted stratified analyses according to ethnicity, cancer type, and quality score. Only results synthesized from no fewer than 2 studies are shown.

In total, our meta-analysis includes 9 studies regarding the rs5742714 polymorphism, which contains 4741 cases and 7267 controls. In overall analysis, no significant association was identified between rs5742714 and cancer risk in any of the 5 models (n = 9, case = 4741, control = 7267, Table 3). In the stratified analysis of ethnicity, no significant association was identified between rs5742714 and cancer risk among the Asian population (n = 7, case = 3395, control = 5863, Table 3). In the stratified analysis of cancer type, no significant association was identified between rs5742714 and the risk of the gastric (n = 2, case = 1283, control = 2135, Table 3) or pancreatic cancer (n = 2, case = 971, control = 2123, Table 3). The results synthesized from studies that scored no less than 12 (n = 7, case = 4213, control = 6730, Table 3) did not display any difference in terms of the results of the overall analysis.

In total, our meta-analysis includes 16 studies regarding the rs6214 polymorphism, which contain 8700 cases and 13,847 controls. In overall analysis, no significant association was identified between rs6214 and cancer risk in any of the 5 models (n = 16, case = 8700, control = 13,847, Table 3). In the stratified analysis of ethnicity, no significant association was identified between rs6214 and cancer risk among the Caucasian (n = 6, case = 4385, control = 6903, Table 3) or Asian (n = 6, case = 2815, control = 5240, Table 3) population. The results of the stratified analysis of cancer type demonstrate that rs6214 reduces the risk of breast cancer under the allele, the heterozygote, and dominant models (n = 4, case = 3550, control = 4617, Table 3 and Figure 2, A vs G: OR, 0.94, 95% CI,0.88–1.00, $P = .044$; GA vs GG: OR, 0.88, 95% CI, 0.80–0.97, $P = .012$; AA + GA vs GG: OR, 0.89, 95% CI, 0.81–0.97, $P = 0.011$), as well as reducing the risk of pancreatic cancer under the recessive model (n = 2, case = 778, control = 1,930, Table 3 and Figure 2, AA vs GA + GG: OR, 0.68, 95% CI,0.53–0.87, $P = .003$). No significant association was identified between rs6214 and the risk of colorectal cancer in this analysis (n = 3, case = 831, control = 2551, Table 3). The results synthesized from studies that scored no less than 12 (n = 12, case = 7302, control = 11,521, Table 3) did not display any difference in terms of the results of the overall analysis.

In total, our meta-analysis includes 9 studies regarding the rs6220 polymorphism, which contain 8127 cases and 10,085controls. In overall analysis, no significant association

Table 1

Characteristics of the studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Cancer type	Genotyping method	Control source
Al-Zahrani	2006	UK	Caucasian	Breast cancer	Taqman	PB
Canzian	2006	Europe	Caucasian	Breast cancer	Taqman	PB
Johansson	2007	Sweden	Caucasian	Prostate cancer	Taqman	PB
Chia	2008	USA	Mix	TGCT	Taqman	PB
Lonn	2008	USA	Mix	Brain tumor	Taqman	HB
Suzuki	2008	USA	Mix	Pancreatic cancer	Taqman	HB
Khoury-Shakour	2009	Israel	Mix	Breast cancer	Taqman	PB
Feik	2010	Austria	Caucasian	Colorectal cancer	Taqman	PB
Ennishi	2011	Japan	Asian	Stomach cancer	Taqman	HB
Nakao	2011	Japan	Asian	Pancreatic cancer	Taqman	HB
Dong	2012	USA	Mix	Pancreatic cancer	MassArray and TaqMan	HB
Karimi	2013	Iran	Iranian	Colorectal cancer	PCR-RFLP	HB
Ong	2014	Netherlands	Caucasian	Gastrointestinal Cancer	Taqman	PB
Qian	2014	China	Asian	Prostate cancer	Taqman	HB
Jiang	2015	China	Asian	Gastric cancer	Taqman	HB
Lu	2015	China	Asian	ALL	Taqman	HB
Cao	2016	China	Asian	RCC	Taqman	HB
Shi	2016	Canada	Mix	Breast cancer	Illumina GoldenGate	PB
Costa-silva	2017	Brazil	Brazilian	Breast cancer	Taqman	HB
Mao	2017	China	Asian	Osteosarcoma	Taqman	HB

TGCT = testicular germ cell tumors, ALL = acute lymphoblastic leukemia, RCC = renal cell carcinoma, PB = population-based, HB = hospital-based, PCR-RFLP = PCR restriction fragment length polymorphism.

Table 2

***IGF1* polymorphisms genotype distribution and allele numbers in cases and controls.**

	Genotype (N)								Allele numbers (N)					
	Case				Control				Case		Control		HWE	Score
rs5742714	Total	GG	GC	CC	Total	GG	GC	CC	G	C	G	C		
Chia2008	551	449	98	4	683	565	109	9	996	106	1239	127	0.160	15
Suzuki2008	795	629	154	12	721	591	124	6	1412	178	1306	136	0.857	12
Ennishi2011	703	427	238	38	1462	902	479	81	1092	314	2283	641	0.101	12
Nakao2011	176	106	64	6	1402	861	463	78	276	76	2185	619	0.133	12
Qian2014	664	448	195	21	702	492	195	15	1091	237	1179	225	0.396	12
Jiang2015	580	328	177	75	673	368	253	52	833	327	989	357	0.357	12
Lu2015	744	539	188	17	1087	725	316	46	1266	222	1766	408	0.125	12
Cao2016	355	249	99	7	362	225	114	23	597	113	564	160	0.104	11
Mao2017	173	112	53	8	175	115	50	10	277	69	280	70	0.156	10
rs6214	Total	GG	GA	AA	Total	GG	GA	AA	G	A	G	A		
Al-Zahrani2006	2040	706	987	347	2191	705	1130	356	2399	1681	2540	1842	0.006	12
Canzian2006	779	282	366	131	1527	503	753	271	930	628	1759	1295	0.709	15
Khoury-Shakour2009	90	44	36	10	93	37	42	14	124	56	116	70	0.715	12
Feik2010	121	37	60	24	1730	648	837	245	134	108	2133	1327	0.336	15
Ennishi2011	703	162	342	199	1512	328	685	499	666	740	1341	1683	0.001	9
Nakao2011	176	39	94	43	1402	314	668	420	172	180	1296	1508	0.119	12
Dong2012	602	306	234	62	528	204	240	84	846	358	648	408	0.342	12
Karimi2013	167	78	22	67	277	120	38	119	178	156	278	276	<0.001	7
Ong2014 (HNC)	433	153	210	70	437	147	214	76	516	350	508	366	0.901	14
Ong2014 (EC)	469	155	230	84	474	187	221	66	540	398	595	353	0.956	14
Ong2014 (CRC)	543	183	269	91	544	194	271	79	635	451	659	429	0.317	15
Qian2014	664	178	322	164	702	210	336	156	678	650	756	648	0.326	12
Lu2015	744	163	373	208	1087	282	562	243	699	789	1126	1048	0.244	12
Cao2016	355	90	168	97	362	109	182	71	348	362	400	324	0.750	11
Shi2016	641	220	323	98	806	261	399	146	763	519	921	691	0.762	15
Mao2017	173	49	84	40	175	51	86	38	182	164	188	162	0.877	10
rs6220	Total	AA	AG	GG	Total	AA	AG	GG	A	G	A	G		
Al-Zahrani2006	2028	1077	763	188	2184	1169	868	147	2917	1139	3206	1162	0.407	15
Canzian2006	789	405	325	59	1531	813	592	126	1135	443	2218	844	0.215	15
Johansson2007	2586	1315	1062	209	1632	881	615	136	3692	1480	2377	887	0.053	15
Chia2008	572	294	232	46	699	355	273	71	820	324	983	415	0.088	15
Lonn2008	471	247	187	37	466	214	219	33	681	261	647	285	0.021	8
Suzuki2008	774	380	322	72	706	362	286	58	1082	466	1010	402	0.886	12
Feik2010	121	60	53	8	1730	912	666	152	173	69	2490	970	0.056	15
Lu2015	744	234	366	144	1087	354	547	186	834	654	1255	919	0.306	12
Costa-silva2017	42	14	22	6	50	16	30	4	50	34	62	38	0.053	9

HWE = Hardy–Weinberg equilibrium, HNC = head and neck cancer, EC = esophageal carcinoma, CRC = colorectal cancer.

was identified between rs6220 and cancer risk in any of the 5 models (n = 9, case = 8127, control = 10,085, Table 3). The results of the stratified analysis of ethnicity demonstrate that rs6220 is associated with a significantly increased cancer risk among the Caucasian population under the allele model (n = 4, case = 5524, control = 7077, Table 3, G vs A: OR, 1.06, 95% CI, 1.00–1.13, $P = .043$). The results of the stratified analysis of cancer type suggest that rs6220 is associated with a significantly increased risk of breast cancer under the homozygote model (n = 3, case = 2859, control = 3765, Table 3, GG vs AA: OR, 1.23, 95% CI, 1.02–1.48, $P = .031$). The results synthesized from studies that scored no less than 12 showed that rs6220 increased cancer risk under the allele model (n = 7, case = 7614, control = 9569, Table 3, G vs A: OR, 1.06, 95% CI, 1.00–1.11, $P = .033$). The instability of the rs6220 results in the analyses stratified by score demonstrates that rs6220 tends to increase cancer risk.

The number of studies used in this assessment was limited. Thus, more studies on the associations between the rs5742714, rs6214, and rs6220 polymorphisms and cancer risk are warranted to confirm these conclusions, and the molecular mechanisms via which these polymorphisms function should also be explored.

3.3. Sensitivity analysis

Sensitivity was evaluated by deleting each study once at a time. The corresponding ORs were not altered by any single study for rs5742714, rs6214, or rs6220 (Fig. 3 and Supplementary Table 2, http://links.lww.com/MD/C721), demonstrating that the results were relatively stable in our meta-analysis.

3.4. Publication bias

A Begg test and an Egger test were performed to determine the publication biases of the studies. No statistical evidence of publication bias was observed in any of the 5 models for rs5742714, rs6214, or rs6220 (Table 4).

4. Discussion

The IGF signaling system plays an important role in cell proliferation, differentiation, and apoptosis.[1] IGF1 promotes cell proliferation via the RAS-mitogen-activated protein kinase (MAPK) signaling pathway.[38,39] Moreover, it is also a potent anti-apoptotic molecule that activates the

Table 3

Meta-analysis of the association between rs5742714, rs6214, and rs6220 polymorphisms and cancer risk.

		Allele model			Homozygote model			Heterozygote model			Dominant model			Recessive model		
Subgroup	**No.**	**OR (95% CI)**	P_{OR}	P_h	**OR (95% CI)**	P_{OR}	P_h	**OR (95% CI)**	P_{OR}	P_h	**OR (95% CI)**	P_{OR}	P_h	**OR (95% CI)**	P_{OR}	P_h
rs5742714		C vs G			CC vs GG			GC vs GG			CC+GC vs GG			CC vs GC+GG		
Overall	9	0.98 (0.86–1.11)*	.705	.003	0.86 (0.58–1.30)*	.480	.001	0.98 (0.89–1.06)	.563	.101	0.98 (0.87–1.10)*	.704	.048	0.87 (0.58–1.32)*	.522	.001
Asian	7	0.94 (0.81–1.09)*	.403	.004	0.83 (0.52–1.30)*	.406	.001	0.94 (0.85–1.03)	.184	.128	0.94 (0.82–1.07)*	.334	.064	0.84 (0.53–1.33)*	.458	<.001
Gastric cancer	2	1.05 (0.94–1.18)	.399	.614	1.27 (0.79–2.06)*	.328	.084	0.92 (0.69–1.22)*	.547	.067	0.99 (0.86–1.15)	.925	.432	1.32 (0.73–2.37)*	.354	.031
Pancreatic cancer	2	1.10 (0.92–1.31)	.285	.229	1.05 (0.36–3.10)*	.925	.098	1.15 (0.94–1.41)	.182	.858	1.14 (0.93–1.39)	.198	.527	1.11 (0.34–3.03)*	.978	.092
Quality score≥12	7	1.02 (0.90–1.15)*	.769	.027	1.01 (0.67–1.50)*	.982	.011	1.00 (0.88–1.13)*	.962	.080	1.01 (0.89–1.14)*	.914	.092	1.01 (0.67–1.53)*	.946	.006
rs6214		A vs. G			AA vs. GG			GA vs. GG			AA+GA vs. GG			AA vs. GA+GG		
Overall	16	1.00 (0.92–1.08)*	.926	<.001	1.01 (0.87–1.19)*	.864	<.001	0.98 (0.90–1.07)*	.653	.063	0.99 (0.89–1.01)*	.836	.001	1.01 (0.90–1.15)*	.831	<.001
Caucasian	6	1.04 (0.94–1.15)*	.471	.025	1.09 (0.90–1.33)*	.375	.046	0.95 (0.87–1.03)	.213	.135	1.02 (0.88–1.17)*	.831	.038	1.07 (0.96–1.19)	.218	.297
Asian	6	1.67 (0.93–1.22)*	.359	.003	1.15 (0.88–1.48)*	.304	.006	1.09 (0.97–1.23)	.135	.976	1.11 (0.99–1.24)	.076	.419	1.08 (0.85–1.37)*	.545	.001
Breast cancer	4	0.94 (0.88–1.00)	.044	.610	0.90 (0.79–1.03)	.116	.540	0.88 (0.80–0.97)	.012	.807	0.89 (0.81–0.97)	.011	.830	0.97 (0.86–1.09)	.602	.371
Colorectal cancer	3	1.08 (0.95–1.23)	.215	.138	1.16 (0.91–1.46)	.241	.132	1.07 (0.87–1.33)	.485	.630	1.09 (0.91–1.31)	.368	.292	1.13 (0.91–1.41)	.276	.231
Pancreatic cancer	2	0.77 (0.58–1.03)*	.074	.043	0.63 (0.38–1.04)*	.068	.087	0.84 (0.49–1.45)*	.528	.021	0.77 (0.47–1.26)*	.300	.025	0.68 (0.53–0.87)	.003	.394
Quality score≥12	12	0.99 (0.90–1.10)*	.884	<.001	1.01 (0.84–1.21)*	.940	<.001	0.98 (0.90–1.07)*	.640	.018	0.98 (0.87–1.12)*	.811	<.001	1.01 (0.88–1.17)*	.844	.003
rs6220		G vs A			GG vs AA			AG vs AA			GG+AG vs AA			GG vs AG+AA		
Overall	9	1.04 (1.00–1.10)	.078	.653	1.01 (0.98–1.23)	.093	.306	1.03 (0.97–1.03)	.322	.158	1.05 (0.98–1.11)	.164	.418	1.09 (0.98–1.21)	.123	.344
Caucasian	4	1.06 (1.00–1.13)	.043	.930	1.13 (0.98–1.30)	.106	.130	1.07 (0.98–1.15)	.121	.176	1.08 (1.00–1.16)	.061	.661	1.04 (0.80–1.36)*	.748	.033
Breast cancer	3	1.06 (0.98–1.15)	.137	.836	1.23 (1.02–1.48)	.031	.151	1.00 (0.90–1.11)	.982	.410	1.03 (0.94–1.14)	.503	.861	1.20 (0.81–1.77)*	.371	.063
Quality score≥12	7	1.06 (1.00–1.11)	.033	.866	1.11 (0.99–1.24)	.09	.182	1.06 (0.99–1.13)	.107	.516	1.07 (1.00–1.14)	.052	.888	1.05 (0.89–1.24)*	.564	.061

OR=odds ratio, 95% CI=95% confidence interval, P_{OR}=pool P value, P_h=P value of heterogeneity test

*indicates that the OR=95% CI=and corresponding P_{OR} were calculated based on the random-effects model, otherwise=the fixed-effects model was used.

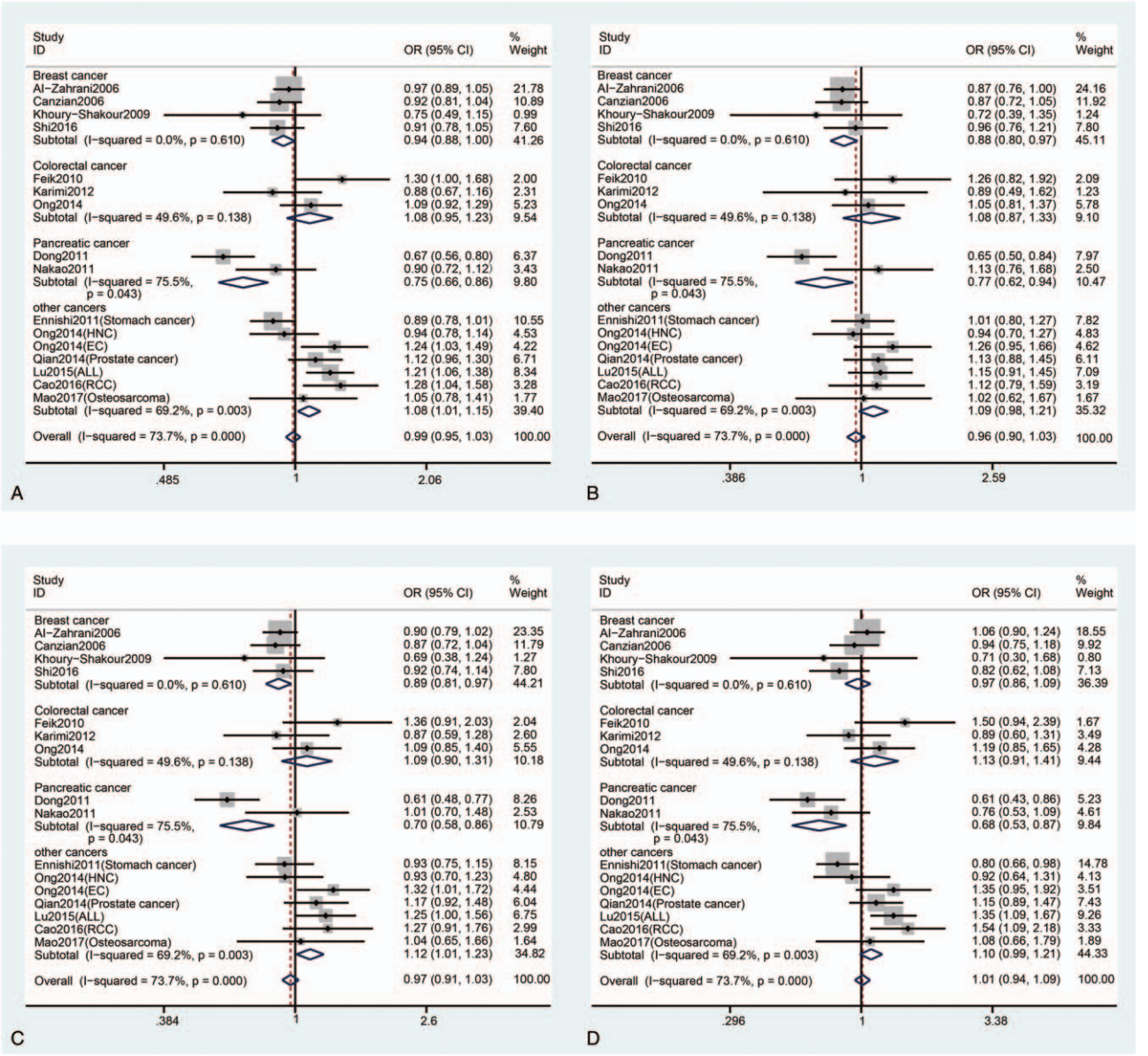

Figure 2. Stratification analyses by cancer type between rs6214 polymorphism and cancer risk. A: allele model; B: heterozygote model; C: dominant model; D: recessive model. The squares and horizontal lines correspond to the study specific OR and 95% CI. The area of the squares reflects the weight. The diamond represents the summary OR and 95% CI. The fixed-effects model was used. CI = confidence interval, OR = odds ratio.

phosphatidylinositol 3-kinase (PI-3K)-AKT pathway.[40,41] Several *IGF1* polymorphisms have been found to be associated with elevated IGF1 levels in the circulation, thus increasing the risk of cancer.[12,27] The previous meta-analyses of the relationship between *IGF1* polymorphism and cancer focused on studies of *IGF1* CA repeat variants. For the first time, we have systematically reviewed and investigated the relationship between the SNPs in the *IGF1* gene's 3'-UTR sequences and cancer risk. We have synthesized the results from those groups contained in 2 or more studies. Thus far, for some types of cancer, there is only a single study. We reviewed these studies in the discussion.

In the present meta-analysis, 3 *IGF1* polymorphisms were included: rs5742714, rs6214, and rs6220. The criteria for selecting these SNPs were as follows: the SNP should be located in the 3'-UTR region of the *IGF1* gene, the SNP should have been reported to have a relationship with cancer risk previously, and the minor allele frequency (MAF) of a selected SNP should be no less than 5% in most of the populations in the 1000 Genomes Project Phase 3 (Supplementary Table 3, http://links.lww.com/MD/C721). Supplementary Figure 1, http://links.lww.com/MD/C721 shows the linkage disequilibrium (LD) for the 3 SNPs.

The rs5742714 C allele has been reported as a protective mutation in childhood acute lymphoblastic leukemia (ALL) and renal cell carcinoma (RCC). Additionally, the GC and CC genotypes have been reported to reduce the risk of childhood ALL and RCC as compared to the GG genotype.[26,27] Cao et al explored the potential functionality of rs5742714, finding that carriers with the GG genotype had higher levels of IGF1 expression in their renal tissues than carriers with the GC or CC genotype. Further, the rs5742714 C allele was observed to create

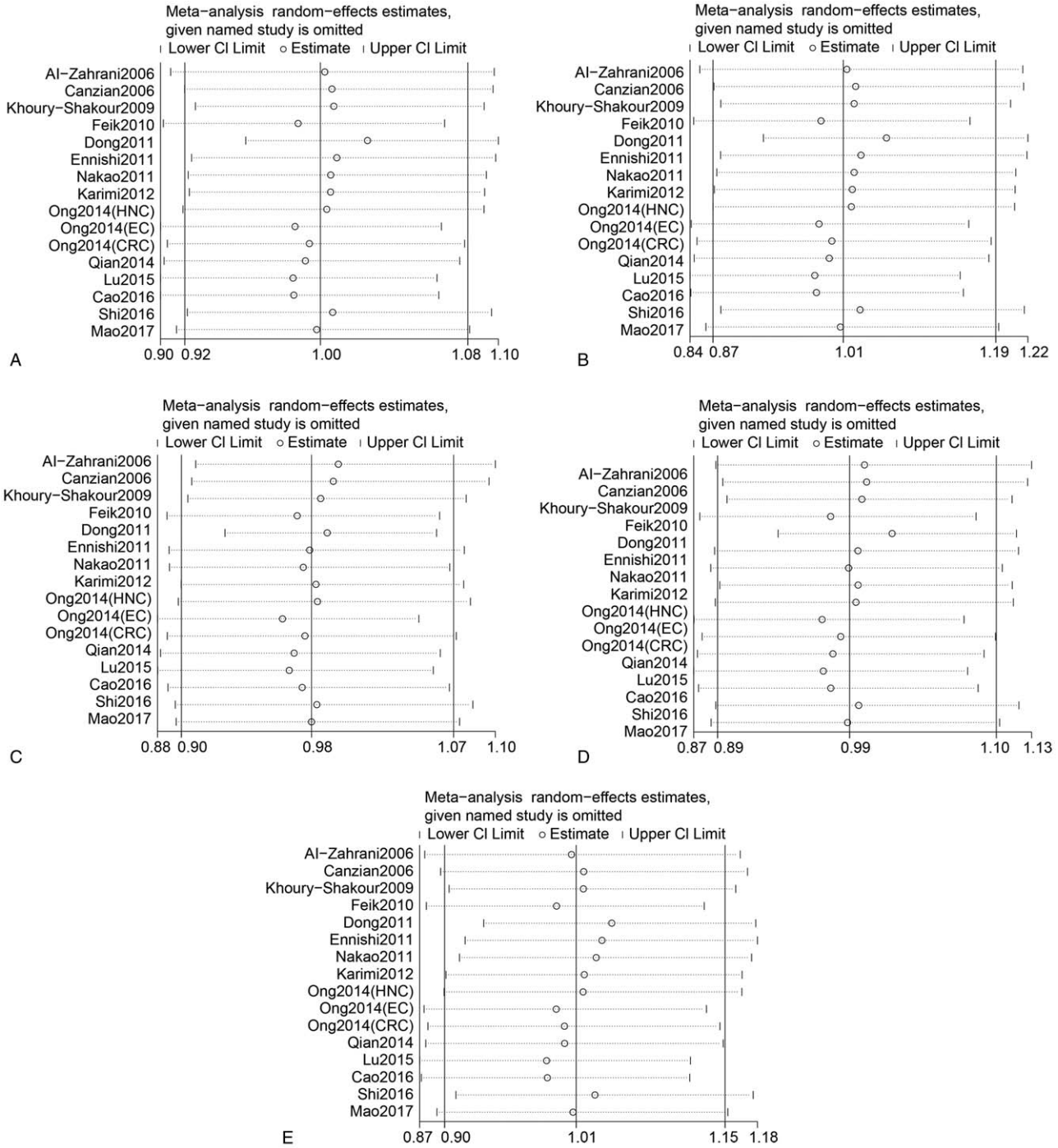

Figure 3. Sensitivity analyses between rs6214 polymorphism and cancer risk. A: allele model; B: homozygous model; C: heterozygous model; D: dominant model; E: recessive model. The random-effects model was used.

a microRNA binding site for hsa-mir-580, unlike the G allele.[27] Naoko et al reported that among patients with BMIs 25 or greater at age 20, pancreatic cancer risk was increased with the presence of the C allele for rs5742714.[21] Thus, in the present meta-analysis, we suggest that rs5742714 is not significantly associated with gastric or pancreatic cancer risk.

rs6214 is located in the 3'-UTR region of exon 4 in *IGF1* and does not cause any amino acid change itself. However, it may have regulatory functions or could be linked with functional alleles at exon 4, leading to a change in the amino acid sequence in the IGF1.[42] Vella et al (2008) tested IGF1 protein levels at birth and at age 7 or 8 years in children who had a different genotype of rs6214. They found that rs6214 polymorphism could increase IGF1 concentrations, but no association was shown between this polymorphism and growth or glucose metabolism.[43] Lu et al reported that rs6214 polymorphism could increase expression of IGF1 mRNA, thus, the difference was not statically significant.[26] Al-Zahrani et al reported that

Table 4

Publication bias analyses.

Polymorphism	Genetic model	Egger's test t	Egger's test 95% CI	Egger's test *P*	Begg's test *P*
rs5742714	C vs G	−0.23	−6.291~5.185	.826	.917
	CC vs GG	−1.26	−5.558~1.702	.249	.466
	GC vs GG	0.47	−3.734~5.581	.654	.917
	CC + GC vs GG	0.17	−4.688~5.421	.869	.917
	CC vs GC + GG	−1.43	−5.715~1.402	.195	.602
rs6214	A vs G	0.24	−2.718~3.404	.814	.893
	AA vs GG	0.23	−2.627~3.246	.824	.822
	GA vs GG	1.10	−0.891~2.762	.290	.822
	AA + GA vs GG	0.88	−1.449~3.478	.392	.444
	AA vs GA + GG	−0.09	−2.698–2.477	.928	.753
rs6220	G vs A	−1.21	−2.569~0.831	.266	.076
	GG vs AA	−0.84	−2.950~1.399	.427	.602
	AG vs AA	−0.56	−3.105~1.915	.592	.602
	GG + AG vs AA	−0.89	−2.760–1.252	.404	.602
	GG vs AG + AA	−0.57	−3.202–1.952	.584	.754

that rs6214 was not associated with circulating IGF1 levels among Caucasian women.[12] In fact, the rs6214 polymorphism A allele has been reported to increase childhood ALL risk,[26] as well as increasing esophageal adenocarcinoma (EAC) and head and neck cancer (HNC) risk in women.[23] For the present meta-analysis, it was observed that rs6214 reduced the risk of breast cancer under the allele, the heterozygote, and the dominant models, as well as reducing the risk of pancreatic cancer under the recessive model.

It has been reported that the rs6220 G alleles are significantly associated with increasing levels of IGF1,[14] thus increasing prostate cancer risk. Furthermore, rs6220 has been found to reduce the risk of the low-grade gliomas.[16] Interestingly, Al-Zahraniet et al found that there was a statistically significant association between rs6220 and circulating IGF1 levels in females, though, not in males.[12] Moreover, women who have the rs6220 GG genotype had higher IGF1 plasma levels and increased breast density.[29] In the present meta-analysis, it was observed that rs6220 was significantly associated with increasing the risk of breast cancer under the homozygote model. Even if the 3'-UTR sequences cannot translate into proteins, they may contain sequences that are critical for transcriptional regulation, mRNA stability or cellular localization.[17] The biological functions of these polymorphisms in 3'UTR should be explored more in future studies.

The present meta-analysis has several limitations. First, we only included studies published in English. Thus, important studies published in other languages may have been overlooked. Second, the number of studies is relatively small, especially in the stratified analysis. For instance, there is only one study available for rs5742714 regarding ALL, and there is only 1 study available for rs6220 regarding the Asian population, so a pooled study could not be performed for this type of cancer or this ethnicity. Finally, due to the limited information contained in the included articles, we could not analyze adjusted ORs regarding other factors such as gender, age, alcohol intake, and smoking history, which may have influenced the association.

In conclusion, in this study, we systematically reviewed and meta-analyzed the relationship between *IGF1* gene 3'-UTR polymorphisms and cancer risk for the first time. We found that rs5742714, rs6214, and rs6220 were not associated with overall cancer risk. In fact, rs6214 reduced the risk of breast and pancreatic cancer, while rs6220 increased the risk of breast cancer. The study also indicated that rs6220 increased overall cancer risk among Caucasian populations. We need well-designed studies with larger sample sizes to explore the relationship between *IGF1* 3'-UTR polymorphisms and cancer risk in the future.

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