The association between IGF1 Gene 3’-UTR polymorphisms and cancer risk
A Meta-analysis
Gui-Ping Xu, PhD, Wei-Xian Chen, PhD, Wen-Yue Xie, PhD, Li-Fang Wu, PhD,*

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 rs62214 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, rs62220 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, rs62220 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.[11] 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.[12–11] For example, Jiang et al report that the rs5742714 can increase the risk of gastric cancer,[12] 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...
mass indexes (BMIs) of 25 or greater at the age of 20. 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 (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 I² statistic were used to assess heterogeneity. 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. Otherwise, the random-effects model was applied. 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.3,6,17

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.12-33 There is 1 article containing data for different types of cancer,12,33 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.

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=0.044; GA vs GG: OR, 0.88, 95% CI, 0.80–0.97, 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=0.003). 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 10,085 controls. In overall analysis, no significant association was identified between rs6220 and cancer risk in any of the 5 models (n=9, case=8127, control=10,085, Table 3). In the stratified analysis of ethnicity, no significant association was identified between rs6220 and cancer risk among the Asian population (n=7, case=3939, control=6848, Table 3). In the stratified analysis of cancer type, no significant association was identified between rs6220 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.

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       | Brain tumor   | Taqman           | PB              |
| Lorrin            | 2008 | USA     | Mix       | Pancreatic cancer | Taqman           | HB              |
| Suzuki            | 2008 | USA     | Mix       | Breast cancer | Taqman           | PB              |
| Khoury-Shakour     | 2009 | Israel  | Mix       | Colorectal cancer | Taqman           | PB              |
| Felix             | 2010 | Austria | Caucasian | Stomach cancer | Taqman           | HB              |
| Emnishi           | 2011 | Japan   | Asian     | Pancreatic cancer | Taqman           | HB              |
| Nakao             | 2011 | Japan   | Asian     | Prostate cancer | Taqman           | PB              |
| Dong              | 2012 | USA     | Mix       | Pancreatic cancer | MassARRAY and TaqMan | HB              |
| Karimi            | 2013 | Iran    | Iranian   | Colorectal cancer | PCR-RFLP         | PB              |
| 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           | PB              |
| 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.
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 = 23, score = 5.524, control = 7077, Table 3, G vs A: OR, 1.13, 95% CI, 1.00–1.26, 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, 1.02–1.49, 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
| Subgroup          | Allele model | Homozygote model | Heterozygote model | Dominant model | Recessive model |
|-------------------|--------------|------------------|-------------------|----------------|-----------------|
|                   | OR (95% CI) | P<sub>OR</sub>  | P<sub>h</sub>     | OR (95% CI) | P<sub>OR</sub>  | P<sub>h</sub>     | OR (95% CI) | P<sub>OR</sub>  | P<sub>h</sub>     |
| rs5742714         |              |                  |                   |                |                 |                   |              |                 |                 |
| Overall           | C vs G       |                  |                   |                |                 |                   |              |                 |                 |
|                   | 9.98 (0.86-1.11)  | .705             | .003              | 0.86 (0.58-1.30)  | .480          | .001              | 0.98 (0.89-1.07)  | .480          | .001              |
| Asian             | 7.94 (0.81-1.09)  | .403             | .004              | 0.83 (0.52-1.30)  | .406          | .004              | 0.94 (0.86-1.03)  | .480          | .001              |
| Gastric cancer    | 2.01 (0.94-1.18)  | .399             | .014              | 1.27 (0.79-2.00)  | .562          | .047              | 0.92 (0.69-1.22)  | .562          | .047              |
| Pancreatic cancer | 2.11 (0.92-1.31)  | .286             | .229              | 1.05 (0.36-3.10)  | .925          | .098              | 1.15 (0.94-1.41)  | .858          | .072              |
| Quality score<12  | 7.10 (0.90-1.15)  | .769             | .272              | 1.01 (0.67-1.50)  | .982          | .011              | 1.00 (0.88-1.13)  | .962          | .080              |
| Overall           | A vs G       |                  |                   |                |                 |                   |              |                 |                 |
|                   | 0.94 (0.81-1.09)  | .403             | .004              | 0.83 (0.52-1.30)  | .406          | .004              | 0.94 (0.86-1.03)  | .480          | .001              |
| Caucasian         | 6.04 (0.94-1.15)  | .471             | .025              | 1.09 (0.90-1.33)  | .375          | .046              | 0.95 (0.87-1.03)  | .213          | .135              |
| Asian             | 1.67 (0.93-1.22)  | .399             | .003              | 1.15 (0.88-1.48)  | .304          | .006              | 1.09 (0.97-1.23)  | .136          | .097              |
| Breast cancer     | 4.94 (0.88-1.00)  | .044             | .010              | 0.90 (0.73-1.03)  | .116          | .074              | 0.88 (0.80-0.97)  | .012          | .027              |
| Colorectal cancer | 1.08 (0.95-1.23)  | .215             | .138              | 1.16 (0.91-1.46)  | .241          | .132              | 1.07 (0.87-1.33)  | .485          | .132              |
| Pancreatic cancer | 2.07 (0.58-1.03)  | .074             | .043              | 0.63 (0.38-1.04)  | .068          | .087              | 0.84 (0.49-1.45)  | .528          | .021              |
| Quality score<12  | 12.09 (0.90-1.10)  | .884             | <.001             | 1.01 (0.84-1.21)  | .940          | <.001             | 0.98 (0.90-1.07)  | .640          | .018              |
| rs6220            |              |                  |                   |                |                 |                   |              |                 |                 |
| Overall           | G vs A       |                  |                   |                |                 |                   |              |                 |                 |
|                   | 1.04 (1.00-1.10)  | .078             | .653              | 1.01 (0.98-1.03)  | .903          | .306              | 1.03 (0.97-1.03)  | .322          | .158              |
| Caucasian         | 1.04 (1.00-1.10)  | .043             | .930              | 1.13 (0.98-1.30)  | .106          | .130              | 1.07 (0.98-1.19)  | .121          | .176              |
| Breast cancer     | 1.06 (0.98-1.18)  | .836             | .014              | 1.23 (1.02-1.48)  | .031          | .151              | 1.00 (0.90-1.11)  | .982          | .419              |
| Quality score<12  | 7.10 (0.90-1.10)  | .399             | .014              | 1.11 (0.99-1.24)  | .09          | .182              | 1.06 (0.99-1.13)  | .107          | .516              |

OR = odds ratio, 95% CI = 95% confidence interval, P<sub>OR</sub> = pooled P value, P<sub>h</sub> = P value of heterogeneity test.

* indicates that the OR = 95% CI and corresponding P<sub>OR</sub> were calculated based on the random-effects model, otherwise = the fixed-effects model was used.
Several IGF1 polymorphisms have been found to be associated with elevated IGF1 levels in the circulation, thus increasing the risk of cancer. 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 rs5742714C 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.

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.
Naoko et al reported that among patients with BMI 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

![Figure 3](https://example.com/figure3.png)

**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.
that rs6214 was not associated with circulating IGF1 levels among Caucasian women.\cite{6} In fact, the rs6214 polymorphism A allele has been reported to increase childhood ALL risk,\cite{7} as well as increasing esophageal adenocarcinoma (EAC) and head and neck cancer (HNC) risk in women.\cite{8} For the present meta-analysis, it was observed that rs6214 reduced the risk of breast cancer under the allele, the heterozygote, and the dominant model, 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\cite{4} thus increasing prostate cancer risk. Furthermore, rs6220 has been found to reduce the risk of the low-grade gliomas.\cite{5} Interestingly, Al-Zahran et al found that there was a statistically significant association between rs6220 and circulating IGF1 levels in females, though, not in males.\cite{6} Moreover, women who have the rs6220 GG genotype had higher IGF1 plasma levels and increased breast density.\cite{7} 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.\cite{8} 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.

**Author contributions**

Conceptualization: Li-Fang Wu.

Data curation: Gui-Ping Xu.

Formal analysis: Gui-Ping Xu, Li-Fang Wu.

Funding acquisition: Gui-Ping Xu.

Methodology: Li-Fang Wu.

Project administration: Gui-Ping Xu, Li-Fang Wu.

Software: Gui-Ping Xu, Li-Fang Wu.

Validation: Wen-yue Xie.

Writing – original draft: Li-Fang Wu.

Writing – review & editing: Gui-Ping Xu, Wei-Xian Chen, Li-Fang Wu.

Li-Fang Wu orcid: 0000-0003-3334-2923.

**References**

[1] Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nat Rev Cancer 2004;4:503–18.

[2] Holly JM, Perks CM. Insulin-like growth factor physiology: what we have learned from human studies. Endocrinol Metab Clin North Am 2012;41:249–63.

[3] Baserga R, Peruzzi F, Reiss K. The IGF-1 receptor in cancer biology. Int J Relat Cancer 2006;13:273–7.

[4] Renehan AG, Harvie M, Howell A. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and breast cancer risk: eight years on. Endocr Relat Cancer 2006;13:273–8.

[5] Rowlands MA, Gunnell D, Harris R, et al. Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis, Int J Cancer 2009;124:2416–29.

[6] Harrela M, Kosinen H, Kaprio J, et al. Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3, J Clin Endocrinol Metab 1996;89:2612–5.

[7] Verhaeghe J, Loos R, Vlentack R, et al. Copeptide, insulin-like growth factors I and II, and insulin-like growth factor binding protein-1 in cord serum of twins: genetic versus environmental regulation. Am J Obstet Gynecol 1996;175:1186–8.

[8] Hong Y, Brismar K, Hall K, et al. Associations between insulin-like growth factor-I (IGF-II), IGF-binding protein-1, insulin and other metabolic

---

**Table 4**

| Polymorphism | Genetic model | t    | Egger’s test | 95% CI | P  | Begg’s test | P  |
|--------------|---------------|------|--------------|-------|----|-------------|----|
| rs5742714    | G vs A        | -0.23| -2.201–5.185 | .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| -2.638–2.477 | .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 | .604  | .602|             |    |
|              | GG vs AG + AA | -0.57| -3.202–1.952 | .584  | .754|             |    |
[9] Hall K, Hilding A, Thoren M. Determinants of circulating insulin-like growth factor-I. J Endocrinol Invest 1999;22(suppl 5):48–57.

[10] Eeles RA, Kote-Jarai Z, Al Olama AA, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. Nat Genet 2009;41:1116–21.

[11] Mazumder B, Seshadri V, Fox PL. Translational control by the 3'UTR of IGF1 with the risk of gastric cancer in a Chinese population. Cell Physiol Biochem 2015;36:884–92.

[12] Liao L, Wang F, He L, et al. Interaction between IGF1 polymorphisms and the risk of acute lymphoblastic leukemia in Chinese children. Cell Physiol Biochem 2015;36:1346–58.

[13] Cao Q, Liang C, Xue J, et al. Genetic variation in IGF1 predicts renal cell carcinoma susceptibility and prognosis in Chinese population. Sci Rep 2016;6:39014.

[14] Shi J, Aronson KJ, Grundy A, et al. Polymorphisms of insulin-like growth factor-I pathway genes and breast cancer risk. Front Oncol 2016;6:136.

[15] Costa-Silva DR, da Conceição Barros-Oliveira M, Borges RS, et al. Insulin-like growth factor I gene polymorphism in women with breast cancer. Med Oncol 2017;34:59.

[16] Miao J, Zhang G, Chen Z. Genetic polymorphisms of insulin-like growth factor-I gene variation and breast cancer risk are associated with osteosarcoma risk and prognosis. Med Sci Monit 2017;23:5892–8.

[17] Dong X, Li Y, Tang H, et al. Insulin-like growth factor axis gene polymorphisms modify risk of pancreatic cancer. Cancer Epidemiol 2012;36:206–11.

[18] Tian X, Dai S, Sun J, et al. Association between TP53 Arg72Pro polymorphism and leukemia risk: a meta-analysis of 14 case-control studies. Sci Rep 2016;6:24097.

[19] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

[20] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Nat Cancer Inst 1959;22:719–48.

[21] DerSimonian R, Laird N. Meta-analysis in clinical trials. Contr Clini Trials 1986;7:177–88.

[22] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[23] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629.