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Association between the IGFBP-3 rs2854744 polymorphism and cancer risk: a meta-analysis

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Abstract

Background Recently, the association of IGFBP-3 polymorphism and cancer risk has attracted many attentions. Previous studies have shown that IGFBP-3 rs2854744 was associated with cancer, but the results were conflicting.

Method and results We performed a meta-analysis including 33 studies with 24,688 cases and 28,972 controls to seek the association among them. A significant increase of cancer risk was found between the IGFBP-3 rs2854744 Polymorphism and cancer risk in Recessive Model (CC vs. AC/AA: OR = 1.097, 95%CI: 1.020, 1.180, $P < 0.05$). While in subgroup analysis, A same increase of breast cancer risk also have been shown in our study in Recessive Model (CC vs. AC/AA: OR = 1.126, 95%CI: 1.007, 1.260, $P < 0.05$).

Conclusions The results of our meta-analysis concluded that the IGFBP-3 rs2854744 polymorphism was closely related with the increase of cancer risk while further large size case–control studies are required.

Keywords IGFBP-3, Polymorphism, Cancer

Introduction

As an evolutionarily conserved axis believed to regulate carbohydrate metabolism, the growth hormone-insulin-like growth factor (GH-IGF) axis is recognized for its role in maintaining the physiological function and metabolism of various tissues [1, 2]. The insulin-like growth factors (IGFs) are crucial in modulating cell proliferation and apoptosis [3, 4]. Numerous in vitro studies have demonstrated that IGFs act as potent catalysts for the proliferation of various cancer cell types while also exerting an inhibitory effect on cell apoptosis. This dual role significantly contributes to tumor cell growth [5, 6]. The interaction between IGFs and their receptors is modulated by insulin-like growth factor binding proteins (IGFBPs). Among these, IGFBP-3 is particularly significant, as it regulates over 90% of circulating IGFs in the serum [7]. These findings provide a basis for hypothesizing a link between IGFBP-3 and cancer risk. Recent research has shown that the IGFBP-3 rs2854744 polymorphism is significantly associated with reduced levels of IGFBP-3 in blood, as evidenced by both in vitro and in vivo studies [8, 9]. The studies conducted have yielded varying and sometimes conflicting results regarding the association between IGFBP-3 rs2854744 polymorphism and cancer risk. Mehta's study suggested that low IGFBP-3 levels are associated with an increased risk of

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prostate cancer. In contrast, Morris and colleagues found no significant association between IGFBP-3 levels and prostate cancer risk [10, 11]. Nomura's research indicated that decreased IGFBP-3 levels are linked to a higher incidence of colorectal cancer, a finding that Teramukai's study corroborated [12, 13]. To further investigate the relationship between IGFBP-3 rs2854744 polymorphism and cancer risk, we conducted a meta-analysis to examine the association of this gene polymorphism with overall cancer risk and its impact on various cancer types. Previous studies have demonstrated that IGFs play a role in mediating cell proliferation across several tissues, including lung, prostate, breast, and colorectal epithelial cells [14]. Therefore, we categorized the malignant tumor types in our analysis as lung cancer, colorectal cancer, breast cancer, prostate cancer, and other cancers.

Method

Identification of eligible studies

A literature search was preformed basing on the PubMed database, Web of Science, Chinese Wan Fang databases and Chinese National Knowledge Infrastructure (CNKI) with the key words: "IGFBP3" and ("polymorphism" or "single nucleotide polymorphism" or "SNP" or "variation")and("cancer"or "carcinoma" or " tumor") until August 1,2023. Searching was performed without limitation on language or publication years. Clinical trial number: not applicable.

Exclusion and inclusion criteria

Studies were picked out if they met the following conditions: (1)case and control studies; (2) focusing on the association between IGFBP3 rs2854744 SNP and cancer risks; (3) providing detail genotype frequencies. Those studies with no detail genotype frequencies were excluded.

Data extraction

We extracted data for all eligible studies according to different cancer types and different genotypes, and collected the first author of these studies, the year of publication, the type of cancer, the numbers of cases and controls, and the frequency of each genetype in the cases and controls.

Statistical analysis

Chi-square tests were employed to assess Hardy–Weinberg equilibrium in the gene frequencies of the control groups across all included studies. To analyze the association between the IGFBP3 rs2854744 single nucleotide polymorphism (SNP) and cancer risk, we utilized five genetic models: the allele model (A vs. C), the heterozygote model (AC vs. AA), the homozygote model (CC vs. AA), the dominant model (AC/CC vs. AA), and the recessive model (CC vs. AC/AA). The strength of the association was quantified using the Odds Ratio (OR) with 95% Confidence Intervals (95% CI). The Q statistic test, based on the chi-square distribution, was conducted to evaluate between-study heterogeneity. A p-value of less than 0.10 or an I^2 statistic greater than 50% was considered indicative of significant heterogeneity [15]. In the presence of heterogeneity, a random-effects model was applied to calculate the pooled OR for each study. Publication bias was assessed using Begg's funnel plot. All statistical analyses were performed using Stata software, version 11.0.

Results

Characteristics of eligible studies

There were 7431 potentially eligible studies were searched by the initial screening. According to inclusion and exclusion criteria, 14 articles were excluded for the reason of no detailed genotyping information, 5259 articles were not focus on cancer and 2125 articles were not related to rs2854744. The specific process was shown in Fig. 1. After all, there were 33 eligible studies, including 24,688 cases and 28,972 controls, relevant to the association between IGFBP-3 rs2854744 polymorphism and cancer risk. In the 33 eligible studies, 7 of them were studies of Breast Cancer (BC), 12 studies were of Prostate Cancer (PC), 6 studies were of Colorectal Cancer (CC), only 2 studies were of Lung Cancer (LC) and 6 studies were of Other Cancer (OC) (details shown in Table 1).

Meta-analysis results

In the overall analysis, we found a significant association between IGFBP3 rs2854744 polymorphism and the risk of cancer in recessive model(CC vs. AC/AA: OR = 1.097, 95%CI: 1.020,1.180;$P < 0.05$ $I^2 < 50\%$), Same results were shown both in homozygote model(CC vs. AA: OR = 1.177,95%CI: 1.056,1.311; $P < 0.05$ $I^2 > 50\%$) and allele model (A vs. C: OR = 1.060, 95%CI: 1.008, 1.115; $P < 0.05$ $I^2 > 50\%$). However, the heterozygote model and dominant model had proved no obvious association between the IGFBP3 rs2854744 polymorphism and cancer risk.We used the random effects model to pool the result, all of these was shown in Fig. 2.

The sub-group analyses were performed to evaluate the influence of cancer types. An increased risk of breast cancer was fund in recessive model (CC vs. AC/AA: OR = 1.126, 95%CI: 1.007, 1.260; $P < 0.05$), homozygote model (CC vs. AA: OR = 1.204, 95%CI: 1.035, 1.401; $P < 0.05$) and allele model (A vs. C: OR = 1.071, 95%CI: 1.008, 1.137; $P < 0.05$). No association was fund both in prostate cancer and colorectal cancer between the IGFBP-3 rs2854744 Polymorphism and them. While in Lung cancer, all five models have shown a tendency of decrease risk between the IGFBP-3 rs2854744

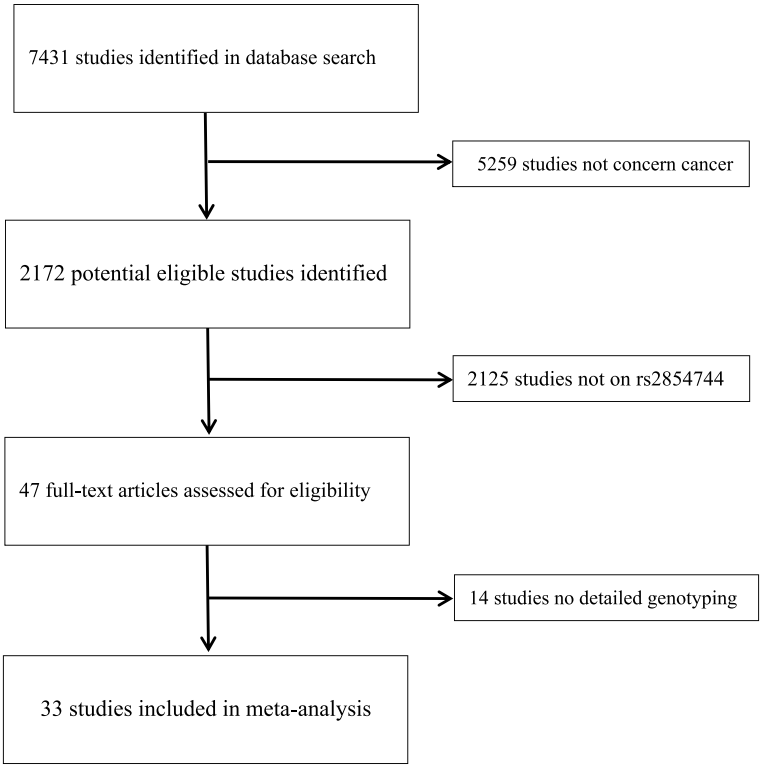

Fig. 1 Study flow chart explaining the selection of the 33 eligible article

Polymorphism and it, however, the research of this topic seems to be so pool.

Heterogeneity

No significant heterogeneity was fund in colorectal cancer, breast cancer and prostate cancer but for lung cancer and other cancer.

Publication bias

We used the Begg's funnel plot test to evaluate the publication bias. Since no obvious asymmetry was fund in all five genetic models, it is reasonable to believe that there was no significant publication bias among our study. The detailed result was shown in Fig. 3.

Discussion

In our meta-analysis, we examined 33 studies encompassing 24,688 cancer cases and 28,972 healthy controls to assess the association between the IGFBP-3 rs2854744 single nucleotide polymorphism (SNP) and cancer risk. The IGFBP-3 rs2854744 polymorphism was associated with an increased risk of cancer, but this increased risk was not observed in all types of cancer. In subgroup analyses, the increased risk was significant only in breast cancer, but not in most other cancers. Even in lung cancer, the effect was inverse, although it is not convincing because of the small number of data.

Previous studies had shown that the IGFBP-3 rs2854744 polymorphism was not associated with the risk of colorectal cancer [16, 17], and our study confirmed this view with newer and more complete data on the basis of them. Although only breast cancer was found to be associated with IGFBP-3 rs2854744 polymorphism in subgroup analyses, positive associations were found in other categories of cancers (including esophageal cancer and bladder cancer) in both allele and dominant model subgroup analyses. It is just that there are too few studies related to this classification of cancers and IGFBP-3 rs2854744 polymorphism to definitively verify the association of individual diseases with IGFBP-3 rs2854744 polymorphism.

In our study, it seems that for most cancers, the IGFBP-3 rs2854744 polymorphism may increase the risk of disease or show a trend of increasing the risk of disease, but this trend was shown in the opposite direction in only two studies on lung cancer, although the data were not statistically significant. Study had shown that in the circulatory system, the majority of IGF-1 is bound to IGFBP-3. The IGFBP-3 protein can regulate IGF-1 activity through competitive inhibition [18]. IGFBP-3 inhibits the biological activity of IGF by blocking its binding to the receptor; conversely, it can enhance IGF action by preventing its degradation [19, 20]. On the other hand,the effect of IGFBP-3 on cancer cell growth is influenced by both time and concentration, varying according

Table 1 Characteristics of eligible studies

Author	Year	cancertype	Case			Control			*p*-value(HWE)
			AA	AC	CC	AA	AC	CC	
Wong et. al	2005	CC	166	90	16	480	306	35	0.112
Ren et. al	2004	BC	641	405	63	708	455	44	0.005
Cheng et. al	2006	PC	687	1002	590	720	954	581	8.426
Cheng et. al	2006	BC	502	673	389	598	891	431	4.520
Moon et. al	2006	LC	131	73	5	95	91	23	8.631
Wagner et. al	2005	BC	57	210	156	122	289	238	4.152
Hernandez et. al	2007	PC	112	197	92	113	183	70	7.889
Wang et. al	2003	PC	189	100	18	152	105	15	5.693
Schildkra et. al	2005	PC	18	55	27	23	41	28	3.090
Al-Zahrani et. al	2006	BC	834	2150	1327	940	2203	1306	8.457
Slattery et. al	2006	CC	497	1090	690	631	1465	838	8.440
Canzian et. al	2006	BC	200	368	208	369	743	407	4.106
Nam et. al	2003	PC	135	233	115	145	274	129	9.841
Chen et. al	2006	PC	55	91	67	47	103	63	6.895
Li et. al	2004	PC	97	217	126	139	225	115	2.029
Han et. al	2008	LC	236	152	22	247	141	23	6.274
Pechlivan et. al	2007	CC	135	314	165	122	262	163	3.915
Chen et. al	2008	OC	353	192	31	419	199	29	3.902
Elisabeth et. al	2010	CC	37	59	25	504	845	381	4.501
Chen et. al	2008	OC	353	192	31	419	199	29	1.567
Zhao et. al	2015	OC	26	51	33	45	55	28	4.391
Mohammad et. al	2011	OC	22	85	55	82	155	87	2.778
Touraj et. al	2014	CC	43	126	92	61	154	124	1.433
Christopher et. al	2009	OC	49	155	113	33	148	114	0.473
Zhang et al	2015	PC	1926	1059	147	1616	786	87	0.626
Qian et. al	2014	PC	408	225	31	424	246	32	0.588
Safarinejad et. al	2011	PC	23	85	60	89	163	84	0.741
Park et. al	2009	PC	128	76	21	140	76	9	0.762
H. Li et. al	2016	BC	85	46	9	96	55	9	0.428
Temitope et. al	2012	CC	83	111	46	106	153	66	0.174
Guiming et. al	2016	PC	48	447	922	22	292	694	0.444
Wang et. al	2013	OC	11	52	35	45	70	35	0.930
Xiaobin et. al	2015	BC	246	179	40	483	277	39	0.608
Gu Jun et. al	2014	OC	242	138	24	268	136	20	0.112

Type of cancer: '*CC*' for colonrectal cancer, '*BC*' for breast cancer, '*PC*' for prostate cancer; '*LC*' for lung cancer and '*OC*' for other cancer

to the patient [21]. This complex physiological mechanism may partly explain the difference.

Among the 33 eligible studies [16, 17, 20, 22–48], Canzian and colleagues identified a significant association between the –202 A > C polymorphism and an increased risk of breast cancer in Caucasian populations. Similarly, Wagner's study demonstrated that the CC alleles of the IGFBP-3 rs2854744 polymorphism were significantly associated with an increased risk of breast cancer in Polish individuals [26]. Our study also confirmed this association between the IGFBP-3 A-202C polymorphism and breast cancer. In contrast, for prostate cancer, Wang's study found no differences in allele frequencies among patients, a finding corroborated by Nam [28, 33]. However, Hernandez's research indicated that individuals with the CC genotype at the rs2854744 locus of the IGFBP-3 gene had a significantly increased risk of prostate cancer [27]. Our results showed no significant association between the IGFBP-3 A-202C SNP and prostate cancer. Zhiqiang's meta-analysis reached a similar conclusion, although they initially excluded a study for questionable reasons. Subsequently, they identified that the IGFBP-3 rs2854744 SNP was indeed related to prostate cancer susceptibility [49]. No significant association was identified between the IGFBP-3 rs2854744 polymorphism and colorectal cancer risk across the six eligible studies examined.

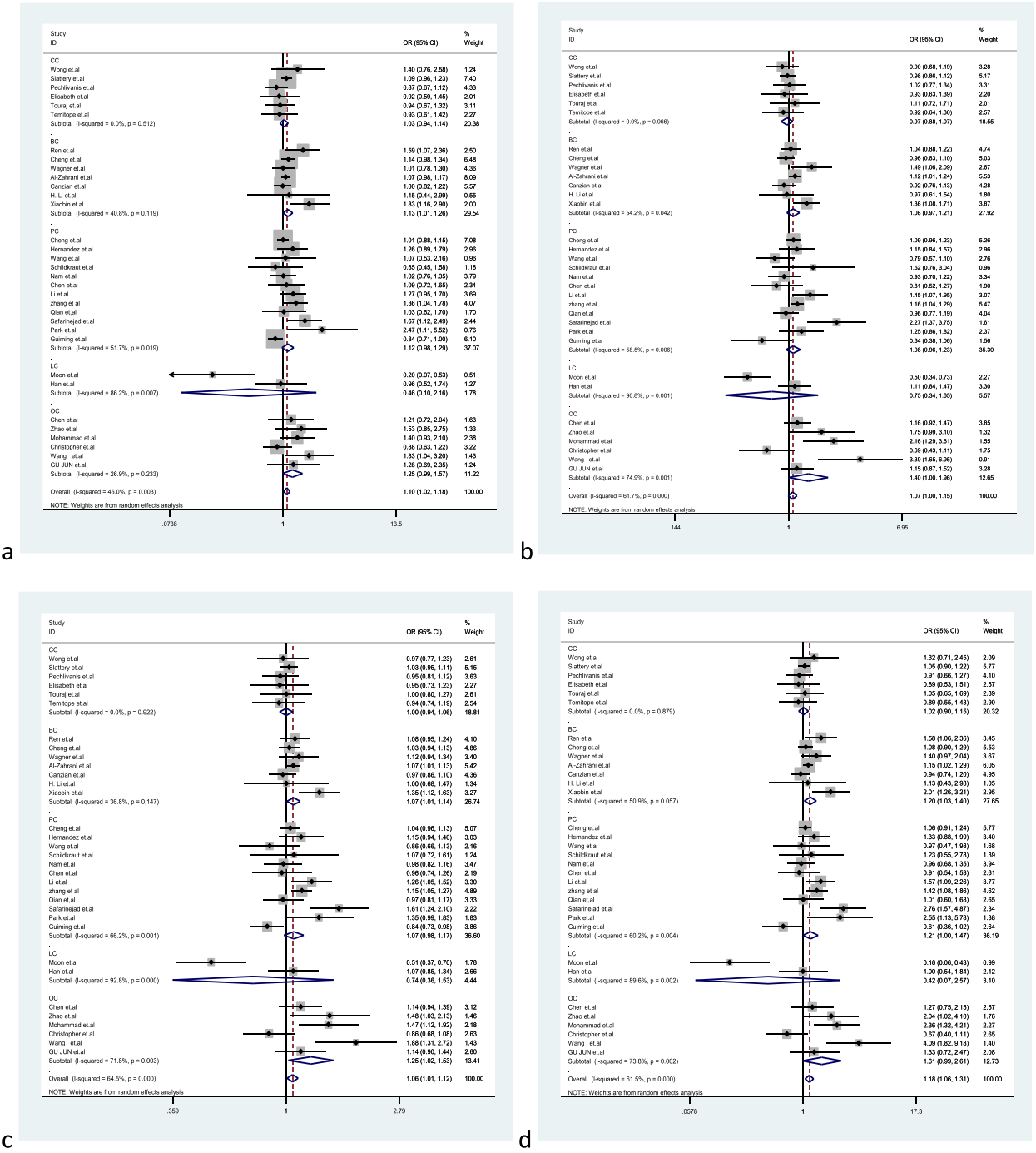

Fig. 2 Forest plots of IGFBP3 rs2854744 polymorphism and cancer for all eligible studies. **a** recessive model: CC vs. AC/AA. **b** dominant model: AC/CC vs. AA. **c** allele model: A vs. C. **d** homozygote model: CC vs. AA

Regarding limitations, due to the limited number of studies and the fact that many hospitals in the included studies enrolled patients with more mixed races and presented data that did not separate these, we were unable to perform subgroup analyses based on ethnicity. However, existing studies have shown that ethnic differences play A large role in the association between IGFBP-3 A-202C polymorphism and cancer. Additionally, factors such as environmental influences and lifestyle should also be considered. Moreover, most control groups in our study were hospital-based rather than population-based, which also warrants consideration. Finally, only studies published in English and Chinese were included in the analysis.

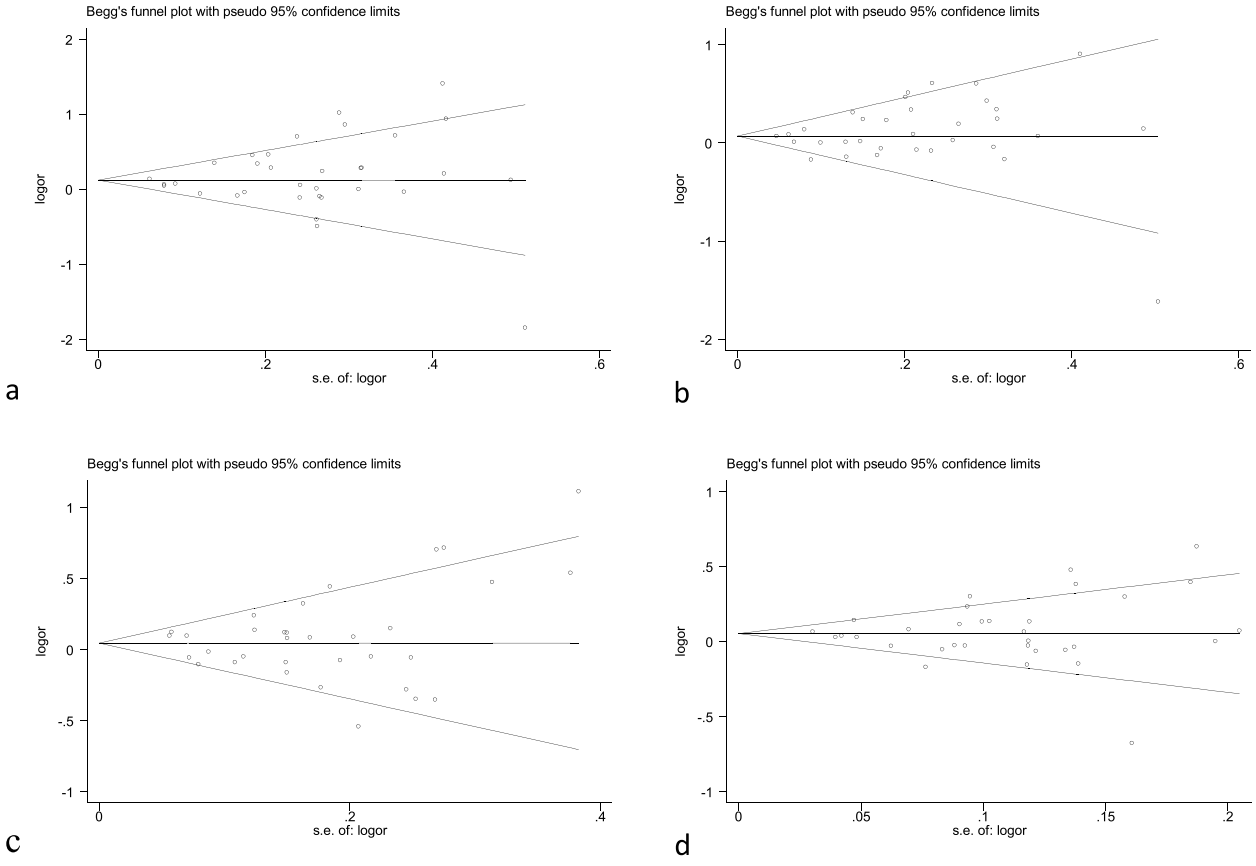

Fig. 3 Funnel plots for all publications **a** homozygote model **b** recessive model **c** heterozygote model. **d** allele model

Our meta-analysis has demonstrated a significant association between the IGFBP-3 rs2854744 polymorphism and cancer risk, with a notable impact on breast cancer. To substantiate these findings, additional large-scale case–control studies are necessary.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-026-02355-0.

Supplementary Material 1.

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Not applicable.

Authors' contributions
Dan Sun performed the experiments and wrote the article. Lihua Xu and Gang Hu performed the experiments. Yajuan Chen revised the article.Na Wang and wanju Wang designed the study and reviewed the article. All authors read and approved the final manuscript as submitted.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Not Applicable.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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