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New concept of the *Axin2* rs2240308 polymorphism and cancer risk: an updated meta-analysis

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Previous meta-analyses reported that the variant T allele of *Axin2* rs2240308 is associated with a decreased cancer risk. However, more recent findings have been inconsistent. Therefore, we carried out an updated meta-analysis to examine whether this polymorphism is still associated with a decreased cancer risk**.** Twelve articles, including 14 case-control studies (2,215 cases and 2,481 controls), were included in our study. Surprisingly, different from previous meta-analyses, no significant association between *Axin2* rs2240308 polymorphism and cancer risk was observed (dominant model: OR=0.85; 95% CI=0.68-1.06). In further stratified analyses, rs2240308 was significantly associated with a decreased cancer risk only in Asians (dominant model: OR=0.76; 95% CI=0.66-0.88), while for Caucasians the variant showed no significant association with cancer risk (dominant model: OR=1.09; 95% CI=0.67-1.76). Moreover, the rs2240308 variant exhibited a significant association with a decreased risk of lung cancer and prostate cancer. These findings provided new evidence that differed from previous meta-analyses; *Axin2* rs2240308 may not modify general cancer susceptibility. Similar with previous meta-analyses, our analysis indicated that *Axin2* rs2240308 may modify cancer susceptibility in an ethnicity- and/or type-specific manner. These findings indicate that further replication studies with large sample sizes are warranted to re-evaluate the relationship between *Axin2* rs2240308 and cancer risk, especially in Caucasians.

Key words: Axin2, rs2240308, polymorphism, cancer, meta-analysis

The continuing global demographic and epidemiologic transitions signal an ever-increasing cancer burden over the next decades, particularly in developing countries, with over 20 million new cancer cases expected annually as early as 2025 [1]. Cancers are considered to be multifactorial diseases, and their occurrences are related to environmental, genetic and lifestyle factors. Remarkably, with the rapid development of genotyping technologies such as genome-wide association studies (GWAS) and next-generation sequencing (NGS), our understanding of the genetic factors that confer cancer risk has substantially broadened.

The Wnt signalling pathway plays a crucial role during embryogenesis, while aberrations in this pathway are implicated in a variety of human cancers. *Axin2*, a key component of the Wnt signalling pathway, plays an important role in the regulation of cell proliferation, cytometaplasia, migration, apoptosis and other important cellular functions, and it has demonstrated a close relationship with the development of some cancers [2, 3]. Specifically, the relationship between genetic polymorphisms of the *Axin2* gene and cancer sensitivity has attracted much interest. The *Axin2* rs2240308 polymorphism has been widely implicated in cancer risk; however, the results of studies exploring this association were inconclusive. For example, a previous study reported that a rs2240308 variant genotype significantly increased the risk of colorectal cancer in Mexican individuals [4]. In contrast, the same variant exhibited no significant association of colorectal cancer risk among Iranian people and resulted in an effect value that was opposite relative to the study of Mexican populations [5]. Regardless, an increasing number of studies have given special attention to the association between *Axin2* rs2240308 and several common types of cancer such as lung cancer[6-8], prostate cancer[9, 10], colorectal cancer [4, 5, 8], ovarian cancer [11], head and neck cancer [8], breast cancer [12], papillary thyroid carcinoma [13], hepatocellular carcinoma [14] and astrocytoma [15]. Moreover, several studies

summarized the associations of *Axin2* rs2240308 with cancer risk by meta-analyses [16-18]. However, some of these results are controversial. For example, the meta-analysis performed by Wu et al. did not integrate all the articles that were published at that time (Table 1). Clearly, the association analyses between *Axin2* rs2240308 and cancer susceptibility are still necessary. Therefore, we performed an updated meta-analysis using all published data to date to more precisely characterize the association between *Axin2* rs2240308 polymorphism and cancer risk.

Materials and methods

Identification and eligibility of relevant studies. Relevant literature was collected by searching PubMed and Web of Science (the last search update was Aug 31, 2016) using the following keywords: ("*Axin2*" or "Axis inhibition protein 2") and ("cancer", "carcinoma", "tumor", "tumour", or "neoplasm") and ("polymorphism", "variation", "variant", or "mutation"). Additionally, the references in the retrieved articles were reviewed for possible inclusion. Only publications written in English with available full-text articles were included in this meta-analysis. In this meta-analysis, all studies met the following standards: (1) involved the *Axin2* rs2240308 polymorphism and cancer risk; (2) designed as a case-controlled study; and (3) contained available genotype frequency. The chief reasons for exclusion of studies were as follows: (1) not involving the *Axin2* gene; (2) not involving rs2240308 polymorphism research; (3) not related to cancer research; and (4) no relevant data reported. Data for meta-analysis were available from 12 articles including 14 case-controlled studies (Figure 1).

Data extraction. Two investigators (Y.Y. and L.L.) independently extracted data and reached consensus on all of the items. The following information, including the first author's name, year of publication, country of origin, ethnicity, type of cancer, numbers of cases and controls, source of controls and genotyping platform, was sought for each article. Ethnicities were categorized as Asians or Caucasians.

Statistical analysis. The risk of cancer associated with *Axin2* rs2240308 was estimated for each study using the odds ratio (OR) and its 95% confidence interval (95% CI). The between-study heterogeneity was examined with a chi-square-based *Q* statistical test, and $P \leq 0.05$ was considered as statistically significant. We pooled the results using fixed-effect models when the heterogeneity between studies was absent. Otherwise, a random-effects model was chosen. Subsequently, we evaluated the risks of the heterozygous and variant homozygous genotypes relative to the wild-type homozygous genotype and then assessed the risks of the combined heterozygous as well as variant homozygous genotypes relative to the wild-type homozygous genotype while assuming the dominant effects of the variant allele. In addition, we also assessed the risks of the variant homozygous genotypes relative to the combined variant heterozygous as well as wild-type homozygous genotype while assuming the recessive effects of the variant allele. Additionally, based on ethnicity (divided into Asians and Caucasians), cancer type, source of controls and sample size, we performed stratification analyses. Funnel plots and Begg's test were utilized to evaluate publication bias. All

Table 1. Characteristics of literature included in the meta-analysis

First Author	Year	Country	Ethnicity	Type of cancer	Case/ Control	Source of controls	Platform	HWE [a]	Included in previous meta-analyses		
									Zhong et al.[16]	Wu et al. [17]	Gong et al. [18]
Rosales-Reynoso	2016	Mexican	Caucasian	Colorectal cancer	201/100	Population-based	PCR-RFLP	0.05			
Aristizabal-Pachon	2016	Brazil	Caucasian	Breast cancer	102/102	Hospital-based	PCR-RFLP	0.00			
Kim	2016	Korea	Asian	HCC [b]	245/483	Hospital-based	Golden gate	0.79			
Liu	2016	China	Asian	PTC [c]	56/50	Hospital-based	Sequenom	0.08	√	√	
Liu	2014	China	Asian	Lung cancer	520/555	Population-based	TaqMan	0.46	√	√	√
Ma	2014	China	Asian	Prostate cancer	103/100	Hospital-based	SNaPshot	0.15	√	√	√
Mostowska	2014	Poland	Caucasian	Ovarian cancer	258/282	Hospital-based	HRM [d]	0.55	√	√	√
Naghibalhossaini	2012	Iran	Asian	Colorectal cancer	110/179	Not report	PCR-RFLP	0.10	√		√
Pinarbasi	2011	Turkish	Caucasian	Prostate cancer	84/100	Hospital-based	PCR-RFLP	0.88	√	√	√
Gunes	2010	Turkish	Caucasian	Astrocytoma	100/100	Hospital-based	PCR-RFLP	0.50	√	√	√
Gunes	2009	Turkish	Caucasian	Lung cancer	100/100	Not report	PCR-RFLP	0.50	√	√	√
Kanzaki	2006	Japan	Asian	Lung cancer	160/110	Population-based	PCR-RFLP	0.86	√	√	√
Kanzaki	2006	Japan	Asian	Colorectal cancer	113/110	Population-based	PCR-RFLP	0.86	√	√	√
Kanzaki	2006	Japan	Asian	HNC [e]	63/110	Population-based	PCR-RFLP	0.86	√	√	√

[a] Hardy-Weinberg equilibrium (HWE)
[b] hepatocellular carcinoma (HCC)
[c] papillary thyroid carcinoma (PTC)
[d] high-resolution melting curve analysis (HRM)
[e] head and neck cancer (HNC)

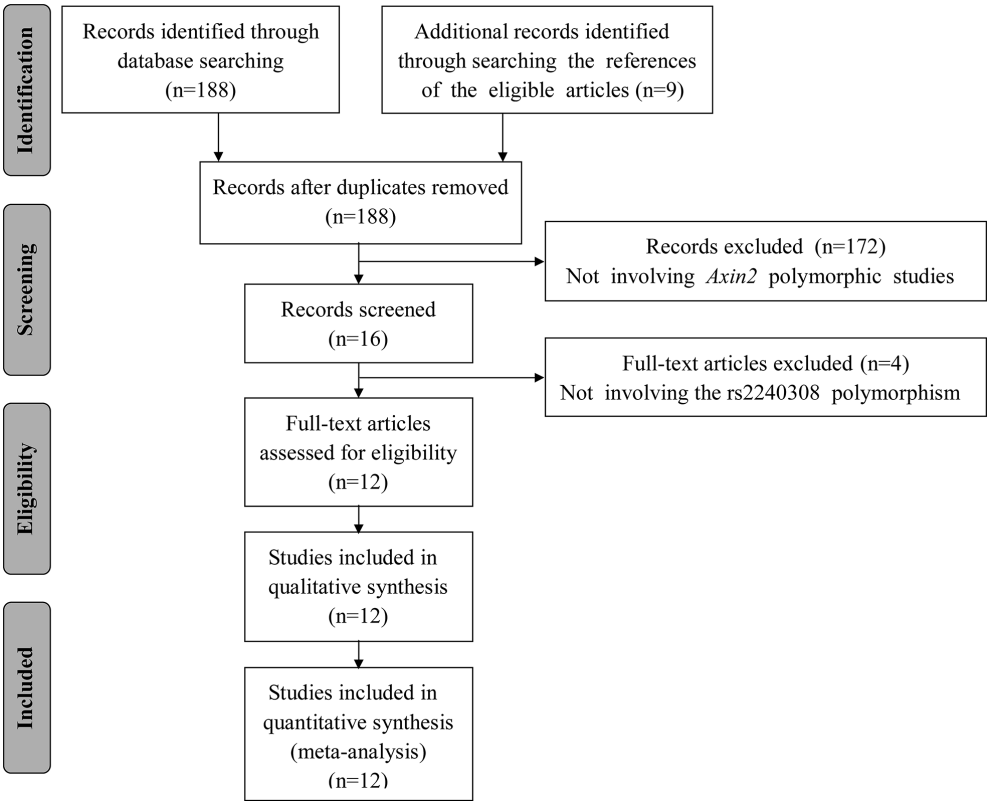

Figure 1. Flow diagram of the study selection process

analyses were performed using the Stata version 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Characteristics of the published studies. Following the application of strict screening criteria, 12 articles, including 14 case-control studies harbouring a total of 2 215 cases and 2 481 controls for lung cancer, prostate cancer, colorectal cancer, ovarian cancer, head and neck cancer, breast cancer, papillary thyroid carcinoma, hepatocellular carcinoma and astrocytoma, were ultimately included in the quantitative analysis. The general characteristics of the included studies are listed in Table 1. Among the included studies, 8 were carried out among Asian populations, while 6 studies were carried out in Caucasian populations. The distribution of genotypes among the controls was consistent with Hardy-Weinberg equilibrium (HWE) for 13 studies, with the exception of the study performed by Aristizabal-Pachon et al [12]. There were 3 studies that reported the effects of *Axin2* rs2240308 in lung cancer, 3 studies in colorectal cancer, 2 studies in prostate cancer, and 1 study each for ovarian cancer, astrocytoma, head and neck cancer, breast cancer, papillary thyroid carcinoma, and hepatocellular carcinoma. Genotyping was performed using PCR-RFLP in 9 studies, TaqMan in 1 study, Sequenom in 1 study, SNaPshot in 1 study, high-resolution melting curve analysis (HRM) in 1 study and Golden gate in 1 study. The distributions of the genotypes and alleles of the *Axin2* rs2240308 polymorphism in each individual study are listed in Supplementary Table 1.

Quantitative synthesis. The evaluations of the associations of *Axin2* rs2240308 with cancer risks are presented in Table 2. All in all, the variant T allele exhibited no significant association with cancer risk in the dominant model (OR=0.85; 95% CI=0.68-1.06, P = 0.000 for the heterogeneity test, I^2 =64.4%; Figure 2**).** The results of other tested models are listed in Table 2 and Figures 3-4**.**

Next, we evaluated the effect of the rs2240308 polymorphism on cancer risk among the subgroups (Table 2). In the stratified analyses, the rs2240308 SNP had a significant association with decreased cancer risk among Asians (dominant model: OR=0.76; 95% CI=0.66-0.88; P=0.185 for the heterogeneity test, I^2=30.5%). In addition, the rs2240308 variant exhibited a significant association with a decreased risk of lung cancer (dominant model: OR=0.69; 95% CI=0.56-0.85; P=0.655 for the heterogeneity test, I^2 =0.0%; Table 2) and prostate cancer (dominant model: OR=0.62; 95% CI=0.41-0.93; P=0.078 for the heterogeneity test, I^2 =67.8%; Table 2). Interestingly, the variant T allele of rs2240308 was significantly associated with decreased cancer risk among studies with

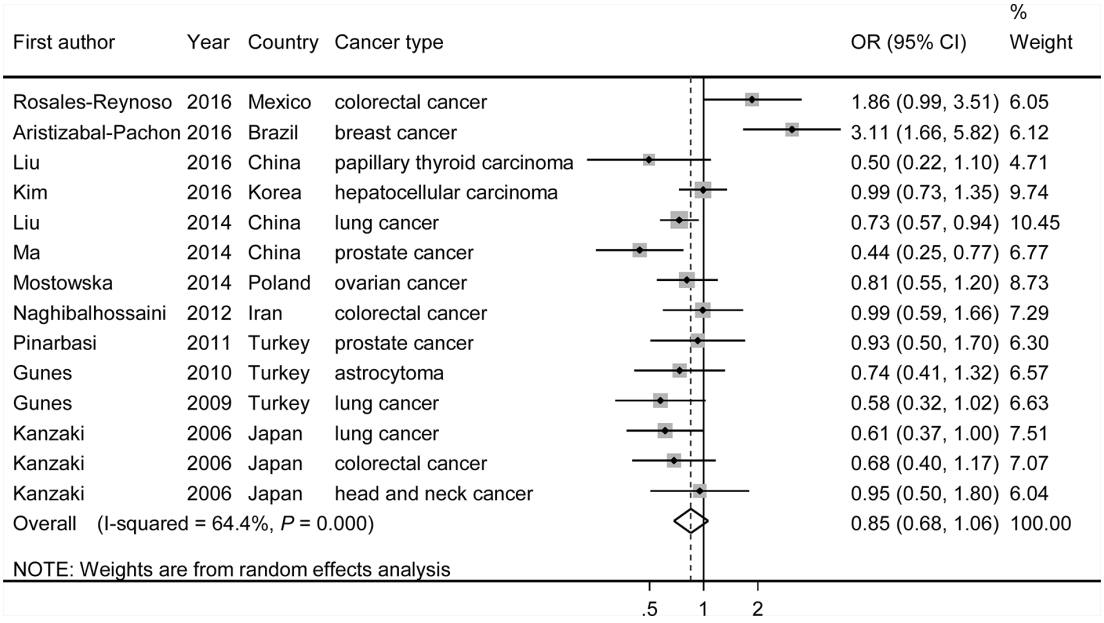

Figure 2. Forest plot of the *Axin2* rs2240308 polymorphism and cancer risk in dominant model

population-based controls (dominant model: OR=0.78; 95% CI=0.65-0.94; *P*=0.061 for the heterogeneity test, I^2 =55.7%; Table 2) and with a sample size ≥ 500 (dominant model: OR=0.82; 95% CI=0.69-0.98; *P*=0.325 for the heterogeneity test, I^2 =11.0%; Table 2).

Test of heterogeneity. For rs2240308, significant heterogeneity was observed after the data were pooled (dominant model: *P* for heterogeneity=0.000, I^2 =64.4%; Table 2). When the subjects were stratified on the basis of ethnicity, the heterogeneity disappeared in the Asian groups (dominant model: *P* for heterogeneity=0.185, I^2 =30.5%). Additionally, in stratified analyses based on the source of controls, the heterogeneity disappeared among studies with population-based controls (dominant model: *P* for heterogeneity=0.061,

Table 2. Summary ORs of the *Axin2* rs2240308 polymorphism and cancer risk

Variables	Studies	CT versus CC			TT versus CC			Dominant model		
		OR(95%CI)	*P* [a]	I^2	OR (95%CI)	*P* [a]	I^2	OR(95%CI)	*P* [a]	I^2
Total	14	0.83(0.68-1.01)	0.018	49.6%	0.92(0.63-1.34)	0.000	69.4%	0.85(0.68-1.06)	0.000	64.4%
Ethnicity										
Asians	8	**0.77(0.66-0.90)**	0.173	31.9%	**0.71(0.55-0.92)**	0.340	11.6%	**0.76(0.66-0.88)**	0.185	30.5%
Caucasians	6	1.01(0.69-1.49)	0.024	61.4%	1.39(0.62-3.15)	0.000	83.5%	1.09(0.67-1.76)	0.001	77.4%
Cancer type										
Lung cancer	3	**0.73(0.59-0.91)**	0.870	0.0%	**0.52(0.36-0.74)**	0.206	36.8%	**0.69(0.56-0.85)**	0.655	0.0%
Colorectal cancer	3	0.96(0.68-1.34)	0.123	52.2%	1.36(0.87-2.11)	0.096	57.2%	1.01(0.74-1.39)	0.060	64.4%
Prostate cancer	2	**0.54(0.35-0.84)**	0.088	65.7%	1.00(0.54-1.87)	0.509	0.0%	**0.62(0.41-0.93)**	0.078	67.8%
Others [b]	6	0.97(0.79-1.18)	0.054	54.0%	1.16(0.56-2.42)	0.001	77.2%	0.99(0.66-1.47)	0.003	71.8%
Source of controls										
Population-based	5	**0.81(0.66-0.98)**	0.237	27.6%	0.82(0.43-1.58)	0.004	73.9%	**0.78(0.65-0.94)**	0.061	55.7%
Hospital-based	7	0.83(0.57-1.19)	0.004	68.6%	1.12(0.60-2.07)	0.001	73.2%	0.88(0.59-1.30)	0.000	75.6%
Not report	2	0.79(0.53-1.18)	0.354	0.0%	0.75(0.43-1.33)	0.051	73.7%	0.78(0.53-1.14)	0.167	47.7%
Sample size										
≥500	3	0.85(0.71-1.02)	0.387	0.0%	**0.72(0.54-0.95)**	0.666	0.0%	**0.82(0.69-0.98)**	0.325	11.0%
<500	11	0.82(0.62-1.09)	0.008	58.0%	1.00(0.57-1.75)	0.000	74.4%	0.86(0.62-1.19)	0.000	70.8%

[a] Random-effects model was used when *P* value for heterogeneity test < 0.05; otherwise, fixed-effect model was used

[b] others include ovarian cancer, head and neck cancer, breast cancer, papillary thyroid carcinoma, hepatocellular carcinoma and astrocytoma

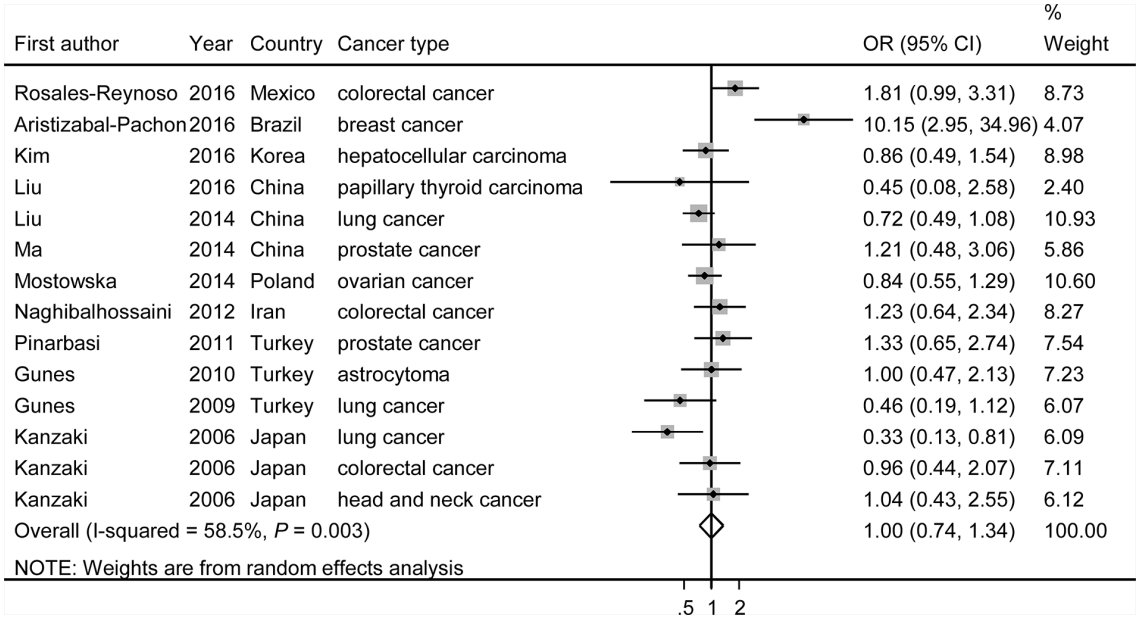

Figure 3. Forest plot of the *Axin2* rs2240308 polymorphism and cancer risk in recessive model

I^2 =55.7%). Moreover, when the studies were stratified on the basis of cancer type, the heterogeneity disappeared for lung cancer (dominant model: *P* for heterogeneity=0.655, I^2 =0.0%), colorectal cancer (dominant model: *P* for heterogeneity=0.060, I^2 =64.4%) and prostate cancer (dominant model: *P* for heterogeneity=0.078, I^2 =67.8%). Furthermore, the heterogeneity also disappeared among studies with a sample size ≥ 500 (dominant model: *P* for heterogeneity=0.325, I^2 =11.0%).

Sensitivity analysis. To test the stability of the rs2240308 results, we conducted sensitivity analyses by sequentially removing each eligible study (Supplementary Table 2). The study by Aristizabal-Pachon et al. [12] that focused on breast cancer was the major contributor of heterogeneity in the

Table 2. Summary ORs of the *Axin2* rs2240308 polymorphism and cancer risk (Recessive model and T versus C model)

Variables	Studies	Recessive model			T versus C		
		OR(95%CI)	*P* [a]	I^2	OR (95%CI)	*P* [a]	I^2
Total	14	1.00(0.74-1.34)	0.003	58.5%	0.92(0.77-1.10)	0.000	72.9%
Ethnicity							
Asians	8	0.82(0.64-1.04)	0.383	6.1%	**0.82(0.74-0.92)**	0.240	23.8%
Caucasians	6	1.32(0.73-2.37)	0.001	75.9%	1.11(0.77-1.60)	0.000	83.7%
Cancer type							
Lung cancer	3	**0.61(0.43-0.85)**	0.230	32.0%	**0.73(0.63-0.85)**	0.398	0.0%
Colorectal cancer	3	1.36(0.93-1.99)	0.413	0.0%	1.10(0.90-1.35)	0.071	62.2%
Prostate cancer	2	1.28(0.73-2.27)	0.872	0.0%	0.83(0.62-1.12)	0.099	63.2%
Others [b]	6	1.16(0.66-2.06)	0.008	67.8%	1.03(0.74-1.43)	0.000	79.7%
Source of controls							
Population-based	5	0.88(0.53-1.45)	0.023	64.6%	0.89(0.67-1.17)	0.008	71.2%
Hospital-based	7	1.20(0.74-1.94)	0.013	62.7%	0.98(0.72-1.32)	0.000	79.0%
Not report	2	0.86(0.51-1.45)	0.079	67.5%	0.86(0.66-1.11)	0.062	71.3%
Sample size							
≥500	3	0.79(0.61-1.03)	0.833	0.0%	**0.85(0.75-0.97)**	0.398	0.0%
<500	11	1.09(0.71-1.67)	0.002	63.6%	0.94(0.73-1.21)	0.000	77.5%

[a] Random-effects model was used when *P* value for heterogeneity test < 0.05; otherwise, fixed-effect model was used

[b] others include ovarian cancer, head and neck cancer, breast cancer, papillary thyroid carcinoma, hepatocellular carcinoma and astrocytoma

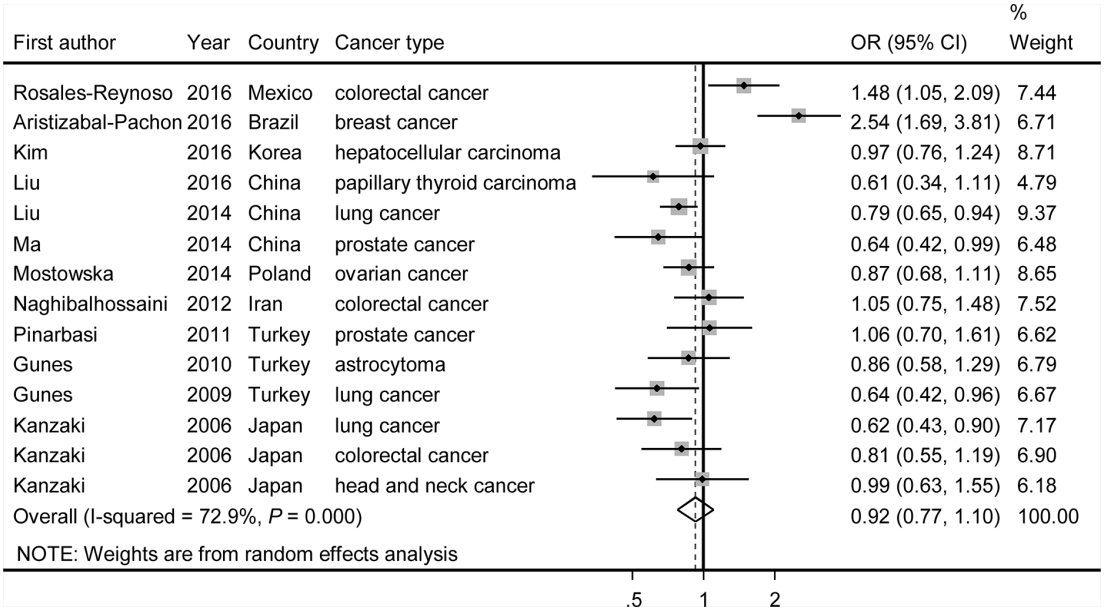

Figure 4. Forest plot of the *Axin2* rs2240308 polymorphism and cancer risk in allele (T vs C) model

dominant model (I^2=64.4%, *P* for heterogeneity=0.000). After the removal of this study, the heterogeneity was significantly reduced (I^2 =36.3%, *P* for heterogeneity=0.093). As expected, similar results were observed in other genetic models (i.e., CT versus CC and TT versus CC), indicating that the study by Aristizabal-Pachon et al. [12] emphasizing breast cancer markedly changed the pooled OR.

Publication bias. We utilized funnel plots and Begg's test to evaluate potential publication biases of the studied literature. The shapes of the funnel plots were symmetrical (Figure 5). Moreover, a Begg's test provided further statistical evidence for the absence of publication bias (dominant model: *P*= 0.70).

Discussion

Previous meta-analyses reported that the variant T allele of *Axin2* rs2240308 was associated with a decreased cancer risk. However, more recent findings have been inconsistent. Therefore, we performed an updated meta-analysis to examine whether this polymorphism was associated with a decreased cancer risk**.** In this study, we performed a meta-analysis by pooling 12 articles, including 14 case-control studies (2,215 cases and 2,481 controls), and demonstrated no significant association between *Axin2* rs2240308 polymorphism and cancer risk. However, similar with previous meta-analysis, in stratified analyses, rs2240308 was associated with a decreased cancer risk in Asian populations.

The SNP rs2240308 at 17q24.1 is a missense mutation located at exon 1 of *Axin2*. Axin2 is an important tumour suppressor, and methylation and mutation of the *Axin2* gene could cause abnormal expression of Axin2, resulting in tumourigenesis [2]. In addition, Axin2 may control the level of β-catenin in the cytoplasm by promoting β-catenin degradation, thereby functioning as a negative regulator of the Wnt signalling pathway [19, 20]. Given the importance of the Wnt signalling pathway for adult stem cell biology, it is not surprising that Wnt signalling pathway mutations are frequently observed in cancers, most notably of tissues that normally depend on Wnt for self-renewal or repair[19].

We further performed functional annotation for the *Axin2* rs2240308 variant based on publicly available datasets or tools. PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) predicted that amino acid substitution resulting from rs2240308 may be damaging and affect the normal function of the Axin2 protein. We then evaluated whether the rs2240308 variant modulated mRNA expression levels through transcriptional mechanisms. Based on the Encyclopedia of DNA Elements (ENCODE) DNase I hypersensitive site (DHS) sequencing data set, we found that rs2240308 is within open chromatin regions associated with gene regulatory elements, indicating that rs2240308 may affect transcription factor binding. Furthermore, ChIP-Seq data from the ENCODE project showed that rs2240308 was located in a region that may affect the binding of numerous transcription factors, including MYC, CTBP2 and MBD4. The MYC transcription factor acts as an oncogene that was overexpressed in lung cancer cells and was associated with lung cancer metastasis [21, 22]. CTBP2 plays a significant role in tumour initiation, progression and response to therapy, which could promote prostate cancer cell proliferation through c-Myc signalling [23]. MBD4 protein functions as

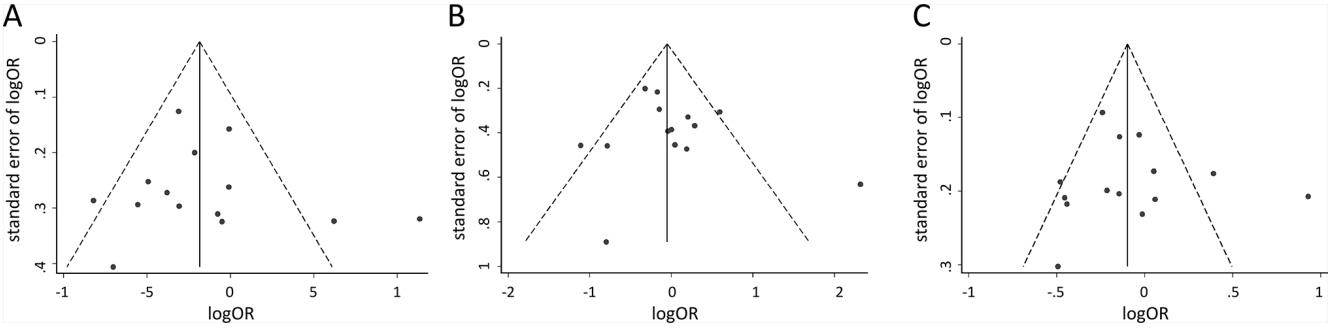

Figure 5. A) funnel plot of the *Axin2* rs2240308 polymorphism and cancer risk in dominant model, B) funnel plot of the *Axin2* rs2240308 polymorphism and cancer risk in recessive model, C) funnel plot of the *Axin2* rs2240308 polymorphism and cancer risk in allele (T vs C) model

a DNA repair enzyme and plays an important role in maintaining genome integrity and carcinogenesis. In addition, *MBD4* Glu346Lys polymorphism is associated with cervical cancer susceptibility in Chinese populations [24]. It is plausible that variation in the *Axin2* rs2240308 may result in the aberrant activities of certain transcription factors. In turn, those factors may regulate the expression of the same target genes nearby or throughout the genome, hence activating crucial signalling pathways that are involved in carcinogenesis. However, these results are preliminary and require further experimental investigation.

Different from previous meta-analyses, in our study no overall significant association existed with *Axin2* rs2240308 polymorphism and any cancer type. However, in subsequent analyses stratified by ethnicity, rs2240308 was associated with a decreased cancer risk in Asians, while no significant association was observed in Caucasians. There are several reasons for the inconsistent results. First, the difference may be due to genetic heterogeneity between different ethnicities. Second, the difference may owe to the utilization of different genotyping methods, which included PCR-RFLP, Sequenom, TaqMan Real-Time PCR, etc. Additionally, different types of cancer involve random errors, which may also potentially account for the differences in findings between Asian and Caucasian populations.

Nevertheless, further studies with large sample sizes are warranted to evaluate the relationship between rs2240308 and cancer risk, especially in Caucasians.

The strength of this meta-analysis is that we systemically reviewed the relationships between *Axin2* rs2240308 and tumour susceptibility using all published data up to the present moment (the last search update was Aug 31, 2016). In contrast, it seems that the previous meta-analyses performed by Wu et al. and Gong et al. did not integrate all articles that were published at that time, which may have affected the accuracy of the results. Therefore, different from previous meta-analyses, our study provided precise evidence for the first time that *Axin2* rs2240308 may not modify general cancer susceptibility. Similar findings to previous meta-analyses were that *Axin2* rs2240308 may modify cancer susceptibility in an ethnicity- and/or type-specific way, which may be valuable for the research of tumour pathogenesis mechanisms and identification of potential diagnostic targets. In addition, compared with previous meta-analyses, in the stratified analyses we have reported for the first time that a variant T allele of rs2240308 was significantly associated with a decreased cancer risk among studies with relatively large sample sizes (≥500), indicating the important role of sample size in study design. Moreover, the well-designed functional annotation that further verified our findings is another advantage of this study. However, there are also some limitations that must be addressed. First, significant heterogeneity between studies was observed. Among the 12 published articles containing 14 case-control studies included in our meta-analysis, some of the studies were population-based, while others were hospital-based. Second, in some studies, detailed information (e.g., age, gender, smoking status, and alcohol consumption) was not provided, which limited further stratification analyses. Additionally, if we had been able to acquire more detailed information, we would have achieved more precise estimations by adjusting for other potential covariates. Third, we did not consider the possibility that different cancers have different incidence/prevalence rates in different populations, so our conclusions should be interpreted cautiously. Fourth, for the study performed by Kanzaki et al., they used the same controls for different cancer types, which may affect the accuracy of the results of their study. Lastly, for the studies performed in Mexico and Brazil, the authors did not clarify whether the research subjects were native Mexicans or Brazilians. Further, we could not exclude the possibility that study subjects from Mexico and Brazil may not be pure populations, as well as there may be some cases that are not Caucasian; therefore, our conclusions should also be interpreted cautiously.

Conclusions

This updated meta-analysis provided new evidence that differed from previous meta-analyses. Specifically, *Axin2*

rs2240308 may not modify general cancer susceptibility. Similar with previous meta-analyses, our analysis indicated that *Axin2* rs2240308 may modify cancer susceptibility in an ethnicity- and/or type-specific manner. In addition to functional evaluations, future studies incorporating subjects from different ethnic backgrounds combined with re-sequencing of the marked region of *Axin2* are warranted.

Supplementary information is available in the online version of the paper.

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