New insights into the association between AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variants and cancer risk

Bin Xu†, Wei Yuan‡, Li Shi†, Li Zuo*, Xing-Yu Wu*, Wei Zhang* and Qiaxian Wen*

Abstract

Background: Many epidemiological studies have investigated association of AXIN2 variants on overall cancer risks; however, the available results remain inconsistent.

Methods: An updated analysis was conducted to ascertain a more accurate estimation of the correlation between AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G polymorphisms and cancer risk. We also used in silico tools to assess the effect of AXIN2 expression on cancer susceptibility and overall survival time.

Results: A total of 4281 cases and 3955 control participants were studied. The overall results indicated that AXIN2 148 C/T variant was associated with cancer risk (allelic contrast: OR = 0.88, 95% CI 0.77–0.99, $P_{\text{heterogeneity}} = 0.004$; dominant model: OR = 0.82, 95% CI 0.69–0.96, $P_{\text{heterogeneity}} = 0.022$), especially for lung and prostate adenocarcinoma. Similar results were observed in 1365 C/T polymorphism (OR = 0.71, 95% CI 0.61–0.98, $P_{\text{heterogeneity}} = 0.873$; dominant model: OR = 0.66, 95% CI 0.47–0.94, $P_{\text{heterogeneity}} = 0.775$). Moreover, in subgroup analysis by ethnicity, similar findings were obtained for Asian and Caucasian populations. Results from in silico tools suggested that AXIN2 expressions in lung adenocarcinoma were lower than that in normal group.

Conclusions: Our findings indicated that AXIN2 148 C/T and 1365 C/T variants may be associated with decreased cancer susceptibility.

Keywords: AXIN2, Polymorphism, Cancer, Analysis, In silico
human chromosome 17q23–q24 and composed of 10 exons, which encodes a protein consisting of 843 amino acids [14]. Loss of heterozygosity of this gene was previously identified in a number of carcinomas such as hepatoblastoma, hepatocellular carcinoma, melanoma, gastrointestinal, ovarian, synchronous endometrial carcinomas [15–18]. Association between AXIN2 variants and carcinoma susceptibility has also been reported by previous publications. These SNPs including 148 C>T (rs2240308), 1365 C/T (rs9915936), and rs4791171 A/G (NC_000017.10) [19–24]. Study population of these genetic variants has involved numerous ethnicities such as Brazilians, Iranians, Chinese, Saudi Arabians, Indians and Poles [20–27]. These studies also evaluated various malignancies; nevertheless, there were ambiguous conclusions on the relationship between the AXIN2 polymorphisms and cancer risk among different case-control studies.

For AXIN2 148 C>T polymorphism, a case–control study observed no statistically significant correlation between controls and prostate adenocarcinoma in Turkish population [27]. However, another two studies identified notable decreased risks in Iranian colorectal cancer subjects and Chinese prostate adenocarcinoma participants [21, 22]. Therefore, a meta analysis with all eligible data based on the inclusion criteria was conducted to further assess the associations between AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G polymorphisms and cancer risk [19–33].

Materials and methods

Literature retrieval strategy

PubMed, Web of Science, Google Scholar, and China Wanfang Databases were systematically searched to identify all eligible published articles on AXIN2 variants and cancer susceptibility. The following terms were utilized for searching abstracts and titles: “Axin OR AXIN2”, “polymorphism OR SNP OR variant”, and “cancer OR adenocarcinoma OR carcinoma OR tumor”. The latest search was conducted on Jan 31, 2019 with no language restrictions. Furthermore, we also carefully screened and manually searched the review or original publications for more eligible studies.

Study selection

Two authors independently chose the eligible studies based on the inclusion criteria: (a) case–control studies that evaluated the association between AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variants and cancer risk; (b) studies that involved available information for measuring odds ratio (OR) with 95% confidence intervals (CIs); (c) genotype distribution in controls must be conformed to Hardy-Weinberg equilibrium (HWE).

Data extraction

All related information was independently screened by two investigators (L Shi and B Xu) from each enrolled study, including the name of first author, year of publication, country of origin, ethnicity, source of control, genotyping method, cancer type, total number of participants, P value for HWE, age range, genotyping data of AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variants in cases and controls. Disagreement should be resolved by discussion with a third author (W Zhang). If the controversial content still existed, it should be addressed by all investigators to reach a consensus.

Statistical analysis

The strength of the relationship between AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G polymorphisms and cancer susceptibility was measured by calculating OR with 95% CI. A total of four genetic models were adopted in the current analysis, including allelic comparison model (M-allele vs. W-allele), homozygote contrast model (MM vs. WW), heterozygote model (MW vs. WW), and dominant model (MM + MW vs. WW). The χ²-test-based Q test was performed to investigate P value for heterogeneity among eligible researches. If P<0.05, indicating that a significant heterogeneity was found, we employed the random-effects model (DerSimonian–Laird method) [34]. On the other hand, the fixed-effects model (Mantel–Haenszel method) was carried out [35]. We adopted qualitative funnel plot to assess possible publication bias by calculating the standard error of log(OR) for each research plotted against its log(OR). We further conducted quantitative Egger’s test to evaluate funnel plot asymmetry [36]. The web-based program was applied to check for deviations from the Hardy–Weinberg equilibrium (HWE) of distribution frequencies (http://ihg2.helmholtz-muenchen.de/cgibin/hw/hwa1.pl) [37]. The P value more than 0.05 suggested an HWE balance. Moreover, we applied leave-one-out sensitivity analyses to calculate the stability of pooled results [38]. All of the above analyses were conducted by STATA software v11.0 (Stata Corporation, TX).

In silico analysis of AXIN2 expression

An online gene expression database was adopted to investigate the AXIN2 expression in lung and prostate adenocarcinoma tissues and the paracancerous tissues. (http://gemini.cancer-pku.cn/) [39]. RNA expression profiles of 446 pathologically diagnosed lung adenocarcinoma (including 387 Caucasians, 51 African-Americans, and 8 Asians) and 153 prostate adenocarcinoma tissues (containing 147 Caucasians and 6 African-Americans) were evaluated by this database. The Cancer Genome
Atlas (TCGA) samples were also utilized to investigate the high and low expression of AXIN2 on cancer susceptibility and overall survival time. Moreover, the String online server was applied to assess the gene–gene correlation of AXIN2 (http://string-db.org/).

Results
Characteristics of studies
As was shown in Table 1, 15 articles were finally retrieved in the present analysis, which contains 22 case–control studies for AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variants. There were 2909 cancer subjects and 2907 control volunteers for 148 C/T polymorphism, 587 cancer subjects and 605 controls for 1365 C/T variant, 785 cases and 443 controls for rs4791171 A/G variant. Furthermore, we checked the minor allele frequencies (MAF) of three AXIN2 variants by Trans-Omics for Precision Medicine (TOPMed) online (https://www.ncbi.nlm.nih.gov/snp/) (Fig. 1). MAF of AXIN2 148 C/T were: in Africans, 0.119; Asians, 0.426; Europeans, 0.526; Americans, 0.561; others (including Pacific Islanders), 0.470; Global, 0.474. MAF of AXIN2 1365 C/T were: in Africans, 0.069; East Asians, 0.192; Europeans, 0.114; Americans, 0.100; others, 0.090; Global, 0.104. Finally, MAF of AXIN2 rs4791171 A/G were: in Africans, 0.267; East Asians, 0.370; Europeans, 0.681; Americans, 0.620; others, 0.670; Global, 0.547. In stratified analysis by ethnicity, seven studies were performed in Caucasian populations, twelve studies were in Asian descendants, and two were done in Arabians and one was in Latin descendants. Eight studies were conducted using population based controls and the rest 14 studies were utilizing hospital based controls. The classical genotyping method, PCR-restriction fragment length polymorphism (RFLP) was adopted in nine of these studies.

Quantitative synthesis
In the overall analysis, we identified a significant correlation between AXIN2 148 C/T variant and cancer risk (allele contrast: OR = 0.88, 95% CI 0.77–0.99, \( P_{\text{heterogeneity}} = 0.004, P = 0.041 \); heterozygote comparison: OR = 0.84, 95% CI 0.75–0.95, \( P_{\text{heterogeneity}} = 0.112, P = 0.004 \); dominant genetic model: OR = 0.82, 95% CI 0.69–0.96, \( P_{\text{heterogeneity}} = 0.022, P = 0.015 \) (Table 2). In subgroup analysis by race, we observed positive results in Asians (allele contrast: OR = 0.85, 95% CI 0.73–0.98, \( P_{\text{heterogeneity}} = 0.016, P = 0.027 \); dominant genetic model: OR = 0.80, 95% CI 0.66–0.96, \( P_{\text{heterogeneity}} = 0.030, P = 0.020 \)) and Caucasians (dominant genetic model: OR = 0.76, 95% CI 0.59–0.98, \( P_{\text{heterogeneity}} = 0.701, P = 0.036 \), (Fig. 2). Moreover, subgroup analysis by cancer type suggested that 148 C/T variant was associated with a decreased cancer risk in lung adenocarcinoma (allele contrast: OR = 0.74, 95% CI 0.65–0.84, \( P \) value for heterogeneity = 0.602, \( P < 0.001 \); dominant genetic model: OR = 0.70, 95% CI 0.59–0.84, \( P_{\text{heterogeneity}} = 0.803, P < 0.001 \), Fig. 3). Similar finding was indicated in prostate adenocarcinoma (heterozygote comparison: OR = 0.54, 95% CI 0.35–0.84, \( P_{\text{heterogeneity}} = 0.088, P = 0.006 \); dominant genetic model: OR = 0.62, 95% CI 0.41–0.93, \( P_{\text{heterogeneity}} = 0.078, P = 0.022 \)). In subgroup analysis by source of control, similar results were also observed in population-based studies. Furthermore, we identified notable correlation between AXIN2 1365 C/T variant and cancer risk (allele contrast: OR = 0.71, 95% CI 0.61–0.98, \( P_{\text{heterogeneity}} = 0.873, P = 0.038 \); heterozygote comparison: OR = 0.63, 95% CI 0.44–0.91, \( P_{\text{heterogeneity}} = 0.668, P = 0.014 \); dominant model: OR = 0.66, 95% CI 0.47–0.94, \( P_{\text{heterogeneity}} = 0.775, P = 0.021 \). For rs4791171 A/G polymorphism, no significant association was indicated (allele comparison, OR = 0.99, 95% CI 0.85–1.17, \( P_{\text{heterogeneity}} = 0.786, P = 0.864 \); homozygote contrast, OR = 0.94, 95% CI 0.66–1.33, \( P_{\text{heterogeneity}} = 0.873, P = 0.728 \); heterozygote contrast, OR = 0.86, 95% CI 0.62–1.17, \( P_{\text{heterogeneity}} = 0.522, P = 0.322 \); dominant model, OR = 0.89, 95% CI 0.66–1.19, \( P_{\text{heterogeneity}} = 0.575, P = 0.429 \).

In silico analysis of AXIN2 expression
Results from in silico tools suggested that AXIN2 expression in normal group was higher than that in lung adenocarcinoma tissue (Fig. 4a). However, no obvious difference was indicated for prostate adenocarcinoma (Fig. 4b). Moreover, we explored whether the AXIN2 expression had an effect on the overall survival time of lung adenocarcinoma patients. However, Kaplan–Meier estimate showed no vital difference of overall survival time between high and low AXIN2 expression groups (\( P = 0.40, \) Fig. 5).

Publication bias and sensitivity analyses
Egger's test and Begg's funnel plot were utilized to evaluate publication bias in all of enrolled studies. We demonstrated no publication bias for AXIN2 148 C/T polymorphism (allelic contrast, \( t = -0.52, P = 0.614 \); TT vs. CC, \( t = -0.66, P = 0.519 \); heterozygote comparison, \( t = -0.30, P = 0.771 \); TT + TC vs. CC, \( t = -0.34, P = 0.741 \), AXIN2 1365 C/T variant (allelic comparison, \( t = 2.20, P = 0.159 \); TC vs. CC, \( t = 2.18, P = 0.161 \) and rs4791171 A/G polymorphism (G-allele versus A-allele, \( t = -0.55, P = 0.680 \); homozygote contrast, \( t = -0.62, P = 0.645 \); GA vs. AA, \( t = -0.72, P = 0.602 \); dominant model, \( t = -0.78, P = 0.577 \). As shown in Fig. 6, results from funnel plots appeared symmetrical in the overall analysis under dominant model, which indicated a lack of publication bias. Sensitivity analyses were also utilized to assess the pooled OR by omission of any one study. The
## Table 1 Basic information for included studies of the correlation between AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variations and cancer risk

| Author/year | Origin | Ethnicity | Source | Cancer | Method          | Age range | Age range | Case     | Control    | Case     | Control    | Case     | Control    | HWE      |
|-------------|--------|-----------|--------|--------|-----------------|-----------|-----------|----------|-----------|----------|-----------|----------|-----------|----------|
|             |        |           |        |        |                 |           |           | Case     | Control    |          |            |          |            |          |
| 148 C/T     |        |           |        |        |                 |           |           |          |            |          |            |          |            |          |
| Kanzaki 2006 [26] | Japan | Asian | PB | LC | PCR–RFLP | 66.4 (mean) | NA         | 160      | 109       | 8        | 71        | 81       | 15        | 52       | 42        | 0.863    |
| Kanzaki 2006 [26] | Japan | Asian | PB | HNC | PCR–RFLP | 66.4 (mean) | NA         | 63       | 109       | 9        | 29        | 25       | 15        | 52       | 42        | 0.863    |
| Kanzaki 2006 [26] | Japan | Asian | PB | CRC | PCR–RFLP | 66.4 (mean) | NA         | 113      | 109       | 15       | 44        | 54       | 15        | 52       | 42        | 0.863    |
| Gunes 2009 [19] | Turkey | Caucasian | PB | LC | PCR          | 59.22±9.63 | 57.01±789 | 100      | 100       | 8        | 47        | 45       | 16        | 52       | 32        | 0.501    |
| Gunes 2010 [25] | Turkey | Caucasian | HB | AT | PCR          | 58.66±8.04 | 57.01±789 | 100      | 100       | 16       | 45        | 39       | 16        | 52       | 32        | 0.501    |
| Pinarbasi 2011 [27] | Turkey | Caucasian | HB | PC | PCR          | 70.38±7.78 | 68.55±447 | 84       | 100       | 19       | 35        | 30       | 18        | 48       | 34        | 0.883    |
| Nghahil 2012 [21] | Iran  | Asian | HB | CRC | PCR–RFLP | NA         | NA        | 110      | 179       | 19       | 57        | 34       | 26        | 98       | 55        | 0.096    |
| Liu 2014 [28] | China  | Asian | PB | LC | RT-PCR      | 57.78±9.89 | 52.21±10.56 | 498      | 533       | 47       | 216       | 235     | 67        | 255      | 211       | 0.457    |
| Ma 2014 [22] | China  | Asian | PB | PC | PCR          | 71.2 (mean) | 70.4 (mean) | 103      | 100       | 11       | 31        | 61       | 9        | 52       | 39        | 0.153    |
| Mostowska 2014 [24] | Poland | Caucasian | HB | OC | PCR–RFLP | 58.4±9.7  | 57.4±7.5  | 228      | 282       | 46       | 115       | 67    | 65        | 146      | 71        | 0.546    |
| Yadav 2016 [23] | India  | Asian | HB | GBC | Taqman | 52.05±10.06 | 43.2±11.5 | 564      | 250       | 119      | 253       | 192   | 44        | 108      | 98        | 0.138    |
| Liu 2016 [32] | China  | Asian | PB | PTC | MassARRAY | 45.13±19.07 | 41.9±10.22 | 53       | 50        | 2        | 24        | 27   | 4        | 29       | 17        | 0.084    |
| Kim 2016 [31] | Korea  | Asian | HB | HCC | Goldengate | 53.8±10.3 | 41.1±10.3 | 242      | 482       | 18       | 100       | 124   | 41        | 195      | 246       | 0.789    |
| Rosales 2016 [29] | Mexico | Latin | PB | CRC | PCR–RFLP | 59.03 (mean) | 36.88 (mean) | 188      | 99        | 54       | 109       | 25   | 18        | 59       | 22        | 0.054    |
| Bahl 2017 [30] | India  | Asian | HB | LC | PCR–RFLP | 57.38±10.74 | 53.23±10.44 | 303      | 305       | 54       | 150       | 99   | 80        | 144      | 81        | 0.330    |
|             |        |           |        |        |                 |           |           |          |            |          |            |          |            |          |
| 1365 C/T    |        |           |        |        |                 |           |           |          |            |          |            |          |            |          |
| Bahl 2017 [30] | India  | Asian | HB | LC | PCR–RFLP | 57.38±10.74 | 53.23±10.44 | 303      | 305       | 6        | 29        | 268   | 5         | 51       | 249       | 0.215    |
| Pinarbasi 2011 [27] | Turkey | Caucasian | HB | PC | PCR          | 70.38±7.88 | 68.55±447 | 84       | 100       | 0        | 7         | 77   | 0        | 8        | 92        | 0.677    |
| Gunes 2010 [25] | Turkey | Caucasian | HB | AT | PCR          | 58.66±8.039 | 57.01±789 | 100      | 100       | 0        | 9         | 91    | 0        | 12       | 88        | 0.523    |
| Gunes 2009 [19] | Turkey | Caucasian | PB | LC | PCR          | 59.22±9.63 | 57.01±789 | 100      | 100       | 0        | 9         | 91    | 0        | 12       | 88        | 0.523    |
| rs4791171A/G |        |           |        |        |                 |           |           |          |            |          |            |          |            |          |
| Alanazi 2013 [20] | Saudi Arabian | HB | BC | RT-PCR | 48.0 (mean) | NA        | 99       | 83        | 21       | 44        | 34    | 17        | 44       | 22        | 0.559    |
| Yadav 2016 [23] | India  | Asian | HB | GBC | PCR–RFLP | 52.05±10.06 | 43.2±11.5 | 564      | 250       | 228      | 248       | 88   | 97        | 118      | 35        | 0.926    |
| Parine 2019 [33] | Saudi Arabian | HB | CRC | TagMan | 57.0 (mean) | NA        | 122      | 110       | 27       | 55        | 40    | 24        | 48       | 38        | 0.236    |

*HB* hospital-based, *PB* population-based, *AT* astrocytoma, *BC* breast cancer, *CRC* colorectal cancer, *GBC* gallbladder cancer, *PCR–RFLP* polymerase chain reaction and restrictive fragment length polymorphism, *RT* real time, *NA* not available, *NOS* Newcastle–Ottawa Scale, *HCC* hepatocellular carcinoma, *HNC* head and neck cancer, *HWE* Hardy–Weinberg equilibrium of controls, *LC* lung adenocarcinoma, *PC* prostate adenocarcinoma, *PTC* papillary thyroid carcinoma, *OC* ovarian cancer
results suggested that the current data from pooled ORs were relatively stable. No single study can substantially change the overall OR (Fig. 7).

**Discussion**

To date, large quantities of studies have been conducted to explore whether the variants confer individual’s susceptibility to carcinoma. However, results from the previous publications have yielded controversial results [21, 22]. A previous study based on Indian descendants found a strong protective effect in participants having heterozygous genotype for 1365 C/T variant [30], while another study group did not observe such positive correlation in Turkish population [27]. In 2005, Wu et al. performed a meta-analysis and found that AXIN2 rs2240308 variant may increase the risk of cancer, especially lung cancer in Asian descendants [40]. Two years later, another meta-analysis indicated no obvious correlation between this variant and cancer risk in the overall analysis. Moreover, researches of this article observed that rs2240308 polymorphism was significantly associated with a decreased cancer risk in Asian population [41]. The overall goal of the present study was to evaluate all eligible data based on the inclusion criteria to enhance the statistical powers and draw more accurate conclusions.

In the current study, a total of 4281 cases and 3955 control participants were investigated. The overall results showed evidence that AXIN2 148 C/T variant was associated with decreased cancer risk, especially for lung and prostate adenocarcinoma, which is in line with conclusions identified by Kanzaki et al. Liu et al. and Gune et al. [19, 26, 28]. Similar results were observed in AXIN2 1365 C/T polymorphism (under allelic contrast, heterozygote comparison, and dominant genetic model). Moreover, in subgroup analysis by ethnicity, positive findings were obtained for Asian and Caucasian populations. In the stratified analysis by source of control, similar findings were identified in population-based studies for AXIN2 148 C/T variant, which is consistent with the findings reported by Yu et al. [41]. Moreover, results from in silico tools showed that AXIN2 expressions in lung cancer and prostate cancer are lower than that in normal counterpart. High expression of AXIN2 may have longer OS time than low expression group for lung cancer participants, which were consistent with results derived from the present meta-analysis. Nevertheless, we indicated no significant difference between the high expression and low/medium expression of AXIN2 in prostate cancer patients.

Some limitations of the above analysis should be mentioned. Firstly, the numbers of enrolled articles in the current analysis were still not large enough for the comprehensive analysis, especially for AXIN2 1365 C/T and rs4791171 A/G variants. Four articles towards AXIN2 1365 C/T and three articles for rs4791171 A/G polymorphism were eligible based on the selection criteria. Secondly, insufficient original data from the raw articles limited further evaluation of potential interactions, including relationship between the AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variants and different tumor grade and stage. Thirdly, meta-analysis was based on unadjusted estimates, which may lead to serious confounding bias. Furthermore, gene–gene interaction would also participate in etiological mechanism of carcinoma. As shown in Fig. 8, at least 20 related genes may be involved in such interaction, which are required to be further investigated in future studies. On the other hand, core advantages in current analysis should also be acknowledged. Firstly, a comprehensive study of the correlation of the AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variants with overall cancer susceptibility
### Table 2 Stratified analyses of AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variants on overall cancer risk

| Variables | N   | Case/control | OR (95% CI) M-allele vs. W-allele | P   | OR (95% CI) MM vs. WW | P   | OR (95% CI) MW vs. WW | P   | OR (95% CI) MM+MW vs. WW | P   |
|-----------|-----|------------|-----------------------------------|-----|------------------------|-----|------------------------|-----|--------------------------|-----|
| **148 C/T** |     |             |                                   |     |                        |     |                        |     |                          |     |
| Total     | 15  | 2909/2907   | 0.88 (0.77–0.99)                 | 0.004 | 0.82 (0.63–1.06)       | 0.007 | 0.84 (0.75–0.95)       | 0.112 | 0.82 (0.69–0.96)         | 0.022 |
| Ethnicity |     |             |                                   |     |                        |     |                        |     |                          |     |
| Asian     | 10  | 2209/2226   | 0.85 (0.73–0.98)                 | 0.016 | 0.76 (0.57–1.03)       | 0.040 | 0.078 (0.74–0.96)      | 0.074 | 0.009 (0.66–0.96)        | 0.030 |
| Caucasian | 4   | 512/582     | 0.85 (0.72–1.01)                 | 0.061 | 0.75 (0.53–1.07)       | 0.304 | 0.108 (0.58–1.00)      | 0.896 | 0.053 (0.76–0.98)        | 0.701 |
| Latin     | 1   | 188/99      | 1.48 (1.05–2.09)                 |   –  | 2.64 (1.21–5.78)       |   –  | 0.015 (1.84–3.13)      |   –  | 0.146 (1.86–3.51)        |   –  |
| Cancer type |     |             |                                   |     |                        |     |                        |     |                          |     |
| LC        | 4   | 1061/1047   | 0.74 (0.65–0.84)                 | 0.062 | 0.53 (0.40–0.70)       | 0.360 | <0.001 (0.76–0.93)     | 0.865 | 0.005 (0.70–0.84)        | <0.001 |
| CRC       | 3   | 411/387     | 1.10 (0.90–1.35)                 | 0.071 | 1.36 (0.87–2.11)       | 0.096 | 0.178 (0.96–1.99)      | 0.123 | 0.796 (1.01–1.74)        | 0.060 |
| PC        | 2   | 187/200     | 0.83 (0.62–1.12)                 | 0.099 | 1.00 (0.54–1.87)       | 0.509 | 0.987 (0.54–1.84)      | 0.088 | 0.006 (0.62–0.78)        | 0.078 |
| Others    | 7   | 1250/1273   | 0.98 (0.87–1.11)                 | 0.217 | 0.98 (0.76–1.26)       | 0.363 | 0.862 (0.96–1.15)      | 0.375 | 0.640 (0.96–1.14)        | 0.218 |
| Source    |     |             |                                   |     |                        |     |                        |     |                          |     |
| HB        | 8   | 1684/1748   | 0.94 (0.85–1.04)                 | 0.093 | 0.89 (0.72–1.09)       | 0.128 | 0.267 (0.90–1.09)      | 0.564 | 0.364 (0.92–1.07)        | 0.268 |
| PB        | 7   | 1225/1159   | 0.82 (0.65–1.02)                 | 0.009 | 0.73 (0.44–1.22)       | 0.007 | 0.235 (0.74–0.88)      | 0.083 | 0.001 (0.74–0.97)        | 0.037 |
| **1365 C/T** |     |             |                                   |     |                        |     |                        |     |                          |     |
| Total     | 4   | 587/605     | 0.71 (0.61–0.98)                 | 0.873 | 1.11 (0.34–3.70)       |   –  | 0.859 (0.63–0.99)      | 0.668 | 0.014 (0.66–0.94)        | 0.775 |
| Ethnicity |     |             |                                   |     |                        |     |                        |     |                          |     |
| Asian     | 1   | 303/305     | 0.66 (0.43–0.99)                 |   –  | 1.11 (0.34–3.70)       |   –  | 0.859 (0.53–0.82)      |   –  | 0.010 (0.58–0.92)        |   –  |
| Caucasian | 3   | 284/300     | 0.81 (0.47–1.38)                 | 0.855 | 0.44 (NA)              |   –  | 0.80 (0.46–1.39)       | 0.846 | 0.428 (0.80–0.46–1.39)   | 0.846 |
| **rs4791171 A/G** |     |             |                                   |     |                        |     |                        |     |                          |     |
| Total     | 3   | 785/443     | 0.99 (0.85–1.17)                 | 0.786 | 0.94 (0.66–1.33)       | 0.873 | 0.728 (0.62–1.17)      | 0.522 | 0.322 (0.69–1.19)        | 0.575 |
| Ethnicity |     |             |                                   |     |                        |     |                        |     |                          |     |
| Asian     | 1   | 564/250     | 1.00 (0.80–1.24)                 |   –  | 0.93 (0.69–1.48)       |   –  | 0.773 (0.84–1.63)      |   –  | 0.843 (0.87–1.56)        |   –  |
| Arabian   | 2   | 221/198     | 0.96 (0.73–1.27)                 | 0.511 | 0.96 (0.66–1.62)       | 0.603 | 0.843 (0.87–1.56)      | 0.257 | 0.538 (0.89–0.69–1.36)   | 0.249 |
| **Cancer type** |     |             |                                   |     |                        |     |                        |     |                          |     |
| BC        | 1   | 99/83       | 0.87 (0.57–1.31)                 | 0.497 | 0.80 (0.35–1.84)       | 0.599 | 0.65 (0.33–1.28)       | 0.209 | 0.069 (0.36–1.31)        | 0.255 |
| GBC       | 1   | 564/250     | 1.00 (0.80–1.24)                 | 0.997 | 0.93 (0.59–1.48)       | 0.773 | 0.84 (0.53–1.31)       | 0.484 | 0.88 (0.58–1.34)         | 0.556 |
| CRC       | 1   | 122/110     | 1.04 (0.72–1.51)                 | 0.822 | 1.07 (0.53–2.17)       | 0.854 | 1.09 (0.60–1.96)       | 0.778 | 1.08 (0.63–1.87)         | 0.777 |

*AT* astrocytoma, *BC* breast cancer, *CRC* colorectal cancer, *HB* hospital-based, *PB* population-based, *NA* not available, *LC* lung adenocarcinoma, *PC* prostate adenocarcinoma, *GBC* gallbladder cancer

\(^{a}\) *P*-value of Q-test for heterogeneity test (\(P_{\text{het}}\))
is statistically more powerful than single case–control study. All the studies according to the inclusion criteria were accumulated in our analysis. Secondly, genotype distribution of controls is conformed to Hardy–Weinberg equilibrium (HWE) in any of the enrolled studies and no significant publication bias was found, which indicated that conclusions of the present analysis are relatively trustworthy.

**Conclusions**

Taken together, the current study showed evidence that \textit{AXIN2} 148 C/T and 1365 C/T variants may be associated with decreased cancer susceptibility, especially for lung and prostate adenocarcinoma. Future large scale studies with standardized unbiased cases and well-matched cases...
**Fig. 3** Forest plot of TC versus CC genetic model of AXIN2 148 C/T polymorphism in the stratified analyses by cancer type (fixed-effects).

**Fig. 4** In silico analysis of AXIN2 expressions in lung adenocarcinoma (a) and prostate adenocarcinoma (b).
**Fig. 5** Association of AXIN2 expression and the overall survival (OS) time among lung adenocarcinoma participants. Expression of AXIN2 was decreased in lung adenocarcinoma tissue (a). However, no vital influence of overall survival time was indicated between high and low AXIN2 expression groups (b, \( P > 0.05 \)).

**Fig. 6** Begg’s funnel plot of publication bias for AXIN2 148 C/T (a), 1365 C/T (b), and rs4791171 A/G (c) under dominant model.

**Fig. 7** Sensitivity analyses about AXIN2 148 C/T, 1365 C/T, and rs4791171 A/G variants and cancer risk (Dominant genetic model of MM + MW vs. WW). Leave-one-out sensitivity analyses were carried out to assess the stability of the overall results. No single study can substantially change the overall OR for AXIN2 148 C/T (a), 1365 C/T (b), and rs4791171 A/G (c) polymorphisms.
control subjects are needed to ascertain these finding in more detail.

Abbreviations
AT: astrocytoma; BC: breast cancer; CRC: colorectal cancer; GBC: gallbladder carcinoma; HB: hospital-based; PB: population-based; PCR-RFLP: polymerase chain reaction and restrictive fragment length polymorphism; RT: real time; NA: not available; NOS: Newcastle–Ottawa Scale; HCC: hepatocellular carcinoma; LC: lung adenocarcinoma; PC: prostate adenocarcinoma; PTC: papillary thyroid carcinoma; OC: ovarian cancer.

Authors’ contributions
BX and WZ contributed to the design of the study, WY and QW searched the databases, LS, XYW and BX extracted the data, LS and LZ wrote the manuscript, LZ and QW interpreted the results and revised the manuscript. All authors read and approved the final manuscript.

Author details
1 Department of Oncology, Affiliated Hospital of Jiangnan University, Wuxi 214000, Jiangsu, China. 2 Department of Cardiology, Taizhou People’s Hospital, Taizhou 225300, Jiangsu, China. 3 Department of Urology, The Affiliated Changzhou No. 2 People’s Hospital of Nanjing Medical University, Changzhou 213003, Jiangsu, China. 4 Department of Oncology, Taizhou People’s Hospital, 210 Yingchun Road, Taizhou 225300, Jiangsu, China.

Acknowledgements
Not applicable.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. We also declare that there was no non-financial competing interests in the manuscript.

Availability of data and materials
All data generated and analyzed during this study are included in this published article. Please contact author for data requests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

Funding
Not applicable.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 19 February 2019 Accepted: 25 April 2019
Published online: 06 May 2019

References
1. Begum S. Molecular changes in smoking-related lung cancer. Expert Rev Mol Diagn. 2012;12(1):93–106.
2. He Q, Fu Y, Tian D, Yan W. The contrasting roles of inflammasomes in cancer. Am J Cancer Res. 2018;8(4):566–83.
3. Lu B, Li J, Gao Q, Yu W, Yang Q, Li X. Laryngeal cancer risk and common single nucleotide polymorphisms in nucleotide excision repair pathway genes ERCC1, ERCC2, ERCC3, ERCC4, and XPA. Gene. 2014;542(1):64–8.
4. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447(7145):661–78.
5. Parikh H, Wang Z, Pettigrew KA, Jia J, Daugherty S, Yeager M, Jacobs KB, Hutchinson A, Burdett L, Cullen M, Qi L, Boland J, Collins L, Albert TJ, Vatten LJ, Hveem K, Njølstad I, Cancel-Tassin G, Cussenot O, Valeri A, Vimenta J, Thun MJ, Feigelson HS, Oiver WR, Chatterjee N, Thomas G, Albames, D, Chanock SJ, Hunter DJ, Hoover R, Hayes RB, Benndt SJ, Sampson J, Amundadottir L. Fine mapping the KLK3 locus on chromosome 19q13.33 associated with prostate cancer susceptibility and PSA levels. Hum Genet. 2011;129(6):675–85.
6. Hoffmann TJ, Passarelli MN, Graff RE, Smith D, Liu W. Cloning of the human LRP6 gene and its expression in human cells. Gene. 2002;280(1):145–53.
7. Elia T, Elia T, Elia T, Elia T, Elia T, Elia T.
8. Xu et al. Cancer Cell Int          (2019) 19:119
16. Moreno-Bueno G, Gamallo C, Pérez-Gallego L, de Mora JC, Suárez A, Palacios J. Beta-Catenin expression pattern, beta-catenin gene mutations, and microsatellite instability in endometrioid ovarian carcinomas and synchronous endometrial carcinomas. Diagn Mol Pathol. 2001;10(2):116–22.

17. Mazzoni SM, Fearon ER. AXIN1 and AXIN2 variants in gastrointestinal cancers. Cancer Lett. 2014;355(1):1–8.

18. Morin PJ. Beta-catenin signaling and cancer. BioEssays. 1999;21(12):1021–30.

19. Gunes EG, Pinarbasi E, Pinarbasi H, Silig Y. Strong association between lung cancer and the AXIN2 polymorphism. Mol Med Rep. 2012;5(2):1029–35.

20. Alanazi MS, Parine NR, Shaik JP, Alabdulkarim HA, Ajaj SA, Khan Z. Association of single nucleotide polymorphisms in Wnt signaling pathway genes with breast cancer in Saudi patients. PLoS ONE. 2013;8(3):e59555.

21. Naghibalhossaini F, Zamani M, Mokarram P, Khalili I, Rasti M, Mostafavi-Four Z. Epigenetic and genetic analysis of Wnt signaling pathway in sporadic colorectal cancer patients from Iran. Mol Biol Rep. 2012;39(5):6171–8.

22. Ma C, Liu C, Huang P, Kaku H, Chen J, Guo K, Ueki H, Sakai Y, Kumon H, Shimizu K, Watanabe M. Significant association between the Axin2 rs2240308 single nucleotide polymorphism and the incidence of prostate cancer. OncoLett. 2014;8(2):789–94.

23. Yadav A, Gupta A, Yadav S, Rastogi N, Agrawal S, Kumar A, Kumar V, Misra S, Mittal B. Association of Wnt signaling pathway genetic variants in glioblastoma cancer cell line and survival. Tumour Biol. 2016;37(6):8083–9.

24. Mostowska A, Pawlik P, Sajdak S, Markowska J, Pawałowska M, Lianeri M, Jagodzinski PP. An analysis of polymorphisms within the Wnt signaling pathway in relation to ovarian cancer risk in a Polish population. Mol Diag Ther. 2014;18(1):85–91.

25. Gunes EG, Pinarbasi E, Pinarbasi H. AXIN2 polymorphism and its association with astrocytoma in a Turkish population. Mol Med Rep. 2010;3(4):691–4.

26. Kanzaki H, Ouchida M, Hanafusa H, Yano M, Suzuki H, Aoe M, Imai K, Shimizu N, Nakachi K, Shimizu K. Single nucleotide polymorphism of the AXIN2 gene is preferentially associated with human lung cancer risk in a Japanese population. Int J Mol Med. 2016;37(6):8083–9.

27. Pinarbasi E, Gunes EG, Pinarbasi H, Silig Y. AXIN2 polymorphism and its association with prostate cancer in a Turkish population. Med Oncol. 2011;28(4):1373–8.

28. Liu D, Li L, Yang Y, Liu W, Wu J. The Axin2 rs2240308 polymorphism and susceptibility to lung cancer in a Chinese population. Tumour Biol. 2014;35(1):10987–91.

29. Rosales-Reynoso MA, Arredondo-Valdez AR, Wence-Chávez LL, Barros-Núñez P, Gallegos-Arreola MP, Flores-Martínez SE, Sánchez-Corona J. AXIN2 polymorphisms and their association with colorectal cancer in Mexican patients. Genet Test Mol Biomarkers. 2016;20(8):438–44.

30. Bahl C, Sharma S, Singh N, Behera D. Association study between genetic variations in Axin2 gene and lung cancer risk in North Indian population: a multiple interaction analysis. Tumour Biol. 2017;39(4):1010428317695533.

31. Kim SS, Cho HJ, Lee HY, Park JH, Noh CK, Shin SJ, Lee KM, Yoo BM, Lee KJ, Cho SW, Cheong JY. Genetic polymorphisms in the Wnt/beta-catenin pathway genes as predictors of tumor development and survival in patients with hepatitis B virus-associated hepatocellular carcinoma. Clin Biochem. 2016;49(10–11):792–801.

32. Liu X, Li S, Lin X, Yan K, Zhao L, Yu Q, Liu X. AXIN2 is associated with papillary thyroid carcinoma. Iran Red Crescent Med J. 2016;18(2):e20960.

33. Parine NR, Azzam N, Shaik J, Aljabreen AM, Alharbi OA, Almadi MA, Alanazi M, Khan Z. Genetic variants in the WNT signaling pathway are protectively associated with colorectal cancer in a Saudi population. Saudi J Biol Sci. 2019;26(2):286–93.

34. Wu Z, Sun Y, Tang S, Liu C, Zhu S, Wei L, Xu H. AXIN2 rs2240308 polymorphism contributes to increased cancer risk: evidence based on a meta-analysis. Cancer Cell Int. 2015;15:68.

35. Yu Y, Tao Y, Liu L, Yang J, Wang L, Li X, Zhuang X, Chu M. New concept of the Axin2 rs2240308 polymorphism and cancer risk: an updated meta-analysis. Neoplasma. 2017;64(2):269–77.

36. Barili F, Parolari A, Kappetein PA, Freemantle N. Statistical Primer: heterogeneity, random- or fixed-effects model analyses? Interact Cardiovasc Thorac Surg. 2018;27(3):317–21.

37. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719–48.

38. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.

39. Yu Y, Tao Y, Liu L, Yang J, Wang L, Li X, Zhuang X, Chu M. New concept of the Axin2 rs2240308 polymorphism and cancer risk: an updated meta-analysis. Neoplasma. 2017;64(2):269–77.

40. Tobias A, Campbell MJ. Modelling influenza epidemics in the relation to influenza vaccination programmes. J Epidemiol Community Health. 1999;53(6):583–4.

41. Tang Z, Li C, Zhang K, Yang M, Hu X. GE-mini: a mobile APP for large-scale gene expression visualization. Bioinformatics. 2017;33(6):941–3.