CASP8 -652 6N del polymorphism and cancer risk: a meta-analysis of 30 case–control studies in 50 112 subjects

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Disruptions of normal apoptotic pathways, which are mainly mediated by caspases, play an essential role in cancer development. Caspase-8 (CASP8) is encoded by the CASP8 gene and is centrally involved in the apoptosis of T lymphocytes. The association between a six-nucleotide deletion polymorphism (-652 6N del) of the CASP8 gene and the risk of cancer is widely reported; however, study results have been inconsistent and contradictory. To evaluate the association between the CASP8 -652 6N del polymorphism and the risk of cancer and to overcome the limitations of any individual study, a meta-analysis based on a total of 23 700 cases and 26 412 controls from 30 case–control studies was conducted. The results of the overall analysis suggested that the CASP8 -652 6N del polymorphism is associated with decreased risk of cancer for the allelic contrast (del versus ins: odd ratio (OR) = 0.86, 95% confidence interval (CI) = 0.80–0.92), the additive genetic model (del/del versus ins/ins: OR = 0.78, 95% CI = 0.69–0.88), the dominant genetic model (del/del+del/ins versus ins/ins: OR = 0.83, 95% CI = 0.78–0.89) and the recessive genetic model (del/del versus ins/ins+del/ins: OR = 0.84, 95% CI = 0.75–0.93). In addition, after stratification for ethnicity and cancer type, significantly reduced risk was found for Asians and Caucasians as well as for individuals in the colorectal cancer group and the ‘other cancers’ group. Accordingly, there is an association between the CASP8 -652 6N del polymorphism and reduced cancer risk, especially among Asians, Caucasians and those with colorectal cancer. However, further research, such as studies focusing on additional ethnic groups and cancer types, is needed to provide a more exact and comprehensive synthesis conclusion.

Introduction
Apoptosis is a genetically controlled process of programmed cell death. Under normal circumstances, this mechanism is responsible for the safe removal of damaged cells before abnormalities can be replicated and spread. However, excessive or insufficient apoptosis could override the protective nature of the process and result in damage to healthy tissue or uncontrolled cell proliferation, respectively (1). Defective apoptotic pathways have thus been implicated in various human diseases with recently particular focus given to their involvement in cancer development and treatment (2).

The apoptotic process is largely mediated by enzymes called caspases (3,4). Caspase-8 (CASP8) is one key regulator of apoptosis of T lymphocytes and is encoded by the CASP8 gene. The human CASP8 gene contains at least 11 exons spanning ~30 kb on the highly polymorphic chromosome 2q33–34 (4,5). Several studies have confirmed that in addition to rare mutations, a few common variants of the CASP8 gene disrupt the apoptotic mechanism and thus impact the risk of developing various types of cancer, including breast cancer (6,7), colorectal cancer (8), ovarian cancer (9), prostate cancer (10) and several other cancers (11,12). Previous studies have largely focused on two variants of the CASP8 gene: D302H (rs1045485) and -652 6N del (rs3834129). Although the results of studies on the D302H variant have been generally consistent, conclusions on the -652 6N del variant remain inconsistent and inconclusive.

A clearer understanding of the relationship between the -652 6N del polymorphism and risk of cancer is of clinical significance and the well-established mechanism of the variant supports an association. The -652 6N del variant involves a six-nucleotide deletion in the promoter region of the CASP8 gene (13). This polymorphism decreases the activity of caspase-8 by abolishing the binding site of an Sp1 transcriptional activator and rendering the apoptotic pathway less efficient. The resulting reduced rate of apoptosis of T lymphocytes has been associated with increased immune surveillance (14). Through numerous case–control studies, researchers have attempted to establish whether the heightened T lymphocyte activity protects individuals with the genetic variant against cancerous and precancerous cell proliferation (14).

A previous meta-analysis (15) reported on the association between the -652 6N del polymorphism and risk of developing different types of cancer. However, the evidence from this analysis and the resulting publication was limited for several reasons. For instance, the reported pooled effect was based on only 14 case–control studies which is an insufficient number for investigating the risk of multiple types of cancer. In addition, the data extracted were neither clearly shown in the publication’s tables nor described in its text and so it was difficult to determine the types of cancer investigated in each case–control study, the genotype distribution for each included subgroup and other important study features. Furthermore, the meta-analysis involved stratification by only Asian and Caucasian population and did not provide information for risk of cancer among Africans or other ethnic groups. These weaknesses detracted from the power of the pooled results and the external validity of the findings.

Given the amount of data now available, it is important to perform a quantitative synthesis using more rigorous methods.
Here a meta-analysis was conducted to provide an overview of the relevant studies and generate more exact synthesis conclusions on the association between the CASP8 -652 6N del and cancer risk.

Materials and methods

Search strategy
To identify all relevant studies, a computerised literature search was conducted using the electronic databases PubMed and EMBASE and using the following keywords: ‘CASP8’ or ‘caspase-8’, ‘-652 6N del’ or ‘rs3834129’, ‘cancer’, ‘neoplasia’, ‘carcinoma’, ‘tumor’ or ‘tumour’ and ‘polymorphism’ or ‘variant’. Google Scholar was used to supply any of the references that were not retrieved articles were also screened for relevant studies. This search strategy was performed iteratively until no other relevant articles were found. All articles identified through this search strategy had been published on or before October 3, 2011.

Selection criteria
Titles and abstracts of all relevant papers were reviewed. Studies were chosen for inclusion if they met each of the following criteria: (i) the study was a population-based study and did not include subjects with family history of cancer or subjects known to be otherwise predisposed; (ii) the study was a case–control study; (iii) the article provided the sample size, distribution of alleles, genotypes or other information that could help to infer study characteristics; (iv) when multiple publications reported on the same or overlapping data, the most recent or the one including the largest population was selected and (v) the publication language was limited to English and Chinese.

Reviews, editorials, meeting abstracts and commentaries were excluded from our analysis.

Data extraction
Data were extracted independently by two reviewers (F.Z. and Y.Y.). Consensus was reached by discussion, and a third party was involved when necessary. The following information was extracted from each article: first author, year of publication, country where study was conducted, ethnicity of subjects, source of control group (population-based, hospital-based or mixed controls), matched factors of the control group, deviation from Hardy–Weinberg Equilibrium (HWE) of the control group, type of cancer, genotyping method and distribution of alleles and genotypes in the case and control groups.

Statistical analyses
Crude odds ratios (ORs) with their 95% confidence intervals (CIs) for alleles and genotypes were used to assess the strength of association between the CASP8 -652 6N del polymorphism and the risk of developing different types of cancer. Pooled ORs were calculated for the allele contrast, additive genetic model, dominant genetic model and recessive genetic model, respectively. The heterogeneity assumption was assessed using the Cochrane’s χ²-based Q statistic test and the I² test. Heterogeneity was not considered to be significant when P > 0.10 and I² < 50%. When no statistically significant heterogeneity was found, the pooled OR estimate of each study was calculated using the fixed effects model. Otherwise, the random effects model was used. Stratification analyses by cancer type (if a cancer type was investigated in less than three individual studies, it was categorised into the ‘other ethnicity’ group) were conducted to decrease heterogeneity and produce more accurate results. The sensitivity analysis was conducted based on the leave-one-out sensitivity procedure. Possible publication bias was tested using the funnel plot.

All statistical tests were conducted with Review Manager downloaded from the Cochrane Collaboration website (Version 5.1). A P value of 0.05 for any test or model was considered to be statistically significant.

Results

Study inclusion
A total of 45 publications were generated by the search strategy. Among these, 23 publications appeared to have met the inclusion criteria after title and abstract screening and were subjected to further examination. The full text of each of the 23 publications was found and screened based on the inclusion criteria. During the process, four other relevant publications were found through reference screening. After the full text screening of these 27 publications, a total of 20 publications were ultimately included for data extraction and statistical analysis. Among the seven publications excluded after full text screening, one was family-based study (16); one was carried out in BRCA1/2 mutation carriers (17); one was on cancer predisposition (18) and four studies’ full texts lacked information necessary for the analysis (19–22). Among the 20 publications included, 4 analysed multiple studies (13,23–25). One (24) of these articles described four studies investigating the risk of breast cancer among Caucasian samples in either the UK or Germany. Another (23) included two studies based in South Africa that both focused on the risk of cervical cancer but that varied in terms of their samples’ ethnic backgrounds. The third (13) of these articles described six studies, all of which were conducted in China among Asian samples but which varied in terms of type of cancer investigated. The remaining article (25) included two studies that differed in terms of cancer type (prostate versus breast cancer) but were the same in terms of project site and the ethnic composition of cases and controls. After accounting for these four articles that described multiple studies, a total of 30 case–control studies (including 23 700 cancer cases and 26 412 controls) from 20 publications were included in this meta-analysis. The entire selection process is described in Figure 1.

Meta-analysis database
A database was established according to the extracted information from each article. Table I lists the details of the database, including ethnicity of the subjects, source of the control group and genotype frequency of cases and controls, among other study characteristics. The included 30 case–control studies were published between 2006 and 2011, with a total study population of 50 112 participants. Eleven were conducted in China, 5 in India, 3 in the UK, 2 in the USA, 2 in Germany, 2 in Poland, 2 in South Africa, 1 in Greece, 1 in Japan and 1 in Korea. There were 18 studies involving Asian subjects, 10 involving Caucasian subjects, 1 involving African subjects and 1 involving subjects of mixed ethnic background. There were 11 population-based studies, 15 hospital-based studies, 3 studies with mixed controls and 1 study that did not provide information on the source population. There were 6 studies investigating breast cancer, 3 investigating cervical cancer, 3 investigating colorectal cancer, 3 investigating prostate cancer and 15 investigating other types of cancer.

![Fig. 1. Study flow chart for the process of selecting the final 20 publications.](https://example.com/fig1.png)
Table I. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study (first author, year)</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Cancer type</th>
<th>Case/control</th>
<th>Source of control</th>
<th>Genotype method</th>
<th>Deviation from HWE in controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun, 2007 (13)</td>
<td>China</td>
<td>Asian</td>
<td>BC</td>
<td>1119/1004</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Cybulski, 2008 (25)</td>
<td>Poland</td>
<td>Caucasian</td>
<td>BC</td>
<td>618/965</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Frank, 2008 (24)</td>
<td>Germany</td>
<td>Caucasian</td>
<td>BC</td>
<td>1110/1108</td>
<td>Hospital</td>
<td>Fluorescent analysis</td>
<td>No</td>
</tr>
<tr>
<td>Frank, 2008 (24)</td>
<td>UK</td>
<td>Caucasian</td>
<td>BC</td>
<td>1212/1184</td>
<td>Population</td>
<td>Fluorescent analysis</td>
<td>No</td>
</tr>
<tr>
<td>Frank, 2008 (24)</td>
<td>Germany</td>
<td>Caucasian</td>
<td>BC</td>
<td>1143/1155</td>
<td>Mixed</td>
<td>Fluorescent analysis</td>
<td>No</td>
</tr>
<tr>
<td>Frank, 2008 (24)</td>
<td>UK</td>
<td>Caucasian</td>
<td>BC</td>
<td>4470/4560</td>
<td>Population</td>
<td>Fluorescent analysis</td>
<td>No</td>
</tr>
<tr>
<td>Sun, 2007 (13)</td>
<td>China</td>
<td>Asian</td>
<td>Cervical cancer</td>
<td>314/567</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Chatterjee, 2011 (23)</td>
<td>South Africa</td>
<td>Black-African</td>
<td>Cervical cancer</td>
<td>106/257</td>
<td>Hospital</td>
<td>PCR/PCR RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Chatterjee, 2011 (23)</td>
<td>South Africa</td>
<td>Mixed-ancestry</td>
<td>Cervical cancer</td>
<td>339/964</td>
<td>Hospital</td>
<td>PCR/PCR RFLP</td>
<td>Yes</td>
</tr>
<tr>
<td>Sun, 2007 (13)</td>
<td>China</td>
<td>Asian</td>
<td>CRC</td>
<td>918/890</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Pittman, 2008 (26)</td>
<td>UK</td>
<td>Caucasian</td>
<td>CRC</td>
<td>4016/3769</td>
<td>Population</td>
<td>PCR</td>
<td>No</td>
</tr>
<tr>
<td>Theodoropoulos, 2011 (14)</td>
<td>Greece</td>
<td>Caucasian</td>
<td>CRC</td>
<td>402/480</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Cybulski, 2008 (25)</td>
<td>Poland</td>
<td>Caucasian</td>
<td>PC</td>
<td>485/965</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Kesarwani, 2010 (27)</td>
<td>India</td>
<td>Asian</td>
<td>PC</td>
<td>175/198</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>George, 2011 (28)</td>
<td>India</td>
<td>Asian</td>
<td>PC</td>
<td>165/205</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Wang, 2009 (29)</td>
<td>China</td>
<td>Asian</td>
<td>Bladder cancer</td>
<td>365/368</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Gangwar, 2009 (30)</td>
<td>India</td>
<td>Asian</td>
<td>Bladder cancer</td>
<td>212/250</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Li, 2008 (31)</td>
<td>USA</td>
<td>Caucasian</td>
<td>Cutaneous melanoma</td>
<td>805/835</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Ma, 2011 (32)</td>
<td>China</td>
<td>Asian</td>
<td>Epithelial ovarian cancer</td>
<td>218/285</td>
<td>Hospital</td>
<td>MassArray</td>
<td>No</td>
</tr>
<tr>
<td>Limar, 2011 (33)</td>
<td>India</td>
<td>Asian</td>
<td>ESCC</td>
<td>259/939</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Sun, 2007 (34)</td>
<td>China</td>
<td>Asian</td>
<td>ESCC</td>
<td>1018/937</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Srivastava, 2010 (35)</td>
<td>India</td>
<td>Asian</td>
<td>Gallbladder cancer</td>
<td>230/230</td>
<td>Mixed</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Sun, 2007 (13)</td>
<td>China</td>
<td>Asian</td>
<td>GC</td>
<td>420/410</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Lianmarkopoulos, 2011 (36)</td>
<td>Japan</td>
<td>Asian</td>
<td>GC</td>
<td>88/480</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Li, 2010 (57)</td>
<td>USA</td>
<td>Caucasian</td>
<td>Head and neck cancer</td>
<td>1023/1052</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Sun, 2007 (38)</td>
<td>Korea</td>
<td>Asian</td>
<td>Lung cancer</td>
<td>432/432</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Sun, 2007 (13)</td>
<td>China</td>
<td>Asian</td>
<td>Lung cancer</td>
<td>1149/1111</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Xiao, 2011 (39)</td>
<td>China</td>
<td>Asian</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>139/240</td>
<td>Not mentioned</td>
<td>PCR/PAGE</td>
<td>No</td>
</tr>
<tr>
<td>Yang, 2008 (34)</td>
<td>China</td>
<td>Asian</td>
<td>Pancreatic cancer</td>
<td>397/907</td>
<td>Population</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Wang, 2009 (29)</td>
<td>China</td>
<td>Asian</td>
<td>Bladder cancer</td>
<td>365/368</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
<tr>
<td>Zhu, 2010 (40)</td>
<td>China</td>
<td>Asian</td>
<td>Renal cell carcinoma</td>
<td>353/365</td>
<td>Hospital</td>
<td>PCR–RFLP</td>
<td>No</td>
</tr>
</tbody>
</table>

BC, breast cancer; CC, colorectal cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; LC, lung cancer; PAGE, polycracylamide gel electrophoresis; PC, prostate cancer; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

Quantitative synthesis

The relationship between a six-nucleotide deletion polymorphism (-652 6N del) of the CASP8 gene and the risk of different types of cancer was explored in an analysis of 30 case–control studies including 23,700 cases and 26,412 controls. Overall, a significant decreased risk of cancer was associated with the CASP8 -652 6N del polymorphism for the allele contrast (del versus ins: OR = 0.86, 95% CI = 0.80–0.92), the additive genetic model (del/del versus ins/ins: OR = 0.78, 95% CI = 0.69–0.88), the dominant genetic model (del/del+del/ins versus ins/ins: OR = 0.83, 95% CI = 0.78–0.89) and the recessive genetic model (del/del versus ins/ins+del/ins: OR = 0.84, 95% CI = 0.75–0.93).

In the stratified analysis for ethnicity, significantly reduced risk was found for Asians in the allele contrast (del versus ins: OR = 0.77, 95% CI = 0.70–0.84), the additive genetic model (del/del versus ins/ins: OR = 0.60, 95% CI = 0.47–0.75), the dominant genetic model (del/del + del/ins versus ins/ins: OR = 0.75, 95% CI = 0.70–0.80) and the recessive genetic model (del/del versus ins/ins + del/ins: OR = 0.62, 95% CI = 0.54–0.71). Similar results were observed for Caucasians only under the dominant genetic model (del/del + del/ins versus ins/ins: OR = 0.92, 95% CI = 0.87–0.97). No significant associations were observed for the other ethnicity group in any of the four genetic models.

In the stratified analysis for cancer type, a significant association was only detected for the colorectal cancer group in the additive model (OR = 0.90, 95% CI = 0.82–0.98) and for the other cancer group in the allele contrast (del versus ins: OR = 0.77, 95% CI = 0.70–0.84), the additive genetic model (del/del versus ins/ins: OR = 0.67, 95% CI = 0.59–0.75), the dominant genetic model (del/del + del/ins versus ins/ins: OR = 0.75, 95% CI = 0.70–0.80) and the recessive genetic model (del/del versus ins/ins + del/ins: OR = 0.67, 95% CI = 0.54–0.83). The main results on the genotype comparison are shown in Table II, Figures 2 and 3.

Sensitivity analysis

The sensitivity analysis was conducted by leaving out certain studies, such as the study that did not conform to HWE or the study with mixed control sources. The omission of individual studies did not materially alter the results, although on some occasions, the $I^2$-squared value for heterogeneity was reduced. The sensitivity analysis thus confirmed that the results of this meta-analysis were statistically robust.

Publication bias

Funnel plots were performed for all four genetic models to assess publication bias. As shown in Figure 4, the shape of the funnel plot for the additive genetic model did not reveal any obvious asymmetry, which confirms the absence of significant publication bias. Similarly shaped plots (data not shown) were
observed for the allele contrast model, the dominant genetic model and the recessive genetic model.

Discussion

Programmed cell death, or apoptosis, is a normally protective process that enables the body to eliminate harmful cells. However, impaired apoptotic mechanisms can lead to uncontrolled cell proliferation and result in the pathogenesis of human cancer (2). Encoded by the \textit{CASP8} gene, caspase-8 has a central function in apoptotic pathways (41) and changes in the genetically determined structure of this enzyme can influence the rate of apoptosis. More specifically, a six-nucleotide deletion polymorphism (-652 6N del) has been identified in the promoter region of the \textit{CASP8} gene and is associated with decreased RNA expression in lymphocytes due to the alteration of an \textit{Sp1} binding site (13). This variant has been found to decrease \textit{CASP8} activity and apoptotic reactivity of T lymphocytes through the cancer cell \textit{ex vivo} model (13). Due to the functional significance of the \textit{CASP8} -652 6N del variant, several studies have sought to determine its association with the risk of developing different types of cancer. In order to avoid the limitations and potential bias of any individual study, we conducted this meta-analysis to provide more robust statistical evidence on the relationship.

Overall, the 30 studies included in the present analysis were of high quality. Methods of recruitment, total sample numbers, characteristics of participants and inclusion criteria of the sample subjects were generally clearly stated; cases and controls were matched in age and gender and there was no deviation from HWE among controls in all but one study.

The results of the meta-analysis suggested that the minor allele of the -652 6N del was associated with a statistically significant ($P < 0.05$) decrease in overall cancer risk. The synthesis heterogeneity under the four genetic models was generally large. Upon closer review of each included original study, it was found that half of the included studies determined a negative association, while the other half concluded a positive association. The studies’ results were likewise inconsistent in terms of different ethnicities and carcinoma sites, and it seemed that there was no relationship with the period of the study or the population size. Hence, it is necessary to perform stratification analysis by both ethnicity and cancer type.

After stratification by ethnicity, it was found that there was a significant protective association between the -652 6N del polymorphism and overall cancer risk among Asian and Caucasian populations, while no significant effect was found among Africans or those in the other ethnicity group. Among the included studies, 18 were based on Asian samples for a total of 17 109 subjects (7971 cases and 9138 controls) and 10 were based on Caucasian samples for a total of 34 307 subjects (15 284 cases and 16 053 controls), respectively. The sample sizes and numbers of studies for investigating risk in these ethnic groups were determined to be adequate for supporting the observed overall association between -652 6N and risk of cancer. The strength of the association, however, varied between ethnic groups, with statistically significant results under only the dominant genetic model for the Caucasian ethnic group. One explanation for the latter result may be that the studies using Caucasian participants enrolled them from various countries with diverse cultural, environmental and genetic characteristics. It is expected that these factors affected the synthesis results. On the other hand, the Asian populations in the included studies were relatively homogeneous and largely consisted of Han Chinese. This similarity at the population level may explain the significant findings in all possible models among the Asian ethnic group.

After stratification by cancer type, a significant association was found for the other cancers group in all four genetic models and for colorectal cancer in the dominant genetic model. No significant effects were observed for prostate cancer, cervical cancer and breast cancer in any of the four genetic models. This result is inconsistent with that of the previous
meta-analysis (15), in which a significant association between the CASP8 -652 6N del polymorphism and breast cancer was found. There were a total of 15 cancer types in the 30 included studies. Eleven of these cancer types were investigated in two or fewer studies and were therefore classified in the other cancers group for purposes of stratification. Four of the 11 cancer types were evaluated in two studies each and the remaining 7 were investigated in only one study each. Once a statistically significant association was observed for the other cancers group, we separately evaluated the four cancer types with two studies. It was found that there was a significant association between CASP8 -652 6N del and reduced risk for bladder cancer, cervical squamous cell carcinoma and gastric cancer while no significant association was obtained for lung cancer. Stratification into individual cancer types suggested that the observed relationship for the other cancers group was not completely accurate in capturing the specific effect of the polymorphism on the risk of individual cancer types.

Furthermore, despite the overall robust statistical evidence generated through this analysis, some methodological limitations were identified. Firstly, the language of included studies was limited to English and Chinese. Also, since several included studies did not match cases and controls on baseline variables other than age and gender, selection bias may have influenced individual results. Moreover, in the subgroup analyses by ethnicity and cancer type, the sample of studies among Africans and among several cancer types was small and the available studies were limited in sample size. Accordingly, it is required that more studies be conducted to provide a more definitive conclusion that comprehensively explores the relationship between the CASP8 -652 6N del polymorphism and risk of cancer in the overall population.
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Fig. 3. Association between CASP8 -652 6N del polymorphism and cancer risk in dominant model by different ethnicity.

Conclusion

In conclusion, the results of the present meta-analysis support an association between the CASP8 -652 6N del polymorphism and reduced cancer risk, especially among Asians, Caucasians and those with colorectal cancer or cancer(s) identified in the other cancers group. To advance an understanding of this relationship, the following recommendations have been made: (i) further studies with larger sample sizes are required to validate the current findings; (ii) studies conducted with ethnic groups other than Asians and Caucasians are required to gain
and reduced cancer risk, especially among Asians, Caucasians
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Fig. 3. CASP8 -652 6N del polymorphism and cancer risk in dominant model by different ethnicity.

groups other than Asians and Caucasians are required to gain
(i) further studies with larger sample sizes are required to
relationship, the following recommendations have been made:

Chromosomal damage in BD-exposed workers of China

References

Conflict of interest statement: None declared.

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Statistical analysis. F.Z. and Y.Y. collect and extract the data. C.G. participated
in the publication search and helped to draft the manuscript, Y.W. concieves of the study and participates in its design and coordination and helps to draft the manuscript.

Conflict of interest statement: None declared.

Fig. 4. Funnel plot for the additive model.

a more comprehensive and generalisable conclusion and (iii)
additional studies focused on previously less researched cancer
types, such as lung cancer, gastric cancer, are also needed.

CASP8 is associated with risk of glioma. Cancer Epidemiol. Biomarkers
Prev., 17, 987–989.

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