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EPIDEMIOLOGY

Differential effects of MDM2 SNP309 polymorphism on breast cancer risk along with race: a meta-analysis

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Abstract MDM2 SNP309 is a single nucleotide T > G polymorphism present in intron 1 of the MDM2 gene. A variety of case–control studies have been published evaluating the association between MDM2 SNP309 and breast cancer risk. However, the published studies, as well as the subsequent meta-analyses, have yielded contradictory results. This meta-analysis aims to examine whether MDM SNP309 polymorphism may exert a differential effect on breast cancer risk along with race. Eligible articles were identified by a search of MEDLINE, Cochrane and EMBASE bibliographical databases for the period July 1993 to June 2009; 16 case–control studies were eligible (12,986 breast cancer cases, 12,993 controls). Subanalyses in case–control studies conducted on Chinese (3 studies, 892 cases, 1,435 controls) and non-Chinese populations (13 studies, 12,094 cases, 11,558 controls) were performed. All pooled odds ratios (ORs) were derived from fixed-effects models given that the between-study heterogeneity was not statistically significant. Subanalysis on Chinese subjects demonstrated that GT and GG genotype were associated with increased breast cancer risk (pooled OR = 1.272, 95% CI 1.025–1.578 and pooled OR = 1.323, 95% CI 1.034–1.694, respectively); as a result the overall effect of the G allele was statistically significant (pooled OR = 1.287, 95% CI 1.048–1.579). On the contrary, no significant associations between MDM2 SNP309 status and breast cancer risk were demonstrated in non-Chinese populations. In conclusion, the association between MDM2 SNP309 and breast cancer is modified by race. MDM2 SNP309 represents a risk factor for breast cancer in Chinese women but not in non-Chinese women. This phenomenon is analogous to that described in the context of lung cancer.

Keywords Breast cancer · MDM2 polymorphism · SNP309 · Meta-analysis · Race

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Introduction

MDM2 is a well-established negative regulator of the p53 tumor suppressor protein, directly binding to the latter and resulting in its ubiquitination [1]. Apart from this crucial function, MDM2 is also capable of mediating p53-independent actions [2]. In line with its overall role in carcinogenesis, MDM2 is a key molecule involved in breast cancer [3].

A single nucleotide T > G polymorphism present in intron 1 of the MDM2 gene, known as MDM2 SNP309, has drawn the attention of the scientific community, given that it has been associated with enhanced binding affinity of the transcription factor Sp1 and consequently enhanced MDM2 expression [4]. Concerning breast cancer, the discovery of the polymorphism has prompted investigators to conduct a variety of case–control studies, so as to examine whether MDM2 SNP309 is associated with breast cancer risk [5–20], age of onset [7, 11, 15, 16, 18, 19] and prognosis [5, 16, 18, 19].

The above studies have yielded contradictory results; interestingly enough, the existing controversy became evident also at the level of meta-analyses having appeared 2 years ago [21, 22]. Hu et al. [21] reported that SNP309GG is associated with overall cancer risk, after

performing a meta-analysis on 21 case–control studies among which ten were specifically focused on breast cancer; as a result, the researchers characterized MDM2 SNP309 as a "low-penetrance susceptibility tumor marker". On the other hand, Wilkening et al. [22] made the clear distinction between breast, colorectal and lung cancer in their meta-analysis and concluded that SNP309 status does not represent a risk factor for breast cancer.

Nearly 2 years since the above two contradictory meta-analyses, seven more case–control studies on the association between SNP309 and breast cancer have appeared [14–20]; this represents approximately 50% of the number of studies having been included in the previous meta-analyses. Therefore, the need for an updated meta-analysis of results has become evident. This meta-analysis aims to shed light on controversies, assessing directly whether SNP309 status is associated with breast cancer risk.

Method

Trial identification

Eligible articles were identified by a search of MEDLINE, Cochrane and EMBASE bibliographical databases for the period July 1993 to June 2009 (last search: June 20, 2009), using combinations of the following keywords: "breast cancer", "MDM2", "SNP309", "polymorphism" and "mouse double minute 2". In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used and two investigators (KPE and TNS), working independently, searched the literature and extracted data from each eligible case–control study.

Eligible studies and data abstraction

All case–control studies with any sample size examining the association of SNP309 polymorphism with breast cancer (i.e. reporting the frequencies of TT, TG and GG genotypes in cases and controls) were considered eligible for this analysis. For each of the eligible case–control studies, the following data were collected: journal name, year of publication, inclusion and exclusion criteria, demographic characteristics of the population being studied and frequencies of TT, TG and GG genotypes in cases and controls.

Statistics

Based on the genotype frequencies in cases and controls, crude odds ratios (ORs) as well as their standard errors (SE) were calculated. The ORs pertained to genotype GT (heterozygous vs. TT), genotype GG (homozygous vs. TT) and the G allele (G allele carriers, i.e. GT plus GG vs. TT). Three separate analyses were performed: (1) overall association between MDM2 SNP309 status (homozygous, heterozygous, G allele) and breast cancer risk, (2) subanalysis in case–control studies conducted on Chinese populations and (3) subanalysis in case–control studies conducted on non-Chinese populations.

The fixed-effects model (Mantel–Haenszel method), as well as the random effects (DerSimonian Laird) model, were used to calculate the pooled OR. Between-study heterogeneity and between-study inconsistency were assessed by using Cochran Q statistic and by estimating I^2, respectively [23]. In case no significant heterogeneity was detected, the fixed-effects model was chosen. Evidence of publication bias was determined using Begg's formal statistical test [24] and by visual inspection of the funnel plot. For the interpretation of Begg's test, statistical significance was defined as $p < 0.1$. Analyses were conducted using STATA 10.0 (STATA Corp. College Station, TX, USA) and meta-analysis was performed using the "metan" command.

Results

Figure 1 graphically illustrates the trial flow chart. Out of the 28 abstracts retrieved through the search criteria, eight

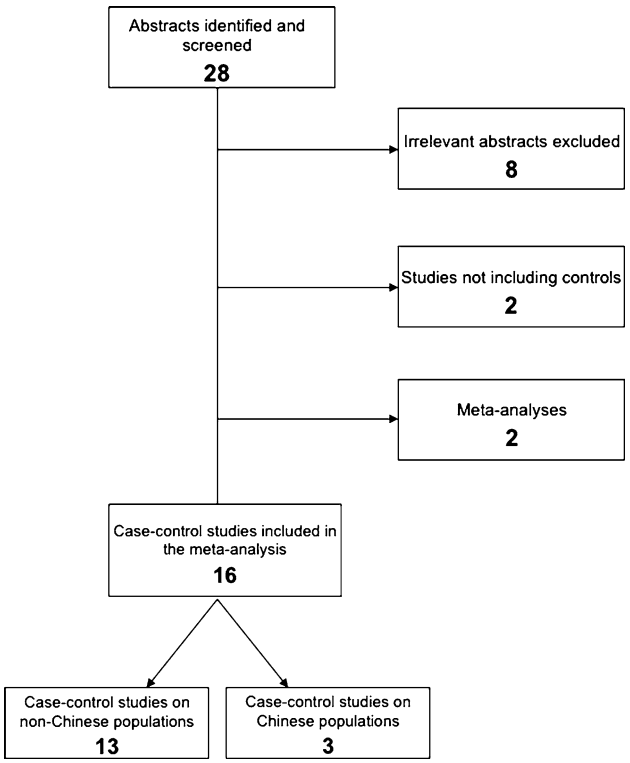

Fig. 1 Study flow chart. Explaining the selection of the 16 eligible case–control studies

studies were irrelevant and two studies were excluded [25, 26] given that they have not included controls in their study design, and two articles were meta-analyses [21, 22]. As a result, 16 case–control studies (12,986 breast cancer cases, 12,993 controls) were included in this meta-analysis [5–20]. Three studies had been performed in Chinese populations [8, 16, 19].

In the overall analysis, GT genotype was associated with increased breast cancer risk (pooled OR = 1.056, 95% CI 1.000–1.115, Fig. 2a). On the contrary, GG genotype was not associated with breast cancer risk (pooled OR = 0.981, 95% CI 0.908–1.060, Fig. 2b). The overall effect of the G allele on breast cancer risk was not statistically significant (OR = 1.036, 95% CI 0.984–1.090, Fig. 2c).

The subanalysis on Chinese subjects (892 cases, 1,435 controls) demonstrated that GT and GG genotype were associated with increased breast cancer risk (pooled OR = 1.272, 95% CI 1.025–1.578, Fig. 3a, and pooled OR = 1.323, 95% CI 1.034–1.694, Fig. 3b, respectively). The overall effect of the G allele was statistically significant (pooled OR = 1.287, 95% CI 1.048–1.579, Fig. 3c).

The subanalysis on non-Chinese subjects (12,094 cases, 11,558 controls) demonstrated that neither GT nor GG genotype were associated with breast cancer risk (pooled OR = 1.042, 95% CI 0.985–1.103, Fig. 4a, and pooled OR = 0.950, 95% CI 0.875–1.030, Fig. 4b, respectively). As expected, the effect of G allele was not statistically significant (pooled OR = 1.021, 95% CI 0.968–1.076, Fig. 4c).

All pooled ORs were derived from fixed-effects models given that the between-study heterogeneity was not statistically significant. The Begg's test did not demonstrate any statistically significant publication bias.

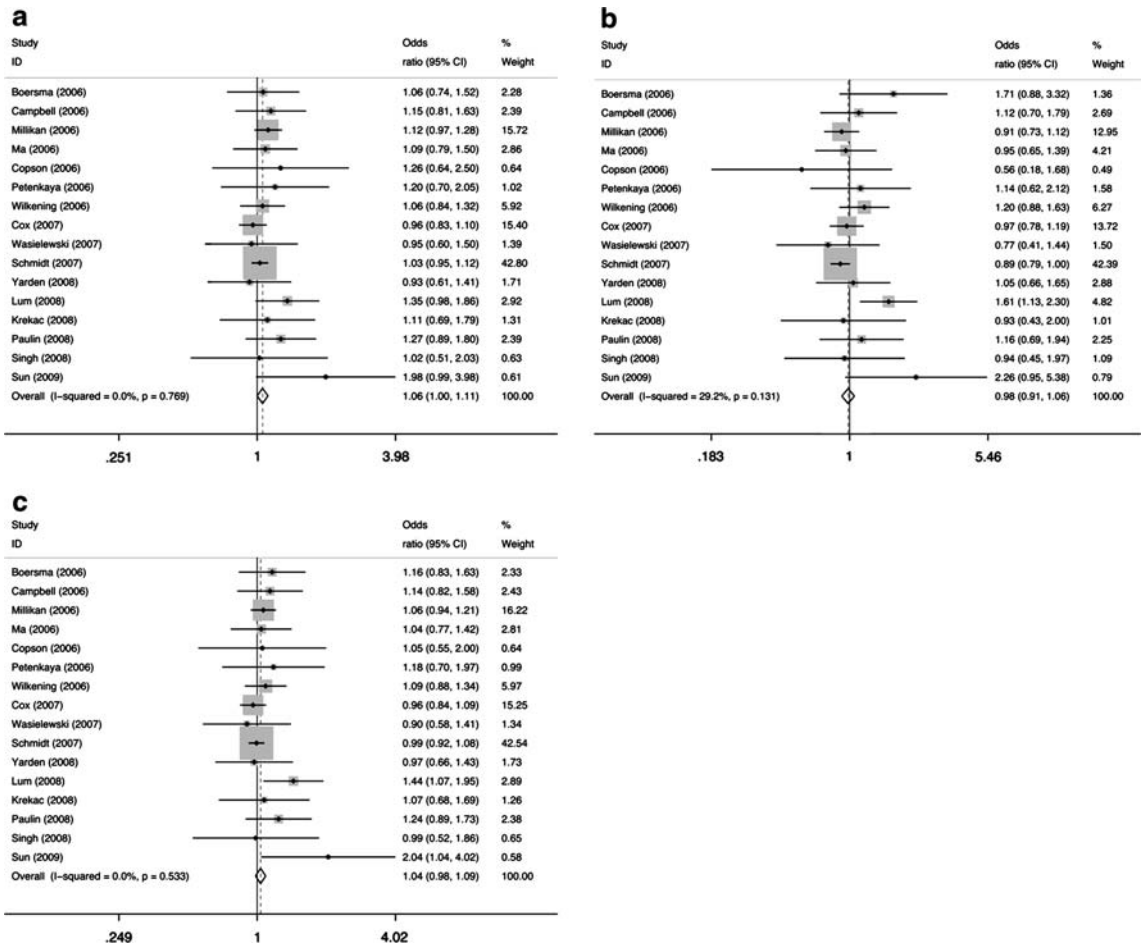

Fig. 2 Forest plot for the overall association between MDM2 SNP309 status and breast cancer risk for **a** genotype GT (heterozygous vs. TT), **b** genotype GG (homozygous vs. TT) and **c** the G allele (G allele carriers, i.e. GT plus GG vs. TT). Each study is shown by the point estimate of the odds ratio (OR) (the size of the square is proportional to the weight of each study) and 95% confidence interval for the OR (extending lines); the pooled OR and 95% confidence interval by fixed-effects calculations are shown by *diamonds*

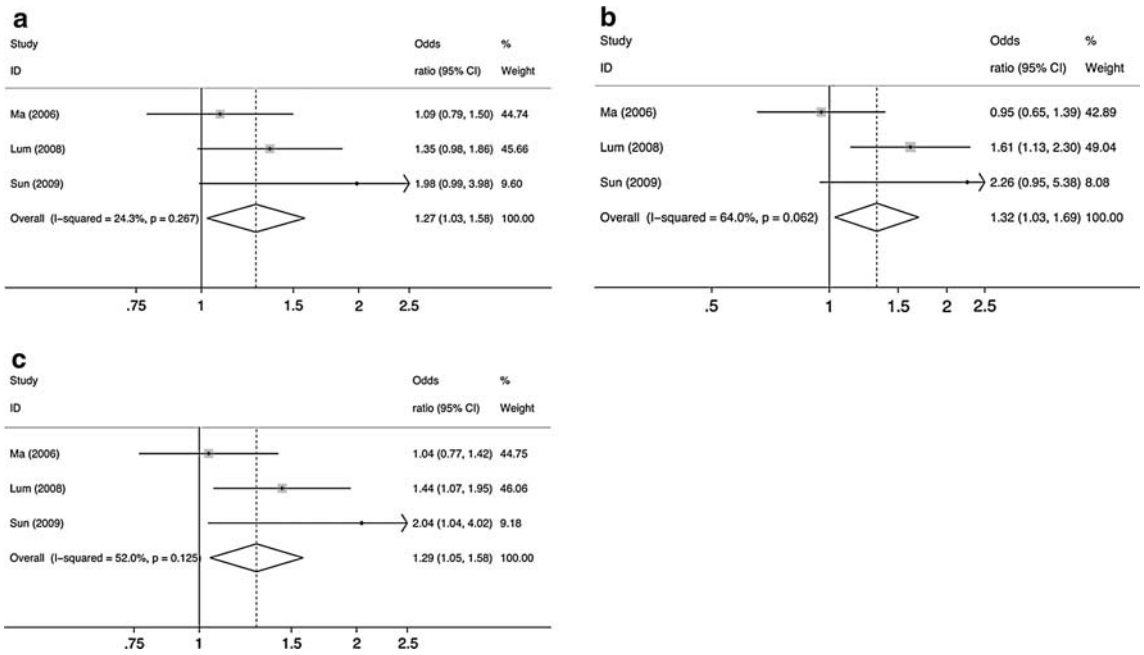

Fig. 3 Forest plot for the subanalysis on Chinese subjects for **a** genotype GT, **b** genotype GG and **c** the G allele

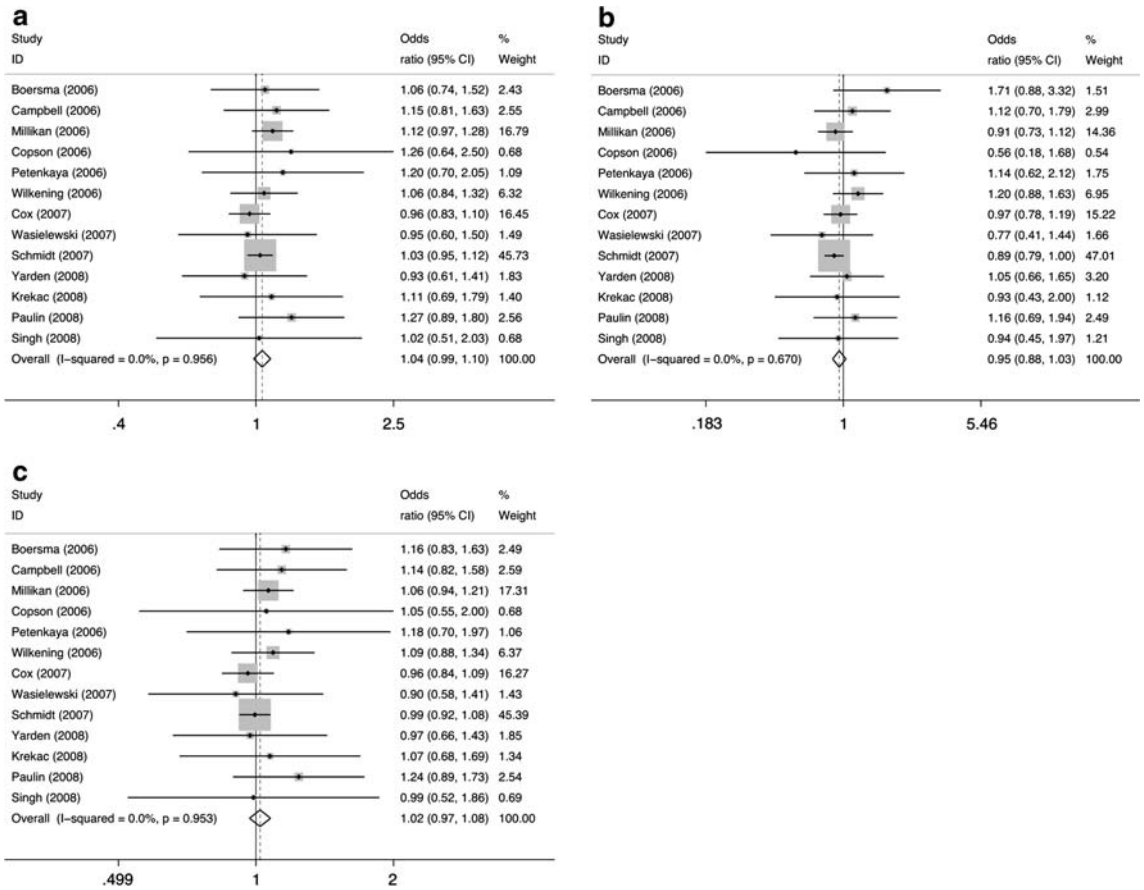

Fig. 4 Forest plot for the subanalysis on non-Chinese subjects for **a** genotype GT, **b** genotype GG and **c** the G allele

Discussion

The main message of this meta-analysis is that the association between MDM2 SNP309 and breast cancer is modified by race. MDM2 SNP309 represents a risk factor for breast cancer in Chinese women but not in non-Chinese women. The present results provide substantial improvement in the understanding of the MDM2 SNP309-breast cancer interplay when compared with those presented by Wilkening et al. [22]. The latter had performed a meta-analysis solely on nine case–control studies pertaining to breast cancer and at that time point, it was not possible to reach such conclusions given that only one Chinese study had appeared [8].

An impressive analogy emerges. In the context of lung cancer, MDM2 SNP309 is associated with elevated lung cancer risk in Asian populations but not in European or African groups, according to the results of a recent meta-analysis [27]. It seems, thus, that race is an effect modifier capable of surpassing tissue specific functions.

Concerning the subanalyses on non-Chinese populations, which are the majority of studies published on MDM2 SNP309 and breast cancer, an essentially null association became evident. Indeed, the functional link between MDM2 SNP309 and breast cancer in Caucasian women remains obscure, as its presence has not led to increased MDM2 protein expression; consequently, SNP309 status seems fairly independent from the well-established MDM2 overexpression in breast cancer [28]. Nevertheless, under the light of the present meta-analysis, it would be tempting to anticipate functional and physiological studies exclusively on Chinese women, so as to investigate the possible physiological effects of the polymorphism therein.

This meta-analysis is the first to demonstrate a physiological interaction between an MDM2 polymorphism and an inherent feature. In the context of lung cancer, a meta-analysis has demonstrated that MDM2 SNP309 is capable of interacting with smoking status; specifically, its relationship with lung cancer is stronger for never smokers [29]. On the other hand, studies on breast cancer have not made such a point yet; the putative interactions between MDM2 SNP309 and well-established risk factors such as oral contraceptive use [30] and obesity [31] would be tempting and meaningful targets for future analyses and meta-analyses.

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