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Meta-analysis of microsomal epoxide hydrolase gene polymorphism and the risk of breast carcinoma

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ABSTRACT. Carcinogenesis of breast carcinoma is very complicated. Previous studies have suggested conflicting results regarding the association between Tyr113His and His139Arg microsomal epoxide hydrolase (*mEH*) gene polymorphisms and risk of breast carcinoma. We conducted a meta-analysis to examine the relationship between these polymorphisms and breast carcinoma risk. We searched the PubMed, EMBASE, and Google Scholar databases to identify relevant studies. After extracting relevant data, the association between *mEH* polymorphisms and susceptibility to breast carcinoma was examined by meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association. Seven studies were identified that included 6357 cases and 8090 controls. The

mEH His-allele was not associated with the risk of breast carcinoma based on the allelic contrast model (OR = 0.99, 95%CI = 0.94-1.04, P = 0.58), dominant genetic model (OR = 1.14, 95%CI = 0.88-1.48, P = 0.33), or recessive genetic model (OR = 1.03, 95%CI = 0.96-1.10, P = 0.43). Similarly, the *mEH* Arg-allele was not associated with breast carcinoma risk based on the allelic contrast model (OR = 0.97, 95%CI = 0.91-1.04, P = 0.44), dominant genetic model (OR = 1.01, 95%CI = 0.84-1.21, P = 0.94), or recessive genetic model (OR = 1.04, 95%CI = 0.96-1.12, P = 0.35). Subgroup analysis based on ethnicity showed no association between the polymorphisms and risk of breast carcinoma. Thus, the Tyr113His and His139Arg *mEH* polymorphisms may not be risk factors for breast carcinoma.

Key words: Meta-analysis; Microsomal epoxide hydrolase; Breast carcinoma; Polymorphism

INTRODUCTION

Breast carcinoma is the most frequent malignancy and represents the second leading cause of cancer death among women worldwide, making it a major health problem in many developed countries (Jemal et al., 2011). However, the pathogenesis of breast carcinoma is not completely understood despite known breast carcinoma risk factors such as reproductive events, exogenous hormones, lifestyle and environment risk factors, and genetic factors (Dumitrescu and Cotarla, 2005).

Candidate genetic risk factors include the X-ray repair cross-complementing group gene (Bu et al., 2014), *RAD51* gene (Zhao et al., 2014), and microsomal epoxide hydrolase (*mEH*) gene, among others. Previous epidemiological studies have investigated the association between *mEH* gene functional polymorphisms and breast carcinoma. However, the results have been inconsistent, largely because of the small sample sizes involved. Therefore, we performed a meta-analysis to comprehensively examine the association between *mEH* polymorphisms and the risk of breast carcinoma. The two most important loci of *mEH* are rs1051740 in exon 3 (Tyr113His) and rs2234922 in exon 4 (His139Arg). Tyr113His of the *mEH* gene decreases enzyme activity by approximately 40%, whereas His139Arg increases this activity by 25%.

MATERIAL AND METHODS

Literature search strategy and inclusion criteria

We systematically searched the PubMed, EMBASE, and Google Scholar databases for case-control studies examining the association between the *mEH* polymorphisms Tyr113His and His139Arg and breast carcinoma risk published through the end of March 2014 using the following medical subject headings (MeSH): (*EPHX1* or *HYL1* or *microsomal epoxide hydrolase* or *mEH*) and (*polymorphism* or *variation* or *genotype* or *genetic* or *mutation*) and (*breast carcinoma* or *breast cancer*). Manual searching of relevant references and review articles was also performed. Studies were included in this meta-analysis if they a) used a case-control

design to assess the association between the Tyr113His and/or His139Arg polymorphisms with risk of breast carcinoma, b) were published in English, and c) provide data sufficient for estimating odds ratios (ORs) (Dura et al., 2012) with 95% confidence intervals (CIs). In the case of multiple studies based on the same population, we selected the study with the largest sample size (Gong et al., 2013; Zhong et al., 2012, 2013a).

Data extraction

Literature searches and identification of eligible papers based on the inclusion criteria were carried out independently by two authors. Data were independently extracted using a predefined form to include the first author's family name, year of publication, country of origin, source of controls, total numbers of cases and controls, Hardy-Weinberg equilibrium (HWE) of controls, and frequencies of the Tyr113His and His139Arg genotypes in cases and controls. Discrepancies were resolved through discussion (Gong et al., 2013; Zhong et al., 2012, 2013a).

Statistical analysis

All statistical tests for this meta-analysis were performed using the Review Manager 5.0 software. The strength of the association between the *mEH* Tyr113His and His139Arg polymorphisms and risk of breast carcinoma was estimated by calculating ORs with 95%CIs based on genotype frequencies in cases and controls. HWE in controls was assessed using the asymptotic test, with $P < 0.05$ considered to be statistically significant.

The significance of pooled ORs was determined using the Z-test, with $P < 0.05$ defined as the significance threshold. Meta-analysis was conducted using a fixed-effect model when $P > 0.10$ for the Q-test, indicating a lack of heterogeneity among studies; otherwise, a random-effect model was used. Small-study bias was assessed using Harbord's modified test (Harbord et al., 2006).

RESULTS

A total of 218 potentially relevant publications through March 31, 2014 were systematically identified in the PubMed, EMBASE, and Google Scholar databases. Of these, most were excluded because they did not satisfy the inclusion criteria (Figure 1). Although we also searched for relevant genome-wide association studies, we found no studies investigating the association between *mEH* Tyr113His and His139Arg polymorphisms and risk of breast carcinoma. Only 7 studies (de Assis et al., 2002; Sarmanová et al., 2004; Spurdle et al., 2007; Justenhoven et al., 2008; Khedhaier et al., 2008; Sangrajrang et al., 2009; Abbas et al., 2010), involving 6357 breast carcinoma cases and 8090 healthy controls, were included in this meta-analysis (Tables 1 and 2). All patients in the case group had incident primary breast carcinoma. Breast carcinoma diagnosis was confirmed by histopathology. Five of the 7 studies were conducted in a Caucasian population (de Assis et al., 2002; Sarmanová et al., 2004; Spurdle et al., 2007; Justenhoven et al., 2008; Abbas et al., 2010). The other 2 studies were in African (Khedhaier et al., 2008) and Asian (Sangrajrang et al., 2009) populations. The polymorphisms were analyzed by polymerase chain reaction-restriction fragment length polymorphism in 4 studies (de Assis et al., 2002; Sarmanová et al., 2004; Justenhoven et al., 2008; Khedhaier et

al., 2008). The matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Abbas et al., 2010), the ABI Prism 7700 Taqman Sequence Detection System (Spurdle et al., 2007), and the ABI Prism 7900 HT Sequence Detection System (Sangrajrang et al., 2009) were used to genotype the polymorphisms in the remaining studies.

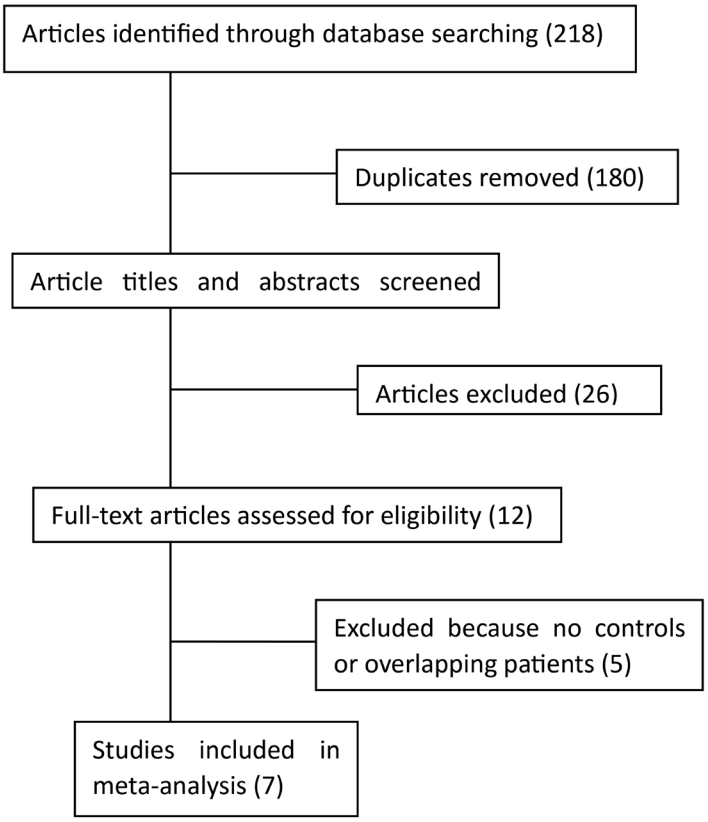

Figure 1. Flow chart of study selection.

Table 1. Characteristics of studies investigating the association between *mEH* exon 3 (rs1051740) and breast cancer risk.

Study	Ethnicity	Recruitment period	Cases/Controls	No. of cases			No. of controls			P_{HWE}
				His/His	Tyr/His	Tyr/Tyr	His/His	Tyr/His	Tyr/Tyr	
de Assis (2002)	Caucasian	-	267/293	50	99	118	41	119	133	0.093
Justenhoven (2008)	Caucasian	2000-2002	605/609	63	246	296	45	269	295	0.144
Khedhaier (2008)	African	1994-2002	306/244	38	119	149	16	115	113	0.070
Abbas (2010)	Caucasian	-	3147/5483	267	1345	1535	490	2322	2671	0.677
Sangrajrang (2009)	Asian	2002-2006	557/487	128	286	143	115	247	125	0.786
Sarmanová (2004)	Caucasian	2001-2003	237/311	45	77	115	39	124	148	0.120
Spurdle (2007)	Caucasian	1992-1999	1238/663	103	496	639	85	262	316	0.010

Table 2. Characteristics of studies investigating the association between *mEH* exon 4 (rs2234922) and breast cancer risk.

Study	Ethnicity	Recruitment period	Cases/Controls	No. of cases			No. of controls			P_{HWE}
				Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His	
de Assis (2002)	Caucasian	-	267/293	13	96	158	12	109	172	0.404
Justenhoven (2008)	Caucasian	2000-2002	601/624	28	182	391	23	213	388	0.395
Abbas (2010)	Caucasian	-	3142/5476	131	954	2057	245	1701	3530	0.031
Sangrajrang (2009)	Asian	2002-2006	562/489	11	147	404	8	128	353	0.470
Sarmanová (2004)	Caucasian	2001-2003	310/238	15	115	180	8	83	147	0.436

All 7 studies described the association between *mEH* Tyr113His polymorphism and risk of breast carcinoma (de Assis et al., 2002; Sarmanová et al., 2004; Spurdle et al., 2007; Justenhoven et al., 2008; Khedhaier et al., 2008; Sangrajrang et al., 2009; Abbas et al., 2010). The distribution of genotypes among controls was not in HWE in the study by Spurdle et al. (2007). Meta-analysis of the 7 studies indicated that the genotype at *mEH* polymorphism rs1051740 was not associated with an increased or reduced risk of breast carcinoma across the genetic models tested: the OR was 0.99 (95%CI = 0.94-1.04) for the His- *vs* Tyr-allele, 1.14 (0.88-1.48) for His/His *vs* Tyr/His+Tyr/Tyr, 1.09 (0.85-1.41) for His/His *vs* Tyr/Tyr, and 1.03 (0.96-1.10) for Tyr/Tyr *vs* His/His+Tyr/His (Figure 2).

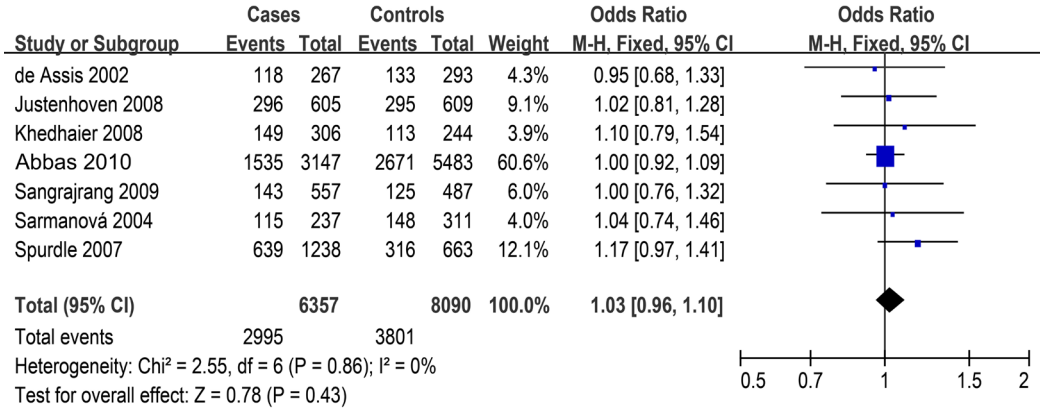

Figure 2. Forest plot describing the association between the Tyr113His *mEH* polymorphism and breast cancer (Tyr/Tyr *vs* His/His+Tyr/His).

Moreover, subgroup analysis based on ethnicity showed that the *mEH* polymorphism rs1051740 was not associated with an increased or reduced risk of breast carcinoma (Table 3).

Only 5 studies (de Assis et al., 2002; Sarmanová et al., 2004; Justenhoven et al., 2008; Sangrajrang et al., 2009; Abbas et al., 2010) described the His139Arg polymorphism. The distribution of genotypes among controls in one study was not in HWE (Abbas et al, 2010). Meta-analysis of the 5 studies indicated that the genotype at *mEH* polymorphism rs2234922 was not associated with an increased or reduced risk of breast carcinoma in the genetic models tested: the OR was 0.97 (0.91-1.04) for the Arg- *vs* His-allele, 1.01 (0.84-1.21) for Arg/Arg *vs* Arg/His+His/His, 0.99 (0.82-1.20) for Arg/Arg *vs* His/His, and 1.04 (0.96-1.12) for His/His *vs* Arg/His+Arg/Arg (Figure 3). Moreover, subgroup analysis based on ethnicity showed that the His139Arg polymorphism was not associated with an increased or reduced risk of breast carcinoma (Table 3).

Table 3. Overall meta-analysis of the association between *mEH* polymorphisms and breast cancer risk.

Genotype comparison	OR (95%CI)	Z (P value)	Genotype comparison	OR (95%CI)	Z (P value)
Tyr113His Total (6357 cases and 8090 controls)			His139Arg Total (4882 cases and 7120 controls)		
His-allele *vs* Tyr-allele	0.99 (0.94-1.04)	0.56 (0.58)	Arg-allele *vs* His-allele	0.97 (0.91-1.04)	0.77 (0.44)
His/His *vs* Tyr/His+Tyr/Tyr	1.14 (0.88-1.48)	0.98 (0.33)	Arg/Arg *vs* Arg/His+His/His	1.01 (0.84-1.21)	0.08 (0.94)
His/His *vs* Tyr/Tyr	1.09 (0.85-1.41)	0.68 (0.49)	Arg/Arg *vs* His/His	0.99 (0.82-1.20)	0.07 (0.94)
Tyr/Tyr *vs* His/His+Tyr/His	1.03 (0.96-1.10)	0.78 (0.43)	His/His *vs* Arg/His+Arg/Arg	1.04 (0.96-1.12)	0.94 (0.35)
Tyr113His Caucasian (5800 cases and 7603 controls)			His139Arg Caucasian (4320 cases and 6631 controls)		
His-allele *vs* Tyr-allele	1.00 (0.91-1.11)	0.02 (0.98)	Arg-allele *vs* His-allele	0.97 (0.91-1.04)	0.85 (0.39)
His/His *vs* Tyr/His+Tyr/Tyr	1.19 (0.86-1.65)	1.08 (0.28)	Arg/Arg *vs* Arg/His+His/His	1.00 (0.83-1.21)	0.00 (1.00)
His/His *vs* Tyr/Tyr	1.13 (0.83-1.53)	0.78 (0.43)	Arg/Arg *vs* His/His	0.99 (0.81-1.19)	0.15 (0.88)
Tyr/Tyr *vs* His/His+Tyr/His	1.03 (0.96-1.10)	0.81 (0.42)	His/His *vs* Arg/His+Arg/Arg	1.04 (0.96-1.13)	1.01 (0.31)

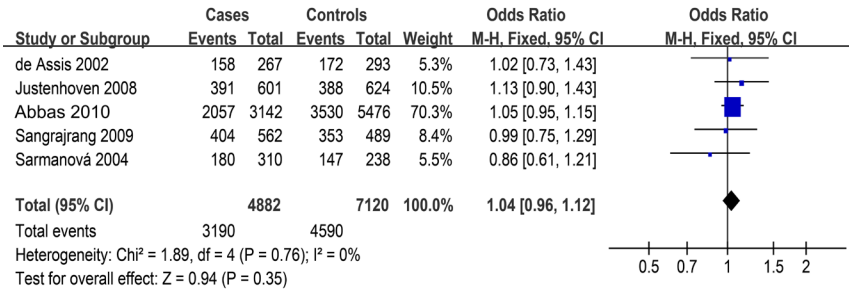

Figure 3. Forest plot describing the association between the His139Arg *mEH* polymorphism and breast cancer (His/His *vs* Arg/His+Arg/Arg).

To test the robustness of these findings, we recalculated ORs and 95%CIs across all studies after systematically removing individual studies. The results after deleting each study were similar to those obtained when all studies were included.

Because only 7 studies were included, we did not assess publication bias or its impact. However, the small-study bias tests revealed no significant bias (P = 0.481; Figure 4).

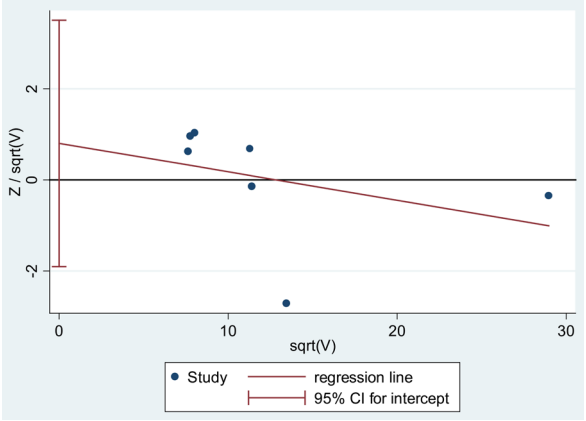

Figure 4. Test for small-study bias in published data on allele contrast (113His- *vs* 113Tyr-) of the *mEH* polymorphism and risk of breast cancer.

DISCUSSION

As an enzyme located on the endoplasmic reticulum, mEH plays a key role in the activation and detoxification of polycyclic aromatic hydrocarbons, aromatic amines, and the hydrolysis of various epoxides. In addition, mEH plays a role in activating certain xenobiotic carcinogens (Fretland and Omiecinski, 2000). Thus, mEH can either promote or inhibit carcinogenesis by activating or detoxifying procarcinogens, and which role it adopts may depend on exposure to different environmental substrates. The Tyr113His mutation in exon 3 decreases enzyme activity, while the His139Arg mutation in exon 4 increases activity.

Various case-control studies have investigated *mEH* polymorphisms and their possible association with various cancers. While a significant association has been observed with ovarian cancer (Goode et al., 2011; Zhong et al., 2013c), hepatocellular carcinoma (Zhong et al., 2013b), and lung cancer (Li et al., 2011), no reliable association has been identified for colorectal cancer (Nisa et al., 2013) or esophageal carcinoma (Dura et al., 2012). Studies examining the association between *mEH* polymorphisms and the risk of breast carcinoma have shown conflicting results. Thus, we carried out this meta-analysis of 7 case-control studies involving 14,447 subjects. We found that in a mixed population and specifically in Caucasian, African, or Asian populations, neither the Tyr113His nor the His139Arg *mEH* polymorphisms were associated with an increased or reduced risk of breast carcinoma.

While our results suggest that neither Tyr113His nor His139Arg is an independent predictor of breast carcinoma risk, these polymorphisms may interact with the environment to affect risk. Indeed, breast carcinoma, like most malignancies, is widely thought to result from the combination of environmental factors and host genetics. However, 3 of the studies (de Assis et al., 2002; Justenhoven et al., 2008; Sangrajrang et al., 2009) in our meta-analysis suggested that *mEH* Tyr113His or His139Arg polymorphisms do not interact with environmental factors to affect breast carcinoma risk. One study (de Assis et al., 2002) found no significant association between *mEH* polymorphisms and risk of breast carcinoma in the overall study group or after stratifying by both menopausal and smoking status. Another study (Sangrajrang et al., 2009) found that there was no significant association between *mEH* genotype and breast carcinoma risk after stratifying based on smoking or alcohol consumption. However, the third study (Justenhoven et al., 2008) found that the wild-type *mEH* genotype had a significant association with lower overall survival in patients who were axillary lymph node-negative, as well as with lower disease-free survival in patients who were axillary lymph node-positive. Thus, *mEH* genotype, although not useful for predicting the risk of breast carcinoma, may have prognostic value, which should be investigated in future studies.

mEH Tyr113His or His139Arg may interact with other genes to affect the risk of breast carcinoma. One study in our meta-analysis (Spurdle et al., 2007) reported that the combination of the His/His *mEH* genotype and the *GSTM1* polymorphism in the gene encoding the detoxifying enzyme glutathione *S*-transferase was marginally associated with a decreased risk of breast carcinoma. Future studies should examine this and other possible gene interactions.

Given the association between hormone levels in breast carcinoma patients and their prognosis (Farhat et al., 2013; Kaaks et al., 2014), it would be useful to assess whether the *mEH* Tyr113His and His139Arg mutations interact with hormone levels to influence patients' prognosis. We were unable to address this question because most of the studies in our meta-analysis did not report detailed data regarding hormone levels.

The findings of this meta-analysis are limited by the design of the included studies. First, the healthy controls in the included studies were not uniformly defined, and it was not possible to determine which controls were population-based and which were hospital-based. Second, the distribution of genotypes among controls was not in HWE in 2 of the included studies, and these 2 studies accounted for 39% of the cases and 40% of the controls in the overall meta-analysis (Spurdle et al., 2007; Abbas et al., 2010). Thus, our results may not be representative of the larger population. Finally, the results may have been affected by confounding factors, including tumor status, age, smoking, hormone levels, body mass index, oral contraceptive use or hormone replacement therapy, age at first menarche, and age at menopause. Most studies in our meta-analysis did not report these data or they aggregated the analysis of these factors in different ways, making it impossible to perform subgroup analyses.

In conclusion, our meta-analysis suggests that neither *mEH* Tyr113His nor His139Arg is associated with the risk of breast carcinoma. Further detailed studies including a larger sample size are needed to clarify the role of *mEH* polymorphism in breast carcinoma, as well as to explore gene-gene and gene-environment interactions that may mediate the association between *mEH* polymorphisms and breast carcinoma risk.

Conflicts of interest

The authors declare no conflict of interest.

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