RESEARCH COMMUNICATION

No Association Between the *CYP1B1* C4326G Polymorphism and Endometrial Cancer Risk: a Meta-analysis

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Abstract

    <u>Purpose</u>: Any association between the *CYP1B1* C4326G polymorphism and endometrial cancer risk remains inconclusive. In order to provide a more precise estimate, we performed the present meta-analysis. <u>Methods</u>: We used fixed effect or random effect models to estimate pooled odds ratios (ORs) with 95% confidence intervals (CIs) for endometrial cancer risk, with the Chi-square-based Q-test used to test for heterogeneity. Begg's and Egger's tests were adopted to check publication bias. <u>Results</u>: Six published case-control studies of association between the *CYP1B1* C4326G polymorphism and endometrial cancer risk covering 6,577 subjects were included in the meta-analysis, but the results indicated no significant correlation with allele contrast and genotype comparisons (G vs C: OR 1.01, 95% CI 0.93-1.09; GG vs CC: OR 1.04, 95% CI 0.88-1.23; CG + GG vs CC: OR 1.08, 95% CI 0.97-1.21; GG vs CC + CG: OR 1.01, 95% CI 0.87-1.17). Heterogeneity hypothesis test did not reveal any heterogeneity and Begg's and Egger's tests did not detect obvious publication bias. <u>Conclusions</u>: There is no association between the *CYP1B1* C4326G polymorphism and endometrial cancer risk.

Key words: *CYP1B1* - endometrial cancer - polymorphism - meta-analysis

Introduction

    Endometrial cancer is a common gynecological malignancy of the female urogenital tract, and its incidence is increasing significantly (Sasaki et al., 2001). More and more attention is being paid on endometrial cancer prevalence around the world. Although endometrial cancer could be caused by any or a combination of the traditional risk factors such as BMI, hypertension, diabetes, smoking, alcohol consumption, hormone therapy, oral contraceptive use, growing number of evidences suggest genetic factors play a crucial role in endometrial cancer etiology through their interactions with the environmental components. It is, therefore, important to identify the gene variants contributing to endometrial cancer pathogenesis. The knowledge of the genetic factors influencing endometrial cancer risk could be instrumental in enhancing the prediction of disease risk and devising efficient therapeutic strategies, based on targeted approach.

    It is well recognized that endometrial cancer is the most frequent "estrogen-sensitive malignancy" in women (Key etal., 1988) and that estrogen and its metabolites are known to be both inducers and promoters of endometrial cancer (Herrington et al., 2001). So far as we know, estrogen metabolism involves two main phases, of which phase 1 involves the conversion of estrogen into catechol metabolites and hydroxy derivatives by the enzymes complex composed of CYP1A1, CYP1A2 and CYP1B1 through hydroxylation (Zhu et al., 1998). It is worth mentioning that convertion estrogens to 4-hydroxy estrogens which induce DNA damage (Han et al., 1994; Newbold et al., 2000). Additionally, 4- hydroxyestrogens can activate the estrogen receptor, thereby increasing the quantity of estrogen within the cells (Zhu et al., 1998). Consequently the metabolic conversion of estrogens to 4-hydroxy estrogens has been postulated to be a major factor in carcinogenesis (Liehr et al., 1990; Hayes et al., 1996).

    CYP1B1 variants are more efficient than wild types in the conversion and accumulation of carcinogenic catechol estrogens (Hanna et al., 2000). Furthermore, the ratio of product formation of 4-hydroxy estrogens to 2-hydroxy estrogens is higher for *CYP1B1* variants compared with their wildtype counterpart (Shimada et al., 1999; Hanna et al., 2000), potentially contributing to higher tissue levels of 4-hydroxy estrogens (Hanna et al., 2000). Thus, inherited alterations in the activity of CYP1B1 leads to differences in estrogen metabolism and thereby, may possibly explain inter-individual differences in endometrial cancer risk associated with

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estrogen-mediated carcinogenesis (Bailey et al., 1998; Hanna et al., 2000). Six polymorphisms of the *CYP1B1* gene have been described of which four result in amino acid substitutions; intron 1-13 C>T, codon Arg48Gly, codon Ala119Ser, codon Leu432 Val (4326C>G), codon 449 T>C and codon Asn453ASer (Bailey 1998; Bejjani et al., 1998; Stoilov et al.,1998). The polymorphisms on codon Ala119Se and codon Leu432 Val have significant effects on the catalytic function of CYP1B1 (Meyer et al., 1986; Hayashi et al., 1991; Li et al., 1998). However, variations in the genes that control the production and metabolism of these hormones and their relationship with endometrial cancer have not been elucidated (Ashton et al., 2010). Previous association studies of polymorphisms in *CYP1B1* mainly focused on the 4326C>G polymorphism and showed inconsistent results.

For the purpose of precisely estimating the association between *CYP1B1* 4326C>G polymorphism and endometrial cancer risk, we performed the following meta-analysis. All literature published about *CYP1B1* 4326C>G polymorphism and endometrial cancer risk were searched and summarized. In order to ensure the analysis quality, Hardy-Weinberg equilibrium (HWE) test, sensitivity analysis and publication bias analysis were adopted in the article together.

Materials and Methods

Search for eligible studies

Databases such as PUBMED, OVID, ScienceDirect, SpringerLink, EBSCO and EMBASE were searched (up until 30 April 2011, using the search strategy: *CYP1B1* AND (polymorphisms OR polymorphism OR variant) AND ("endometrial cancer" OR "endometrial carcinoma"). All studies were searched, and their bibliographies were checked for other relevant publications. Only studies with full text articles which were published in English were included. The search results were limited to humans.

Inclusion criteria

The following criteria were used for the study selection: (a) case–control study evaluating the CYP1B1 polymorphism and endometrial cancer risk; (b) genotype distributions in both cases and controls were available; (c) full text articles; (d) literature published in English; (e) genotype distribution in the control of the study was in agreement with HWE.

Data extraction

Information for meta-analysis was carefully evaluated and extracted from all the eligible publications independently by two of the authors according to the inclusion criteria listed above. Disagreement was resolved by discussion between them. If they could not reach a consensus, then another author was consulted for the settlement of dispute and a final decision was made by the majority of the votes. The following data was collected from each study: first author's name, publication year, country, ethnicity, source of control, genotyping methods, confirmation of diagnosis, numbers genotyped of cases and controls, frequency of allele.

Statistical methods

The strength of association between *CYP1B1* C4326G polymorphism and endometrial cancer risk were measured by OR with 95% CI. The pooled OR was estimated for allele contrast (G vs C) and genotype contrasts (CG vs CC, GG vsCC, CG + GG vs CC, GG vs CG + CC). Heterogeneity assumption was checked by the chi-square-based Q-test (Cochran 1954). A P value greater than 0.05 for the Q-test indicates no heterogeneity among studies, and so the fixed-effects model was used for the meta-analysis (Mantel et al., 1959). Otherwise, the random effects model was used (DerSimonian et al., 1986). Quantification of the heterogeneity was done with the I^2 metric ($I^2 = (Q - df)/Q$), which is independent of the number of studies in the meta-analysis (Higgins et al., 2002). The I^2 values falls within the range 0-100%, with higher values denoting greater degree of heterogeneity ($I^2 = 0$-25%, no heterogeneity; $I^2 = 25$-50%, moderate heterogeneity; $I^2 = 50$-75%, large heterogeneity; $I^2 = 75$-100%, extreme heterogeneity) (Zintzaras et al., 2005). Sensitivity analyses were carried out by limiting a single study at a time into the meta-analysis. An estimate of potential publication bias was carried out by the Begg funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests potential publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. Significant publication bias would be confirmed when P value for bias less than 0.05 in Egger's test.

Owing to meta-analysis focusing on analysis for published literatures, the study was exempt from Ethics Committee approval. All of the statistical tests used in our meta-analysis were performed by STATA version 10.0 (Stata Corporation, College Station, TX).

Results

General information of included studies

Based on above search criteria, a total of 8 studies (Sasaki et al., 2003; McGrath et al., 2004; Rylander-Rudqvist et al., 2004; Doherty et al., 2005; Tao et al., 2006; Hirata et al., 2008; Ashton et al., 2010; Sliwinski et al., 2010;) met the first 4 inclusion criteria. However, 2 studies (Sasaki et al., 2003; Sliwinski et al.,2010) failed to abide by HWE. Therefore, 6 studies (McGrath et al., 2004; Rylander-Rudqvist et al., 2004; Doherty et al., 2005; Tao et al., 2006; Hirata et al., 2008; Ashton et al., 2010) involving 2633 cases and 3944 controls

Table 1. Characteristics of the Studies of *CYP1B1* C4326G Polymorphism and Endometrial Cancer Risk

First author,year	Country	Ethnicity	Cancer type	Source of controls	Diagnostic method	Genotyping method	Cases (n, age)	Controls (n, age)
Ashton, 2010	Australia	Caucasian	NR	PB	histological	TaqMan	191,NR	290,NR
Hirata, 2008	USA	Caucasian	A124, U13	PB	histological	PCR-RFLP	150,60.0±9.8	165,60.0±9.6
Tao, 2006	China	Asian	NR	PB	NR	TaqMan	1037,30-69	1034, 30-69
Doherty, 2005	USA	Mix	Invasive	PB	NR	PCR-RFLP	371,50-69	420, 50-69
McGrath, 2004	USA	Caucasian	Invasive	PB	histological	Pyrosequencing	219,30-50	655, 30-55
Rylander-Rudqvist, 2004	Sweden	Caucasian	Invasive	PB	histological	Minisequencing,DASH	665,50-74	1380,50-74

NR, not report; HB, hospital-based; PB, population-based

Table 2. Distribution of the *CYP1B1* C4326G Polymorphism Genotypes and the Allele Frequency for Endometrial Cancer Patients and Controls (Values in Parentheses are the Corresponding Percentages)

First author, year	Distribution of *CYP1B1* genotypes						HWE for controls	Frequency of *CPY1B1* alleles			
	Cases			Controls				Cases		Controls	
	CC	CG	GG	CC	CG	GG		C	G	C	G
Ashton, 2010	32	88	71	50	139	101	0.9	152(38.9)	230(40.3)	239(61.1)	341(59.)
Tao, 2006	792	232	13	806	206	22	0.06	1816(50.0)	258(50.8)	1818(50.0)	250(49.2)
Rylander-Rudqvist, 2004	195	336	134	425	676	279	0.74	726(32.2)	604(32.9)	1526(67.8)	1234(67.1)
Hirata, 2008	53	64	33	55	72	38	0.16	170(48.2)	130(46.8)	182(51.8)	148(53.2)
Doherty, 2005	115	170	86	145	194	81	0.27	400(51.0)	342(49.0)	384(49.0)	356(51.0)
McGrath, 2004	61	113	45	193	316	146	0.43	235(25.1)	203(25.0)	702(74.9)	608(75.0)

HWE, Hardy–Weinberg equilibrium (HWE was calculated by Fisher's exact probabilities)

Table 3. Results of Meta-analysis for Allele Contrast and Various Genetic Contrasts of *CYP1B1* C4326G Polymorphism

Allele/genetic contrasts	Studies (n)	Alleles/ genotypes (n)	Fixed effects OR(95%CI)	Fixed effects P value	I^2(%)	Q test P value
G vs C	6	13054	1.01(0.93-1.09)	0.9	0	0.94
GG vs CC	6	3971	1.04(0.88-1.23)	0.65	0	0.5
(CG+GG) vs CC	6	6577	1.08(0.97-1.21)	0.18	0	0.98
GG vs (CG+CC)	6	6577	1.01(0.87-1.17)	0.89	0	0.45
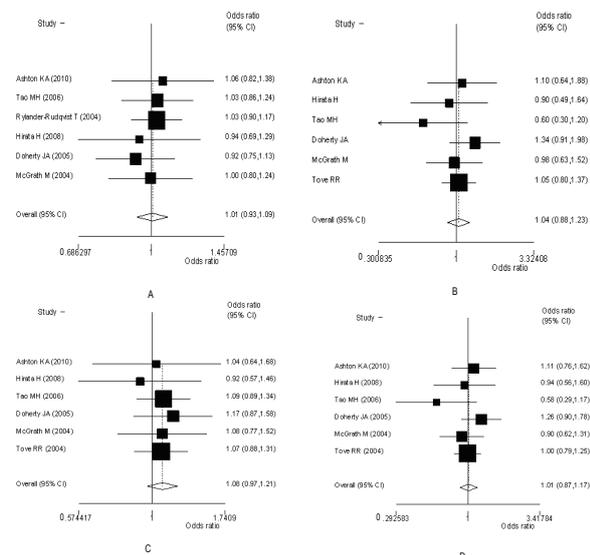
Figure 1. Forest Plots for Associations between the *CYP1B1* Polymoprhism and Endometrial Cancer Risk for All genotype Comparisons. The pooled OR did not reveal and statistically significant asssociations.

were included in final meta-analysis. The related information of studies is listed in Table 1. The genotype distributions and the allele frequency of *CPY1B1*

C4326G polymorphism are showed in Table 2.

Quantitative synthesis

In the meta-analysis of C4326G polymorphism, the summary OR showed no statistically significant association of the G allele with the risk to endometrial cancer as compared to the C allele, OR = 1.01 [95% CI (0.93, 1.09)]; P = 0.90 (Table 3). No inter-study heterogeneity was observed for this allelic variant (I^2 = 0; P = 0.94). In the sensitivity analysis, retrieval of any study didn't change the pooled results materially. The Begg-Mazumdar test, although indicated low power for this meta-analysis, showed no significant publication bias, Kendall's tau = -5; P = 0.45. The Egger's test also showed no publication bias, P = 0.46.

In the genotype contrasts (Table 3), no statistically significant association between *CYP1B1* C4326G polymorphism and endometrial cancer risk was detected (for GG vs CC: OR 1.04, 95% CI 0.88-1.23; for CG + GG vs CC: OR 1.08, 95% CI 0.97-1.21; for GG vs CC + CG: OR 1.01, 95% CI 0.87-1.17).

Further more, no heterogeneity emerged in any genotype contrasts. The negative association results also were not substantially altered and did not draw different conclusions in the sensitivity analysis.
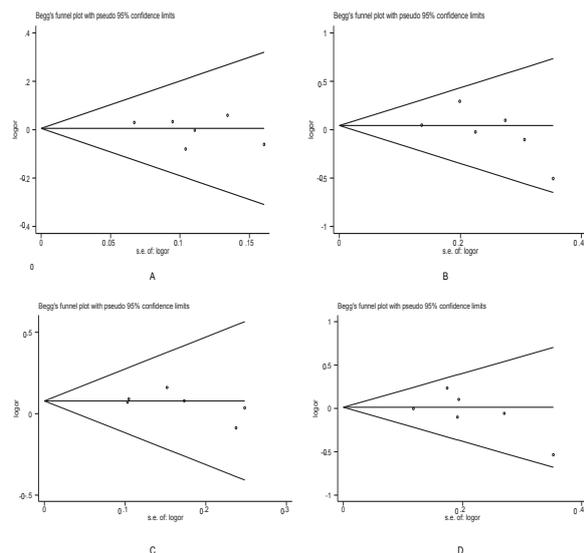
Figure 2. Funnel Plots for all Genotype Comparisons

The appearance of the funnel plots for all genotype comparisons in *CYP1B1* C4326G polymorphism (Figure 2) did not reveal any obvious asymmetry. Also the corresponding results of Egger's test also did not suggest any publication bias in all genotype contracts (for B, GG vs CC model: t= -1.20, P = 0.30; for C, (CG + GG) vs CC model: t = -1.01, P = 0.37; for D, GG vs (CG + CC) model: t = -1.09, P = 0.34).

Discussion

Up to the present day, many epidemiology studies from different part of the world have evaluated the association between CYP1B1 C4326G polymorphism and endometrial cancer risk. Unfortunately, they failed to reach a consistent conclusion. Some studies (Meyer et al.,1986; Shimada et al., 1999; Hanna et al., 2000; Aklillu et al., 2002; Sasaki et al., 2003) reported that CYP1B1 C4326G polymorphism can amplify the risk of endometrial cancer carcinogenesis. Contrary to above standpoint, Ashton et al claimed that CYP1B1 C4326G polymorphism can decrease the risk for the endometrial cancer development (Ashton et al., 2010).

There could be several factors contributing to discordant findings among individual studies. Small sample size is one of them, which often enhances the chance factor for false-positive or false-negative findings. Variation among results of different studies might also be the consequence of different sampling strategies and/or ethnical variation among the study populations. In meta-analysis, however, the false-positive and false-negative results neutralize each others as large number of studies is pooled, and the increase of overall statistical power leads to a more precise and accurate measure of association.

Under the paradoxical circumstances, it is necessarily to perform a meta-analysis to derive a more precise estimation. The pooled result indicated that no

association between CYP1B1 C4326G polymorphism and endometrial cancer risk was found in allele contrast (G vs C) and any genotype contrasts (GG vs CC, CG + GG vs CC and GG vs CC + CG). Our meta-analysis results were strongly supported by some Studies (McGrath et al., 2004; Rylander-Rudqvist et al., 2004; Doherty et al., 2005; Wen et al., 2005; Tao et al., 2006; Hirata et al., 2008; Sliwinski et al.,2010;) from different background.

Heterogeneity is a potential problem that may affect the interpretation of the results. Therefore Hardy-Weinberg equilibrium test must be conducted in control group to ensure the same population genetic background and reliability of association analyses. Unfortunately, two studies (Sasaki et al., 2003; Sliwinski et al., 2010) were not agree with Hardy-Weinberg equilibrium (HWE) and were ruled out. However, because of the neglect of HWE test for some studies in control group (Sasaki et al., 2003; Sliwinski et al., 2010), the meta-analysis concerning association between between C4326G polymorphism and endometrial cancer risk by Fang Wang et al. (2011) derived totally different conclusion from us.

Despite variants in study design, sample sizes, sample selection, ethnicity, and menopausal status, there was no statistically significant heterogeneity among 6 studies included in the meta-analysis. This indicated that it may be appropriate to use an overall estimation of the relationship between CYP1B1 C4326G polymorphism and endometrial cancer risk.

As the publication of findings often depends on the expectation of researchers, false-negative results may be suppressed or false-positive results magnified (Salanti et al., 2005; Zhang et al., 2008). The results of this study, however, did not show any significant publication bias in allele contrast and all genotype contrasts.

In view of complexity of gene polymorphism effect on disease progress and interaction between genetic background and environmental factors, the following aspects may result in negative association between *CYP1B1* C4326G polymorphism and endometrial cancer risk: First, *CYP1B1* C4326G may take on linkage disequilibrium with some SNPs leading to endometrial cancer indeed, which result in negative association between the site and endometrial cancer risk. Second, other genes and environmental factors may influence the association between *CPY1B1* C4326G and endometrial cancer risk.

Some limitations of this meta-analysis must be acknowledged. First, the number of studies contained in the meta-analysis was relatively small. To a certain extent, it may influence the statistical power. Second, our result was based on unadjusted estimates, while meta-regression analysis should be performed if more detailed individual data was available such as BMI, ethnicity, lifestyle, and other environmental factors.

In spite of limitations, some advantages may be

found in the meta-analysis. First, Hardy-Weinberg equilibrium test was conducted in control group in every study. It can identify the homogeneity of population genetic background and ensure the reliability of association analysis. Second, Begg's and Egger's tests did not detect any publication bias, indicating that our results should be unbiased. Third, when sensitivity analysis was performed by omitting one study at a time in all genotype models to check the influence of individual studies on the summary effect estimate, no any study had significant change on overall result. It indicated that the meta-analysis results were robust.

Based on the limits of the study, future investigation about association between CPY1B1 C4326G polymorphism and endometrial cancer risk should pay more attention to homogeneity among studies and comparability between patients and control. In addition, addressing gene-gene and gene-environment interactions is also imperative.

In conclusion, this meta-analysis involving 6 studies and 6,577 subjects suggests that CYP1B1 C4326G polymorphism is not associated with endometrial cancer risk.

Acknowledgments

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