RESEARCH ARTICLE

Lack of Association Between the CYP1A1 Ile462Val Polymorphism and Endometrial Cancer Risk: a Meta-analysis

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Abstract

Purpose: Any association between the CYP1A1 Ile462Val polymorphism and endometrial cancer risk remains inconclusive. For a more precise estimate, we performed the present meta-analysis. Methods: PUBMED, OVID and EMBASE were searched for the studies which met inclusion criteria. Data in all eligible studies were evaluated and extracted by two authors independently. The meta-analysis estimated pooled odds ratio (OR) with 95% confidence interval (CI) for endometrial cancer risk attributable to the CYP1A1 Ile462Val polymorphism. Results: A total of 7 studies were included in this meta-analysis. The results indicated no association between endometrial cancer risk and the CYP1A1 Ile462Val polymorphism (for Val vs Ile allele model [OR 1.09, 95% CI 0.73-1.62]; for Val.Val vs Ile.Ile genotype model [OR 1.54, 95% CI 0.56-4.23]; for (Ile.Val + Val.Val) vs Ile.Ile genotpye model [OR 1.08, 95% CI 0.71-1.63]; for Val.Val vs (Ile.Ile + Ile.Val) genotype model [OR 1.46, 95% CI 0.53-4.04]). Conclusions: This meta-analysis suggests that there is no association between endometrial cancer risk and the CYP1A1 Ile462Val polymorphism.

Keywords: CYP1A1 - endometrial cancer - polymorphism - meta-analysis

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Introduction

It is reported that endometrial cancer is the most frequent "estrogen-sensitivemalignancy" in women (Key et al., 1988) and that estrogen and its metabolites are known to be both inducers and promoters of endometrial cancer (Herrington et al., 2001). With the change of lifestyle, people have more and more chance to expose to estrogen. Prolonged estrogen stimulation factors, including stimulation by nulliparity, late menopause, and obesity, have been identified as risk factors for the development of endometrial cancer (La Vecchia et al., 1986; Elwood et al., 1977). People with these high risk factors should greatly care for their behavior and lifestyle. In recent years, the genetic background was shown to be involved in the etiology of endometrial cancers (Auersperg et al., 1998). Estrogens are metabolized by CYP1A1 and converted into catecholestrogens 2-hydroxyestradiol and 4-hydroxyestradiol (Martucci et al., 1993). It is obviously that genes encoding for enzymes involved in estrogen metabolism such as CYP1A1 have been hypothesized to be involved in the etiology of these pathologies (Herrington et al., 2001). The potential effect of CYP1A1 polymorphism on endometrial cancer risk is under the hypothesis that increased exposure to 2-OH estrogen might decrease, and increased exposure to 4-OH estrogen might increase, endometrial cancer risk (Doherty et al., 2005). So far, three common polymorphisms in CYP1A1 have been identified in white populations. The Ile462Val polymorphism, a 2455A>G transition in exon 7 located near the active site of the enzyme (rs1048943) is one of them (Hayashi et al., 1991). Unfortunately, the conclusions on the association between CYP1A1 Ile462Val polymorphism and endometrial cancer risk from different studies are inconsistent. Some studies reported that no significant association was found between CYP1A1 Ile462Val polymorphism and endometrial cancer risk (Sugawara et al., 2001; McGrath et al., 2007; Ashton et al., 2010). However, other studies concluded that there was a significant association between CYP1A1 Ile462Val polymorphism and endometrial cancer risk (Esteller et al., 1997; Sugawara et al., 2003; Doherty et al., 2005; Seremak-Mrozikiewicz et al., 2005; Esinler et al., 2006; Rebbeck et al., 2006; Hirata et al., 2008; Ashton et al., 2010).

The following meta-analysis was performed for the purpose of precisely estimating the association between CYP1A1 Ile462Val polymorphism and endometrial cancer risk. All studies published about CYP1A1 Ile462Val polymorphism and endometrial cancer risk were searched and summarized. In order to ensure the analysis quality, meta-regression analysis, sensitivity analysis and publication bias analysis were took into account in the study.

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Materials and Methods

Eligible studies searching

PubMed and Embase were searched (up until 2 July 2012, following the search strategy: CYP1A1 AND (polymorphism OR mutation OR variation) AND ("endometrial cancer" or "endometrial carcinoma"). All the eligible studies were retrieved, and their bibliographies were checked for other relevant publications.

Inclusion criteria

Eligible study must meet all the following inclusion criteria: (a) case–control study evaluating the CYP1A1 Ile462Val polymorphism and endometrial cancer risk; (b) listing the frequency of case and control according to different genotype; (c) full text articles; (d) literature published in English. (e) genotype distribution in the control of the study was in agreement with Hardy-Weinberg equilibrium (HWE).

Data extraction

Information used for meta-analysis was evaluated and extracted carefully from all the eligible studies 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. Different descents were categorized as Caucasian, Asian and other.

Statistical methods

The strength of association between CYP1A1 Ile462Val polymorphism and endometrial cancer risk was measured by OR with 95% CI. The pooled OR was estimated for codominant model: Val.Val vs Ile.Ile, dominant model: (Ile.Val + Val.Val) vs Ile/Ile, and recessive model: Val. Val vs (Ile.Ile + Ile.Val) respectively. Heterogeneity assumption was checked by the chi-square-based Q-test (Cochranl, 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 (Esteller et al., 1997). 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) (Cochran, 1954; Higgins et al., 2002; Zintzaras et al., 2005)

Meta-regression analyses were performed to explore the source of heterogeneity. Sensitivity analyses were carried out by excluding one study at a time to examine the influence of individual studies on the summary effect estimate. An estimate of potential publication bias was carried out by the 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. The significance of the intercept was determined by the t-test suggested by Egger ($P<0.05$ suggested existence of statistically significant publication bias) (Egger et al., 1997).

All of the statistical tests used in our meta-analysis were performed by STATA version 10.0 (Stata Corporation, College Station, TX).

Owing to meta-analysis focusing on analysis for published studies, the study was exempt from IRB approval.

Results

Study characteristics

The initial search with the key words and subject terms identified a total of 13 studies. Of these, a total of 9 studies met the inclusion criteria (Esteller et al., 1997; Esteller et al., 1997; Sugawara et al., 2003; Doherty et al., 2005; Seremak-Mrozikiewicz et al., 2005; Esinler et al., 2006; McGrath et al., 2007; Hirata et al., 2008; Ashton et al., 2010). Among them, however, one study (Esteller et al., 1997) was excluded because the same data was repeated in other study (Esteller et al., 1997). Another study (Esinler et al., 2006) was ruled out because of violation of HWE. As a result, 7 studies including 1286 cases and 2111 controls were included in the final meta-analysis. Table 1 lists the studies identified and their main characteristics. There were 6 studies for Caucasians, 1 study for Asians. Genotype distributions in the controls of all studies were in agreement with HWE. Table 2 shows the distribution of

Table 1. Characteristics of the Studies of CYP1A1 Ile462Val Polymorphism and Endometrial Cancer Risk

First author, year	country	ethnicity	cancer type	source of control	diagnose method	genotpying method	case (n,age)	control (n,age)
Doherty JA, 2005	USA	Caucasian	invasive	PB	pathology	PCR-RFLP	371,50-69	420,50-69
Sugawara T, 2003	Japan	Asian	NR	HB	NR	PCR-RFLP	38,NR	31,NR
McGrath M, 2007	USA	Caucasian	invasive	PB	pathology	PCR-RFLP	392,NR	975,NR
Ashton KA, 2010	Australia	Caucasian	NR	HB	pathology	PCR-RFLP	191,NR	271,NR
Hirata H, 2008	USA	Caucasian	Adenocarcinoma 113, unknown 13	PB	pathology	PCR-RFLP	150,60.0±9.8	165,60.0±9.6
Seremak-Mrozikiewicz A, 2005	Poland	Caucasian	adenocarcinomas	PB	pathology	PCR-RFLP	64,44-80	189,35-71
Esteller M, 1997	Spain	Caucasian	endometrioid-type 61, other 19	HB	pathology	PCR-RFLP	80,45-82	60,44-76

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

Table 2. The Distribution of the CYP1A1 Ile462Val Genotypes and the Allele Frequency for Endometrial Cancer Patients and Controls (Values in Parenteses are the Corresponding Percentages)

First author, year	Distribution of CYP1A1 genotypes Case/ Control			HWE	Frequency of CPY1A1 alleles Case		Control	
	Ile.Ile	Ile.Val	Val.Val	for control	Ile	Val	Ile	Val
Doherty JA, 2005	354/386	17/33	0/1	0.52	725(47.4)	17(32.7)	805(52.6)	35(67.3)
Sugawara T, 2003	21/21	16/10	1/0	0.57	58(52.7)	18(64.2)	52(47.3)	10(35.8)
McGrath M, 2007	364/891	27/81	1/3	0.43	755(28.8)	29(25.0)	1863(71.2)	87(75.0)
Ashton KA, 2010	177/257	14/12	2/0	1	368(41.0)	16(53.3)	528(59.0)	14(46.7)
Hirata H, 2008	122/134	27/30	1/1	1	271(47.6)	28(46.7)	298(52.4)	32(53.3)
Seremak-Mrozikiewicz A, 2005	62/181	2/8	0/0	1	126(25.4)	2(20.0)	370(74.6)	8(80.0)
Esteller M, 1997	58/54	20/5	2/1	0.17	136(54.6)	24(77.4)	113(45.4)	7(22.6)

HWE, Hardy–Weinberg equilibrium (HWE was caculated by fisher's exact probabilities)

Table 3. Results of Meta-analysis for Various Genetic Contrasts of CYP1A1 Ile462Val Polymorphism

Genetic contrasts	Studys (n)	Alleles/ Genotypes (n)	Fixed effects or random effects OR(95%CI)	Fixed effectsor random effects P value	I^2(%)	Q test P value
Val vs Ile (△)	7	6793	1.09(0.73-1.62)	0.686	56.1	0.034
Val.Val/Ile.Ile (*)	6	2852	1.54(0.56-4.23)	0.41	0	0.8
(Ile.Val+Val.Val)/Ile.Ile (△)	7	3397	1.08(0.71-1.63)	0.72	53.7	0.04
Val.Val/(Ile.Ile+Ile.al) (*)	6	3144	1.46(0.53-4.04)	0.47	0	0.83

△, Fixed effects; *, random effects

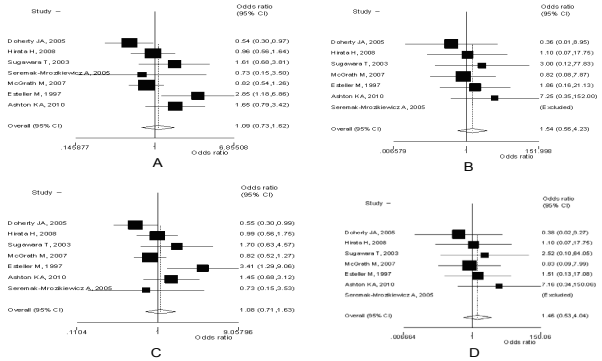

Figure 1. Individual and Pooled Odds Ratio Estimates and Their 95% Confidence Intervals for CYP1A1 Ile462Val Polymorphism: (A) Val vs Ile allele model; (B) Val.Val vs Ile.Ile polymorphism model; (C) (Ile.Val + Val.Val) vs Ile.Ile polymorphism model; (D) Val.Val vs (Ile.Ile + Ile.Val) polymorphism model. The summary pooled OR and its 95% CI are indicated by the white diamond

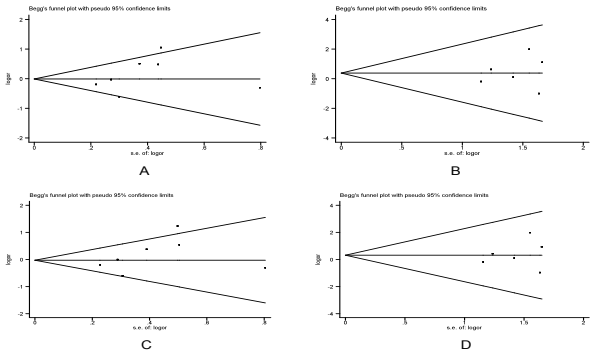

Figure 2. Begg's Funnel Plot (with Pseudo 95% CI) of the Log Odds Ratio Versus the Standard Errors of Log Odds Ratio for CYP1A1 Ile462Val Polymorphism: (A) Val vs Ile allele model; (B) Val.Val vs Ile.Ile polymorphism model; (C) (Ile.Val + Val.Val) vs Ile.Ile polymorphism model; (D) Val.Val vs (Ile.Ile + Ile.Val) polymorphism model

the CYP1A1 Ile462Val genotypes and the allele frequency for endometrial cancer patients and controls.

Quantitative synthesis

Table 3 and Figure 1 displayed the main results of the meta-analysis for CYP1A1 Ile462Val polymorphism. When all the 7 studies were pooled into the meta-analysis, there was no evidence for significant association between CYP1A1 Ile462Val polymorphism and endometrial cancer risk (for Val vs Ile allele model [OR 1.09, 95% CI 0.73-1.62]; for Val.Val vs Ile.Ile genotype model [OR 1.54, 95% CI 0.56-4.23]; for (Ile.Val + Val.Val) vs Ile.Ile genotpye model [OR 1.08, 95% CI 0.71-1.63]; for Val.Val vs (Ile.Ile + Ile.Val) genotype model [OR 1.46, 95% CI 0.53-4.04]). Owing to heterogeneity between studies was found in Val vs Ile allele model and (Ile.Val + Val.Val) vs Ile.Ile genotype model, a meta-regression analysis was used to analyze association between log risk ratio and study characteristics (ethnicity and source of control). As a result, source of control was identified as an important source of heterogeneity existed in Val vs Ile allele model and (Ile.Val + Val.Val) vs Ile.Ile genotype model. Between-study variance Tau-squared decreased from 0.149 to 0 (z = -2.88, P=0.00) in Val vs Ile allele model, and from 0.151 to 0 (z=-2.78, P = 0.01) in (Ile.Val + Val.Val) vs Ile.Ile genotype model.

Sensitivity analyses

The influence of individual studies on the summary effect estimate may be displayed using sensitivity analyses in which the meta-analysis estimates are computed omitting one study at a time. All the results were not obviously altered and did not draw different conclusions. The sensitivity analysis figures for different polymorphism models were not shown.

Publication bias

Begg's test and Egger's test were performed to assess the publication bias of studies. The shapes of the funnel

plots and Egger's test results did not reveal any obvious asymmetry in any Ile462Val polymorphism models. Figure 2 demonstrated the funnel plots for OR of all models. Furthermore, the corresponding Egger's test results also did not suggest any publication bias (data not show) .

Discussion

Endometrial cancer is the seventh most frequent malignancy among women worldwide (Barrena et al., 2009). Despite the fact that endometrial cancer is one of the gynaecological cancers that carries good overall prognosis because it is often detected at early stages of disease, the incidence and mortality rates of endometrial cancer have been increasing (Fader et al., 2009). So far, some studies have reported the association between CYP1A1 Ile462Val polymorphism and endometrial cancer risk. Unfortunately, these results remain controversial. For the purpose of obtaining a more accurate measurement of the association, we performed this meta-analysis. Based on the meta-analysis results, we can learn that there is no association between CYP1A1 Ile462Val polymorphism and endometrial cancer risk.

It is a generally acknowledged fact that estrogen is a risk factor for the development of endometrial cancer. So it is easily to be understood that the change of estrogen metabolism may be connected with the endometrial cancer risk. It is well recognized that estrogens are metabolized by CYP1A1 and converted into catecholestrogens 2-hydroxyestradiol and 4-hydroxyestradiol. Some studies have reported that the Ile462Val polymorphisms are associated with CYP1A1 activity and inducibility (Petersen et al., 1991; Cosma et al., 1993; Kawajiri et al., 1993; Drakoulis et al., 1994; Taioli et al., 1995; Kiyohara et al., 1996; Zhang et al., 1996; Schwarz et al., 2000). The frequency of Ile462Val mutation tended to higher in CYP1A1 high expression population. Moreover, many studies claimed that CYP1A1 Ile462Val polymorphisms are associated with endometrial cancer risk. But the conclusions are contrary to each other. Some study revealed that CYP1A1 Ile462Val polymorphism can decrease the risk for the endometrial cancer development (Hirata et al., 1964; Doherty et al., 2005; Seremak-Mrozikiewicz et al., 2005). However, other studies reported that CYP1A1 Ile462Val mutation can increase the risk for the endometrial cancer development (Esteller et al., 1997; Esteller et al., 1997; Esinler et al., 2006;).

Several factors may contribute 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 results. In meta-analysis, however, the false-positive and false-negative results may neutralize each others as large number of studies are pooled, and the increase of overall statistical power ensure a more accurate estimate of association. This meta-analysis estimated the relationship between Ile462Val polymorphisms and endometrial cancer risk. The summarized result indicated that no associations between CYP1A1 Ile462Val polymorphism and endometrial cancer risk were found. Regardless of dominant model, recessive model or co-dominant models, the result is invariably negative. The meta-analysis results are consistent with some studies (Sugawara et al., 2003; McGrath et al., 2007; Ashton et al., 2010).

Heterogeneity is a potential problem that may affect the interpretation of the results. Significant between-study heterogeneity existed in Val vs Ile allele model and (Ile.Val + Val.Val) vs Ile.Ile polymorphism model. When we performed meta-regression analysis in which source of controls and ethnicity were adopted as independent variables, the heterogeneity among studies was effectively removed. It suggested that source of controls is the main factor contributing to potential heterogeneity. The reason may be that the hospital-based case–control studies have inherent selection biases due to the fact that such controls did not represent the general population very well. Such selection biases may distort the results and lead to significant heterogeneity between hospital-based studies. Therefore, using proper and representative population-based controls is very important to reduce biases in genetic association studies.

Some limitations of this meta-analysis must be acknowledged. First, the number of studies and population contained in this meta-analysis was relatively small. To a certain extent, it influences the statistical power. Second, heterogeneity among studies was found in Val vs Ile allele model and (Ile.Val + Val.Val) vs Ile.Ile genotype model. For the sake of reasonable interpretation for results, the exploration of heterogeneity must be done.

In spite of limitations, some advantages may be found in this meta-analysis. First, it performed meta-analysis in different polymorphism models respectively. So that we can examine the relationship between CYP1A1 Ile462Val polymorphisms and endometrial cancer risk in comprehensive way. Second, meta-regression analysis was used to explore the source of heterogeneity. It enables us to better reasonably explain the results. Third, Begg's and Egger's tests did not detect any publication bias, indicating that our results should be unbiased. Fourth, when sensitivity analysis was performed to check the influence of individual studies on the summary effect estimate by omitting one study at a time in all Ile462Val polymorphism models, any single study didn't have 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 Ieu432Val 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 7 studies and 3397 subjects strongly suggests that CYP1A1 Ile462Val polymorphism is not associated with endometrial cancer risk.

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