CYP1A1 Ile462Val polymorphism contributes to colorectal cancer risk: A meta-analysis

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Abstract

AIM: To study the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk by meta-analysis.

METHODS: A meta-analysis was performed to investigate the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk by reviewing the related studies until September 2010. Data were extracted and analyzed. Crude odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk.

RESULTS: Thirteen published case-control studies including 5336 cases and 6226 controls were acquired. The pooled OR with 95% CI indicated that CYP1A1 Ile462Val polymorphism was significantly related with colorectal cancer risk (Val/Val vs Ile/Ile: OR = 1.47, 95% CI: 1.16-1.86, P = 0.002; dominant model: OR = 1.33, 95% CI: 1.01-1.75, P = 0.04; recessive model: OR = 1.49, 95% CI: 1.18-1.88, P = 0.0009). Subgroup ethnicity analysis showed that CYP1A1 Ile462Val polymorphism was also significantly related with colorectal cancer risk in Europeans (Ile/Val vs Ile/Ile: OR = 1.22, 95% CI: 1.05-1.42, P = 0.008; dominant model: OR = 1.24, 95% CI: 1.07-1.43, P = 0.004) and Asians (Val/Val vs Ile/Ile: OR = 1.40, 95% CI: 1.07-1.82, P = 0.01; recessive model: OR = 1.46, 95% CI: 1.12-1.89, P = 0.005).

CONCLUSION: CYP1A1 Ile462Val may be an increased risk factor for colorectal cancer.

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Key words: CYP1A1; Polymorphism; Colorectal cancer; Meta-analysis

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INTRODUCTION

Colorectal cancer, one of the most prevalent cancers worldwide, ranks fourth in frequency in men and third in women. In recent years, the incidence of colorectal cancer has increased in most countries but its prognosis is still poor. A number of researches have shown that colorectal cancer is possibly related with tobacco and alcohol con-
suggestion as well as other environmental sources. It has been shown that inter-individual differences including single nucleotide polymorphism (SNP) may influence human susceptibility to colorectal cancer.

Metabolic enzymes including phase I and phase II enzymes are involved in activation and detoxification of xenobiotics, which play an important role in the pathogenesis of colorectal cancer. Cytochrome P450, including family 1, subfamily A, polypeptide 1 (CYP1A1), is one of the phase I enzymes, metabolizing a large number of endogenous and exogenous substances, such as polycyclic aromatic hydrocarbons, heterocyclic amines, aromatic amines, and N-nitrosamines. Thus, CYP1A1 plays an important role in human susceptibility to colorectal cancer due to various exogenous factors.

Non-synonymous SNP (rs1048943) leads to amino acid change in exon 7 of CYP1A1 from Ile to Val (nucleotides A-G) at codon 462, which may alter the protein activity and the human susceptibility to colorectal cancer. Since the first study on the relation between colorectal cancer and CYP1A1 Ile462Val polymorphism conducted by Sivaraman et al. in 1994, a large number of epidemiological studies on the relation between colorectal cancer and CYP1A1 Ile462Val polymorphism have been conducted, but their conclusions are different or even contradictory. In this study, a meta-analysis of the published case-control studies was performed to assess the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk.

MATERIALS AND METHODS

Search strategy

Studies on the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk were searched from PubMed from 1994 to September 2010 using the key words “CYP1A1”, “colorectal cancer”, “colon cancer”, “rectum cancer”, and “polymorphism”. Related studies were also searched from the references of original papers or reviews. All studies were selected according to the following criteria: only case-control studies on the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk, sufficient published data for estimating odds ratio (OR) with 95% confidence interval (CI), and selection of the largest or most recent studies when several publications reporting the same or overlapping data. Only the data published in 2007 were selected from two studies by Kiss et al. who reported overlapping data in Hungarians. Finally, 13 case-control studies including 5336 patients with colorectal cancer and 6226 controls were enrolled in our meta-analysis.

Data extraction

Two investigators independently extracted the following data from the included publications, including name of the first author, publication data, country origin, source of control, racial descent of the study population, genotyping method, number of different genotypes, and Hardy-Weinberg equilibrium (HWE) in controls.

Statistical analysis

Crude OR with 95% CI was computed to assess the strength of relation between CYP1A1 Ile462Val polymorphisms and colorectal cancer risk. Codominant model (Val/Val vs Ile/Ile, Ile/Val vs Ile/Ile), dominant model [(Val/Val + Ile/Val) vs Ile/Ile] and recessive model [Val/Val vs (Ile/Val + Ile/Ile)] were evaluated. Subgroup statistical analysis of the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk in Asians and Europeans was performed. Heterogeneity assumption was checked by chi-square based Q-test. Pooled OR estimation of each study was calculated with the random-effect model (DerSimonian and Laird method) when P < 0.10. Otherwise, the fixed-effect model (Mantel-Haenszel method) was selected. The publication bias was evaluated with funnel plot and linear regression asymmetry test as previously described. Statistical analysis was performed using the STATA version 9.2 (Stata Corporation, College Station, TX) and Review Manager (version 4.2, Oxford, England), using two-sided P-values.

RESULTS

Study characteristics

Thirteen published case-control studies including 5336 patients with colorectal cancer and 6226 controls met the inclusion criteria for the meta-analysis. The distribution of studies in different populations is listed in Table 1. The minor allele frequency of Val in controls ranged from 0.30% in Europeans to 0.25% in Asians. Genotyping methods included polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), allele-specific PCR, TaqMan, MassARRAY system, microarray system, and APEX. The distribution of genotypes in controls of all studies was in agreement with HWE except for two studies.

Meta-analysis

The results of meta-analysis and heterogeneity test are shown in Table 2. The colorectal cancer risk was significantly higher in individuals carrying the Val/Val genotype than in those carrying the Ile/Ile genotype (OR = 1.47, 95% CI: 1.16-1.86, P = 0.002, P_heterogeneity = 0.44, Figure 1A). The dominant and recessive models also showed that colorectal cancer risk was significantly related with the CYP1A1 Ile462Val polymorphism [(Val/Val + Ile/Val) vs Ile/Ile: OR = 1.33, 95% CI: 1.01-1.75, P = 0.04, P_heterogeneity < 0.01, Figure 1B; Val/Val vs Ile/Ile: OR = 1.49, 95% CI: 1.18-1.88, P = 0.009, P_heterogeneity = 0.77, Figure 1C] in the total population. Subgroup race analysis showed that the CYP1A1 Ile462Val polymorphism was significantly related with colorectal cancer risk in Europeans [Ile/Ile vs Ile/Ile: OR = 1.22, 95% CI: 1.05-1.42, P = 0.008, P_heterogeneity = 0.25; (Val/Val + Ile/Val) vs Ile/Ile: OR = 1.24, 95% CI: 1.07-1.43, P = 0.004, P_heterogeneity = 0.24] and in Asians [Val/Val vs Ile/Ile: OR = 1.40, 95% CI: 1.07-1.82, P = 0.01, P_heterogeneity = 0.23; Val/Val vs Ile(Ile/Val + Ile/Ile): OR = 1.46, 95% CI: 1.12-1.89, P = 0.005, P_heterogeneity = 0.24].
**DISCUSSION**

CYP1A1, a phase I enzyme encoded by the CYP1A1 gene, has been mapped to chromosome 15q24.1. The CYP group of enzymes is involved in metabolic activation and detoxification of tobacco-derived carcinogen and other xenobiotics. It has been shown that alcohol intake and cigarette smoking are two important risk factors for colorectal cancer, and this study also found that cigarette smoking is a risk factor for colorectal cancer. To date, no consensus conclusion is available whether CYP1A1 polymorphism is associated with the risk of colorectal cancer. However, the results of our study suggest that CYP1A1 Ile462Val polymorphism can increase the risk of colorectal cancer.

**Table 1** Characteristics of case-control studies included in meta-analysis

| Author          | Country / region | Racial descent  | Source of controls | Case (n) | Control (n) | Genotype distribution | Genotyping type | HWE   |
|-----------------|------------------|-----------------|--------------------|----------|-------------|-----------------------|----------------|-------|
| Sivaraman et al. [40], 1994 | USA              | Mixed           | Population control | 43       | 47          | Ile/Ile, Ile/Val      | Allele-specific PCR | 0.230 |
| Ishibe et al. [41], 2000     | USA              | European        | Population control | 212      | 221         | Ile/Ile, Val/Val      | PCR-RFLP        | 0.057 |
| Sachse et al. [42], 2002     | UK               | European        | Population control | 490      | 592         | Ile/Ile, Val/Val      | TaqMan          | < 0.01|
| Slattery et al. [43], 2004   | USA              | European        | Population control | 997      | 1170        | Ile/Ile, Val/Val      | Allele-specific PCR | < 0.01|
| Slattery et al. [44], 2004   | USA              | European        | Population control | 794      | 1010        | Ile/Ile, Val/Val      | Allele-specific PCR | 0.052 |
| Landi et al. [45], 2005      | Italy             | European        | Hospital control   | 362      | 323         | Ile/Ile, Val/Val      | PCR-RFLP        | 0.534 |
| Little et al. [46], 2006     | UK               | European        | Hospital control   | 251      | 396         | Ile/Ile, Val/Val      | PCR-RFLP        | 0.315 |
| Kiss et al. [47], 2007       | Hungary           | European        | Hospital control   | 500      | 500         | Ile/Ile, Val/Val      | Allele-specific PCR | 0.280 |
| Yeh et al. [48], 2007        | China             | Asian           | Hospital control   | 717      | 729         | Ile/Ile, Val/Val      | PCR-RFLP        | 0.800 |
| Yoshida et al. [49], 2007    | Japan             | Asian           | Not report          | 66       | 121         | Ile/Ile, Val/Val      | PCR-RFLP        | 0.071 |
| Pereira Serafin et al. [50], 2008 | Brazil       | Mixed           | Population control | 114      | 114         | Ile/Ile, Val/Val      | PCR-RFLP        | 0.674 |
| Kobayashi et al. [51], 2009  | Japan             | Asian           | Hospital control   | 105      | 225         | Ile/Ile, Val/Val      | MassARRAY system | 0.970 |
| Nisa et al. [52], 2010       | Japan             | Asian           | Population control | 685      | 778         | Ile/Ile, Val/Val      | PCR-RFLP        | 0.750 |

HWE: Hardy-Weinberg equilibrium in control; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; APEX: Arrayed primer extension.

**Table 2** Odds ratio and 95% confidence interval of CYP1A1 Ile462Val polymorphism and colorectal cancer risk

| Contrast               | Racial descent | OR     | 95% CI       | P    |
|------------------------|----------------|--------|--------------|------|
| Val/Val vs Ile/Ile     | Total          | 1.47   | 1.16-1.86    | 0.44 |
| Val/Val vs Ile/Ile     | European       | 1.43   | 0.83-2.48    | 0.93 |
| Val/Val vs Ile/Ile     | Asian          | 1.40   | 1.07-1.82    | 0.23 |
| Val/Val vs Ile/Ile     | Total          | 1.28   | 0.96-1.72    | < 0.01 |
| Val/Val vs Ile/Ile     | European       | 1.22   | 1.05-1.42    | 0.25 |
| Val/Val vs Ile/Ile     | Asian          | 0.91   | 0.79-1.05    | 0.19 |
| Val/Val vs Ile/Ile     | Total          | 1.33   | 1.01-1.75    | < 0.01 |
| Val/Val vs Ile/Ile     | European       | 1.24   | 1.07-1.43    | 0.24 |
| Val/Val vs Ile/Ile     | Asian          | 0.98   | 0.96-1.13    | 0.17 |
| Val/Val vs Ile/Ile     | Total          | 1.49   | 1.18-1.88    | 0.07 |
| Val/Val vs Ile/Ile     | European       | 1.39   | 0.80-2.41    | 0.94 |
| Val/Val vs Ile/Ile     | Asian          | 1.46   | 1.12-1.89    | 0.24 |

*Estimates for random effects. OR: Test for heterogeneity; CYP1A1: Cytochrome P450, including family 1, subfamily A, polypeptide 1; OR: Odds ratio; CI: Confidence interval.

**Publication bias**

Funnel plot and Egger’s test were used to estimate the publication bias of studies. The funnel plots seemed symmetrical in all models (Val/Val vs Ile/Ile: P = 0.17, (Val/ Val + Ile/Val) vs Ile/Ile: P = 0.17, Val/Val vs (Ile/Val + Ile/Ile): P = 0.39, Figure 2). No publication bias concerning the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk was detected.
**A**

**Review:** CYP1A1 Ile462Val polymorphisms and colorectal cancer  
**Comparison:** Val/Val vs Ile/Ile  
**Outcome:** Total

| Study or sub-category | Case n/N | Control n/N | Odds ratio (fixed) | Weight (%) | Odds ratio (fixed) |
|-----------------------|----------|-------------|--------------------|------------|--------------------|
| Sivaraman *et al* [10], 1994 | 2/34 | 0/33 | 0.42 | 5.15 (0.24-111.52) |
| Ishibe *et al* [18], 2000 | 5/181 | 4/190 | 3.36 | 1.32 (0.35-5.00) |
| Sachse *et al* [19], 2002 | 7/422 | 5/544 | 3.80 | 1.82 (0.57-5.77) |
| Slattery *et al* [20], 2004 | 5/915 | 7/1084 | 5.64 | 0.85 (0.27-2.67) |
| Slattery *et al* [20], 2004 | 6/728 | 5/925 | 3.86 | 1.53 (0.46-5.03) |
| Lands *et al* [19], 2005 | 1/334 | 0/298 | 0.47 | 2.69 (0.11-66.17) |
| Little *et al* [22], 2006 | 0/235 | 0/372 | Not estimable |
| Kiss *et al* [13], 2007 | 4/390 | 2/417 | 1.69 | 2.15 (0.39-11.81) |
| Yeh *et al* [23], 2007 | 89/489 | 53/463 | 39.40 | 1.72 (1.19-2.48) |
| Yoshida *et al* [21], 2005 | 3/17 | 0/81 | 0.13 | 39.34 (1.19-2.48) |
| Little *et al* [22], 2006 | 0/235 | 0/372 | Not estimable |
| Sivaraman *et al* [10], 1994 | 11/43 | 14/47 | 4.68 | 0.81 (0.32-2.05) |
| Ishibe *et al* [18], 2000 | 36/212 | 35/221 | 7.45 | 1.09 (0.65-1.81) |
| Sachse *et al* [19], 2002 | 75/490 | 53/592 | 8.43 | 1.84 (1.26-2.67) |
| Slattery *et al* [20], 2004 | 87/997 | 93/1170 | 8.90 | 1.11 (0.82-1.50) |
| Slattery *et al* [20], 2004 | 72/794 | 90/1010 | 8.77 | 1.02 (0.74-1.41) |
| Lands *et al* [19], 2005 | 29/362 | 25/323 | 7.09 | 1.04 (0.59-1.81) |
| Little *et al* [22], 2006 | 16/251 | 24/396 | 6.39 | 1.06 (0.55-2.03) |
| Kiss *et al* [13], 2007 | 114/500 | 85/500 | 8.85 | 1.44 (1.05-1.97) |
| Yeh *et al* [23], 2007 | 317/717 | 319/729 | 9.46 | 1.02 (0.83-1.25) |
| Yoshida *et al* [21], 2005 | 32/66 | 42/121 | 6.70 | 1.77 (0.96-3.26) |
| Pereira Serafim *et al* [25], 2008 | 100/114 | 33/114 | 6.13 | 17.53 (8.79-34.97) |
| Kobayashi *et al* [24], 2007 | 40/105 | 100/225 | 7.71 | 0.77 (0.48-1.24) |
| Nisa *et al* [27], 2010 | 267/685 | 317/778 | 9.44 | 0.93 (0.75-1.15) |
| Total (95% CI) | 4311 | 5131 | 100.00 | 1.47 (1.16-1.86) |
| Total events | 171 | 135 |

Test for heterogeneity: $\chi^2 = 11.04, df = 11$ ($P = 0.44$), $I^2 = 0.3$

Test for overall effect: $Z = 3.17$ ($P = 0.002$)

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**B**

**Review:** CYP1A1 Ile462Val polymorphisms and colorectal cancer  
**Comparison:** Val/Val + Ile/Val vs Ile/Ile  
**Outcome:** Total

| Study or sub-category | Case n/N | Control n/N | Odds ratio (random) | Weight (%) | Odds ratio (random) |
|-----------------------|----------|-------------|--------------------|------------|--------------------|
| Sivaraman *et al* [10], 1994 | 11/43 | 14/47 | 4.68 | 0.81 (0.32-2.05) |
| Ishibe *et al* [18], 2000 | 36/212 | 35/221 | 7.45 | 1.09 (0.65-1.81) |
| Sachse *et al* [19], 2002 | 75/490 | 53/592 | 8.43 | 1.84 (1.26-2.67) |
| Slattery *et al* [20], 2004 | 87/997 | 93/1170 | 8.90 | 1.11 (0.82-1.50) |
| Slattery *et al* [20], 2004 | 72/794 | 90/1010 | 8.77 | 1.02 (0.74-1.41) |
| Lands *et al* [19], 2005 | 29/362 | 25/323 | 7.09 | 1.04 (0.59-1.81) |
| Little *et al* [22], 2006 | 16/251 | 24/396 | 6.39 | 1.06 (0.55-2.03) |
| Kiss *et al* [13], 2007 | 114/500 | 85/500 | 8.85 | 1.44 (1.05-1.97) |
| Yeh *et al* [23], 2007 | 317/717 | 319/729 | 9.46 | 1.02 (0.83-1.25) |
| Yoshida *et al* [21], 2005 | 32/66 | 42/121 | 6.70 | 1.77 (0.96-3.26) |
| Pereira Serafim *et al* [25], 2008 | 100/114 | 33/114 | 6.13 | 17.53 (8.79-34.97) |
| Kobayashi *et al* [24], 2007 | 40/105 | 100/225 | 7.71 | 0.77 (0.48-1.24) |
| Nisa *et al* [27], 2010 | 267/685 | 317/778 | 9.44 | 0.93 (0.75-1.15) |
| Total (95% CI) | 5336 | 6226 | 100.00 | 1.33 (1.01-1.75) |
| Total events | 1196 | 1230 |

Test for heterogeneity: $\chi^2 = 79.39, df = 12$ ($P < 0.00001$), $I^2 = 84.9$

Test for overall effect: $Z = 2.03$ ($P = 0.04$)
CYP1A1 Ile462Val polymorphisms and colorectal cancer

Comparison: Val/Val vs (Ile/Val + Ile/Ile)

Outcome: Total

| Study or sub-category | Case n/N | Control n/N | Odds ratio (fixed) 95% CI | Weight (%) | Odds ratio (fixed) 95% CI |
|-----------------------|----------|-------------|--------------------------|------------|--------------------------|
| Sivarman et al[25], 1994 | 2/34 | 0/47 | 0.39 (0.27-122.64) | 5.72 | 0.39 | 0.27-122.64 |
| Ishibe et al[18], 2000 | 5/212 | 4/221 | 3.30 (1.35-8.41) | 3.10 | 3.30 | 1.35-8.41 |
| Sachse et al[23], 2002 | 7/490 | 5/592 | 3.85 (1.70-8.54) | 1.70 | 3.85 | 1.70-8.54 |
| Slattery et al[20,21], 2004 | 5/997 | 7/1170 | 5.53 (0.84-3.26) | 0.84 | 5.53 | 0.84-3.26 |
| Slattery et al[20,21], 2004 | 6/794 | 5/1010 | 3.77 (1.53-9.75) | 1.53 | 3.77 | 1.53-9.75 |
| Landi et al[23], 2005 | 1/362 | 0/323 | 0.84 (0.26-2.65) | 0.26 | 0.84 | 0.26-2.65 |
| Little et al[22], 2006 | 0/251 | 0/396 | 2.01 (0.37-11.01) | 0.37 | 2.01 | 0.37-11.01 |
| Kiss et al[24], 2007 | 4/500 | 2/500 | 1.71 (0.37-7.10) | 0.37 | 1.71 | 0.37-7.10 |
| Yeh et al[10], 2007 | 89/717 | 53/729 | 39.75 (1.26-122.65) | 1.26 | 39.75 | 1.26-122.65 |
| Yoshida et al[19], 2007 | 5/66 | 5/121 | 2.82 (0.53-14.82) | 0.53 | 2.82 | 0.53-14.82 |
| Pereira Serafim et al[19], 2008 | 3/114 | 0/114 | 0.42 (0.37-14.82) | 0.37 | 0.42 | 0.37-14.82 |
| Kobayashi et al[25], 2009 | 8/105 | 13/225 | 6.60 (1.34-3.35) | 1.34 | 6.60 | 1.34-3.35 |
| Nisa et al[19], 2010 | 36/685 | 41/778 | 31.41 (1.00-0.63) | 0.63 | 31.41 | 1.00-0.63 |
| Total (95% CI) | 5336 | 6226 | 100.00 | 1.49 | 1.49 (1.18-1.88) |
| Total events | 171 | 135 |

Test for heterogeneity: $\chi^2 = 7.35, df = 11 (P = 0.77), I^2 = 0\%$
Test for overall effect: $Z = 3.32 (P = 0.0009)$

Figure 1  Odds ratio of colorectal cancer associated with CYP1A1 Ile462Val for Val/Val vs Ile/Ile genotypes (A), Val/Val + Ile/Val vs Ile/Ile genotypes (B), and Val/Val vs Ile/Ile + Ile/Ile genotypes (C).

Figure 2  Funnel plot analysis showing publication bias for Val/Val vs Ile/Ile genotypes. Each point represents a separate study for the indicated association.

Available on the relation of CYP1A1 Ile462Val polymorphism and colorectal cancer, Pereira Serafim et al[19] demonstrated that the risk of colorectal cancer is 5-fold higher in Brazilians with the Val genotype (OR = 5.14, 95% CI: 1.36-14.82). Sachse et al[23] reported that the risk of colorectal cancer is about 2-fold higher in Europeans with the homozygous Val allele (OR = 2.15, 95% CI: 1.36-3.41). Kiss et al[24] and Yoshida et al[19] also reported that the risk of colorectal cancer is similar to those reported by Pereira Serafim et al[19] and Sachse et al[23] in Hungarians and Asians with the Val genotype. However, other studies from USA and Europe showed that colorectal cancer risk is not significantly related with CYP1A1 Ile462Val polymorphism[10,18,20-22,24,26,27], but positively related with Val allele and smoking (OR = 2.5, 95% CI: 1.3-4.8) in Europeans[20].

The present meta-analysis of 13 eligible case-control studies including 5336 cases and 6226 controls showed that CYP1A1 Ile462Val polymorphism could contribute to colorectal cancer risk. The stratified analysis according to the ethnicity revealed that CYP1A1 Ile462Val polymorphism was positively related with colorectal cancer risk both in Asians and in Europeans. However, no report is available on the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk in Africans. On the other hand, gender factor may change the risk of colorectal cancer sometimes. It was reported that the colorectal cancer risk is 3.1-fold higher in Chinese women with CYP1A1 Val/Val and XRCC3 Thr/Thr genotypes than in those with CYP1A1 Ile and XRCC3 Met alleles[20], suggesting that CYP1A1 Ile462Val polymorphism may be an important risk factor for colorectal cancer.

Heterogeneity is another problem found in our meta-analysis. A significant heterogeneity was observed in Ile/Val vs Ile/Ile and (Val/Val + Ile/Val) vs Ile/Ile. However, subgroup ethnicity analysis showed that the heterogeneity was removed apparently, indicating that the genetic background and environment are different in different ethnicities.
Several limitations in our meta-analysis need to be addressed. First, the results were obtained based on the unadjusted estimates and lacked of original data about the eligible studies, thus limiting the evaluation of effects of gene-gene and gene-environment interactions on the pathogenesis of colorectal cancer. Second, other single nucleotide polymorphisms of CYP1A1 were identified, but no linkage disequilibrium and haplotype analysis of these polymorphisms was performed. Third, the real relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk might have been influenced since the sample size was relatively small in this analysis, thus a further analysis of the relation between CYP1A1 polymorphism and colorectal cancer should be performed.

In conclusion, CYP1A1 Ile462Val polymorphism may contribute to colorectal cancer risk. Further study is needed with a large-scale case-control sample to validate the identified risk in our current meta-analysis, and potential gene-gene and gene-environment interactions should be taken into account when the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk is further studied.

**COMMENTS**

**Background**

Colorectal cancer is one of the most prevalent malignancies worldwide. CYP1A1 is one of the phase I enzymes. Ile to Val transition has been supposed as a risk factor for colorectal cancer. A large number of studies on the association between CYP1A1 and colorectal cancer risk have been conducted, but their conclusions are different or even contradictory.

**Research frontiers**

Many studies indicate that CYP1A1 Ile462Val polymorphism plays an important role in pathogenesis of esophageal cancer in Asians and breast cancer in Caucasians. However, the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk remains controversial and no meta-analysis has been conducted.

**Innovations and breakthroughs**

This meta-analysis systemically assessed the relation between CYP1A1 Ile462Val polymorphism and colorectal cancer risk, showing that the Val allele may be a risk factor for colorectal cancer in both Europeans and Asians.

**Applications**

The results of meta-analysis in this study show that the CYP1A1 Ile462Val polymorphism contributes the human susceptibility to colorectal cancer in both Europeans and Asians, which may help us to make early prevention and treatment of colorectal cancer.

**Peer review**

This is an interesting meta-analysis of the association between CYP1A1 Ile462Val polymorphism and colorectal cancer risk. The authors carefully reviewed the literature and collected the original data. The methods they used in meta-analysis are proper.

**REFERENCES**

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108
2. Storme HH, Engholm G, Hakulininen T, Tryggvadóttir L, Klint A, Gislum M, Kejs AM, Bray F. Survival of patients diagnosed with cancer in the Nordic countries up to 1999-2003 followed to the end of 2006. A critical overview of the results. Acta Oncol 2010; 49: 532-544
3. Poynter JN, Haile RW, Siegmund KD, Campbell PT, Figueiredo JC, Limburg P, Young J, Le Marchand L, Porter JD, Cotterchio M, Casey G, Hopper JL, Jenkins MA, Thibodeau SN, Newcomb PA, Baron JA. Associations between smoking, alcohol consumption, and colorectal cancer, overall and by tumor microsatellite instability status. Cancer Epidemiol Biomarkers Prev 2009; 18: 2745-2750
4. Zisman AL, Nickoloff A, Brand RE, Grochow A, Roy HK. Associations between the age at diagnosis and location of colorectal cancer and the use of alcohol and tobacco: implications for screening. Arch Intern Med 2006; 166: 629-634
5. Tomlinson IP, Webb E, Carvajal-Carmona L, Broderick P, Howarth K, Pittman AM, Spain S, Lubbe S, Walther A, Sullivan K, Jaeger E, Fielding S, Rowan A, Vijayakrishnan J, Domingo E, Chandler I, Kemp Z, Qureshi M, Farnington SM, Tenesa A, Prendergast JG, Barnetson RA, Penegar S, Barclay E, Wood W, Martin L, Gorman M, Thomas H, Peto J, Bishop DT, Gray R, Maher ER, Lucassen A, Kerr D, Evans DG, Schafmayer C, Buch S, Völzke H, Hampe J, Schreiber S, John U, Koessler T, Pharaoh P, van Wezel T, Morreau H, Wijnken JT, Hopper JL, Southey MC, Giles GG, Severi G, Castellvi-Bel S, Ruiz-Ponte C, Carracedo A, Castells A, Forstl A, Hemminki K, Vodicka P, Naccarati A, Lipton L, Ho JW, Cheng KK, Sham PC, Luk J, Agúndez JA, Ladero JM, de la Hoya M, Calders T, Niittymäki I, Tuopanen S, Karhu A, Aaltonen L, Cazier JB, Campbell H, Dunlop MG, Houlston RS. A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3. Nat Genet 2008; 40: 623-630
6. Abuli A, Bessa X, González JR, Ruiz-Ponte C, Cáceres A, Muñoz J, Gonzalo V, Balaguer F, Fernández-Rozadilla C, González D, de Castro L, Clófet J, Bujanda L, Cubiella J, Rened JM, Morillas JD, Lanas A, Riga J, García AM, Latorre M, Saló J, Fernández Bañeres A, Argüello L, Peña E, Villela A, Riestra S, Carreño R, Paya A, Alenda C, Nicola RM, Doyle BJ, Jover R, Llor X, Carracedo A, Castells A, Castellvi-Bel S, Andreu M. Susceptibility genetic variants associated with colorectal cancer risk correlate with cancer phenotype. Gastroenterology 2010; 139: 788-796, 796.e1-e6
7. Nebert DW. Role of genetics and drug metabolism in human cancer risk. Mutat Res 1991; 267: 267-281
8. Murtaugh MA, Sweeney C, Ma KN, Caan BJ, Slattery ML. The CYP1A1 genotype may alter the association of meat consumption patterns and preparation with the risk of colorectal cancer in men and women. J Nutr 2005; 135: 179-186
9. Wang S, Chanock S, Tang D, Li Z, Jedrychowski W, Perera FP. Assessment of interactions between PAH exposure and genetic polymorphisms on PAH-DNA adducts in African American, Dominican, and Caucasian mothers and newborns. Cancer Epidemiol Biomarkers Prev 2005; 14: 405-413
10. Sivaraman L, Leatham MP, Yee J, Wilkens LR, Lau AF, Le Marchand L. CYP1A1 genetic polymorphisms and in situ colorectal cancer. Cancer Res 1994; 54: 3692-3695
11. Little J, Bradley L, Bray MS, Clyne M, Dorgman J, Ellsworth DL, Hansen J, Khoury M, Lau J, O’Brien TR, Rothman N, Stroup D, Taioli E, Thomas D, Vainio H, Wacholder S, Weinberg C. Reporting, appraising, and integrating data on genotype prevalence and gene-disease associations. Am J Epidemiol 2002; 156: 300-310
12. Kiss I, Sándor J, Pajkos G, Bogner B, Hegedűs G, Ember I. Colorectal cancer risk in relation to genetic polymorphism of cytochrome P450 1A1, 2E1, and glutathione-S-transferase M1 enzymes. Anticancer Res 2000; 20: 519-522
13. Kiss I, Orsós Z, Gombos K, Bogner B, Csepeyi A, Tibold A, Varga Z, Pásztí E, Magda I, Zőlyömi A, Ember I. Association between allelic polymorphisms of metabolizing enzymes (CYP 1A1, CYP 1A2, CYP 2E1, mEH) and occurrence of colorectal cancer in Hungary. Anticancer Res 2007; 27: 2931-2937
14. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-826
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188
16. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst
Jin JQ et al. CYP1A1 and colorectal cancer

1959; 22: 719-748

17 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634

18 Ishibe N, Stampfer M, Hunter DJ, Hennekens C, Kelsey KT. A prospective study of cytochrome P450 1A1 polymorphisms and colorectal cancer risk in men. Cancer Epidemiol Biomarkers Prev 2000; 9: 855-856

19 Sachse C, Smith G, Wilkie MJ, Barrett JH, Waxman R, Sullivan F, Forman D, Bishop DT, Wolf CR. A pharmacogenetic study to investigate the role of dietary carcinogens in the etiology of colorectal cancer. Carcinogenesis 2002; 23: 1839-1849

20 Slattery ML, Samowitz W, Ma K, Murtaugh M, Sweeney C, Levin TR, Neuhausen S. CYP1A1, cigarette smoking, and colon and rectal cancer. Am J Epidemiol 2004; 160: 842-852

21 Landi S, Gemignani F, Moreno V, Gioia-Patricola L, Chabrier A, Guino E, Navarro M, de Oca J, Capellà G, Canzian F. A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of colorectal cancer. Pharmacogenet Genomics 2005; 15: 535-546

22 Little J, Sharp L, Masson LF, Brockton NT, Cotton SC, Haites NE, Cassidy J. Colorectal cancer and genetic polymorphisms of CYP1A1, GSTM1 and GSTT1: a case-control study in the Grampian region of Scotland. Int J Cancer 2006; 119: 2155-2164

23 Yeh CC, Sung FC, Tang R, Chang-Chieh CR, Hsieh LL. Association between polymorphisms of biortransformation and DNA-repair genes and risk of colorectal cancer in Taiwan. J Biomed Sci 2007; 14: 183-193

24 Yoshida K, Osawa K, Kasahara M, Miyaishi A, Nakanishi K, Hayamizu S, Osawa Y, Tsutou A, Tabuchi Y, Shimada E, Tanaka K, Yamamoto M, Takahashi J. Association of CYP1A1, CYP1A2, GSTM1 and NAT2 gene polymorphisms with colorectal cancer and smoking. Asian Pac J Cancer Prev 2007; 8: 438-444

25 Pereira Serafim PV, Cotrim Guerreiro da Silva ID, Manoukias Forones N. Relationship between genetic polymorphism of CYP1A1 at codon 462 (Ile462Val) in colorectal cancer. Int J Biol Markers 2008; 23: 18-23

26 Kobayashi M, Otani T, Iwasaki M, Natsukawa S, Shaura K, Koizumi Y, Kasuga Y, Sakamoto H, Yoshida T, Tsugane S. Association between dietary heterocyclic amine levels, genetic polymorphisms of NAT2, CYP1A1, and CYP1A2 and risk of colorectal cancer: a hospital-based case-control study in Japan. Scand J Gastroenterol 2009; 44: 952-959

27 Nisa H, Kono S, Yin G, Toyomura K, Nagano J, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Inejiri K, Fumaki K, Maekawa T, Yasunami Y, Takenaka K, Ichimiya H, Terasaka R. Cigarette smoking, genetic polymorphisms and colorectal cancer risk: the Fukuoka Colorectal Cancer Study. BMC Cancer 2010; 10: 274

28 Nebert DW, Dalton TP. The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. Nat Rev Cancer 2006; 6: 947-960

29 Gonzalez FJ, Idle JR. Pharmacogenetic phenotyping and genotyping. Present status and future potential. Clin Pharmacol Ther 1994; 55: 59-70

30 Akiyama TE, Gonzalez FJ. Regulation of P450 genes by liver-enriched transcription factors and nuclear receptors. Biochim Biophys Acta 2003; 1619: 223-234

31 Sergentanis TN, Economopoulos KP. Four polymorphisms in cytochrome P450 1A1 (CYP1A1) gene and breast cancer risk: a meta-analysis. Breast Cancer Res Treat 2010; 122: 459-469

32 Zhuo WL, Zhang YS, Wang Y, Zhuo XL, Zhu B, Cai L, Chen ZT. Association studies of CYP1A1 and GSTM1 polymorphisms with esophageal cancer risk: evidence-based meta-analyses. Arch Med Res 2009; 40: 169-179

33 Shaik AP, Jamil K, Das P. CYP1A1 polymorphisms and risk of prostate cancer: a meta-analysis. Urol J 2009; 6: 78-86

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