A Meta-Analysis of the Relationship Between NAT2 Polymorphism and Colorectal Cancer Susceptibility

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Key words: N-acetyltransferase 2; colorectal cancer; polymorphism; genetic susceptibility; meta-analysis.

Summary. Background and Objective. Although the association between N-acetyltransferase 2 (NAT2) polymorphism and colorectal cancer (CRC) susceptibility in humans has been extensively investigated, the results are contradictory. The aim of this study was to conduct a meta-analysis of published studies to quantitatively summarize the association between NAT2 polymorphism and risk of CRC.

Material and Methods. Relevant studies that had investigated NAT2 polymorphism and CRC susceptibility were identified through a comprehensive search of Pubmed, EMBASE, Medline, BIOSIS, Wiley-Blackwell, ISI Web of Knowledge, CNKI, and Chinese Biomedicine Database until October 2011. After selection based on the inclusion and exclusion criteria, the relevant data were extracted from each study, and finally a meta-analysis was performed.

Results. Eight phenotype studies (791 cases and 1158 controls) and 45 genotype studies (13 875 cases and 18 879 controls) were included in the present meta-analysis. The pooling of phenotype studies showed no significant association between the NAT2 acetylator status and CRC susceptibility (rapid acetylator, OR, 1.32; 95% CI, 0.92–1.89; \( P=0.14 \); slow acetylator, OR, 0.76; 95% CI, 0.53–1.09; \( P=0.14 \)). The combined ORs for rapid and slow acetylator status and CRC risk in genotype studies were 1.01 (95% CI, 0.94–1.08; \( P=0.86 \)) and 0.99 (95% CI, 0.93–1.06; \( P=0.86 \)), respectively. In the subgroup analysis by regions, no increased risks were found in Asians, Europeans, Americans, or Australasians. Pooling studies were also conducted on the groups of gender, specific tumor sites, and smoking status, but no significant association in genotype distribution between CRC and control was found as well.

Conclusions. These results of our meta-analysis suggest that there is no overall association between NAT2 polymorphism and CRC susceptibility.

Introduction
Colorectal cancer (CRC) is one of the most common cancers in the world. It is generally accepted that human colorectal carcinogenesis is a complex, multistep, and multifactorial process in which many factors, such as dietary and lifestyle habits and/or mild genetic predisposition, are implicated (1). Exposure to carcinogens, such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and other amine compounds, is regarded as a risk factor for developing CRC (2). Studies have shown that individual inherited susceptibility plays an important role in the pathogenesis of tumor. In the last 3 decades, genetic polymorphisms have also been extensively investigated to identify inherited genetic susceptibility for CRC.

N-acetyltransferase 2 (NAT2) is one of these susceptibility genes, which has been considered to have an association with CRC risk. It is a polymorphic gene located on chromosome 8p22 region that contains an 870–bp open reading frame and encodes a protein of 290 amino acids (3). Individuals can be divided into 3 different phenotypes based on the allelic variants of NAT2: fast, intermediate, and slow. These phenotypes are determined by single nucleotide polymorphisms in NAT2 (4). As one of the phase II enzymes, NAT2 plays an essential role in the detoxification and/or bioactivation of several carcinogenic compounds, such as HCAs and PAHs, found in meat and tobacco smoke (5). It is therefore conceivable that increased or decreased activities of this enzyme may be involved in susceptibility to CRC (6).

Since Lang et al. (7) first reported an association between the NAT2 acetylator status and CRC risk, a number of studies have been published to describe the association between NAT2 polymorphisms and CRC risk in humans (8–57). However, the results are not conclusive. Therefore, in the present study, a meta-analysis of all available published studies was carried out to summarize the results of the effect of NAT2 polymorphism on CRC.
Material and Methods

Search strategy

Papers published until October 2011 that had investigated NAT2 polymorphism and CRC susceptibility were identified through a comprehensive search of Pubmed, EMBASE, Medline, Biosis, Wiley–Blackwell, ISI Web of Knowledge, CNKI, and Chinese Biomedicine Database, using the following search key words: acetyltransferase or N-acetyltransferase 2 or NAT2, genetic polymorphism or single nucleotide polymorphism, colon or rectum or colorectal, cancer or carcinoma or tumor. The search was without language restriction and selected only those conducted on human subjects. In addition, the citations in relevant articles were also thoroughly examined to further ensure that all appropriate studies were collected. In situations when multiple studies were published using the same data source, only the one that contained the largest data was taken into account. Unpublished studies were not considered in this literature search.

Inclusion and Exclusion Criteria

All articles involving studies that investigated NAT2 and CRC susceptibility were included. The selection criteria were as follows: 1) case-control studies; 2) evaluation of the association between NAT2 polymorphism and CRC susceptibility; 3) enough information about the number of CRC cases and controls studied with the different NAT2 acetylation status; and 4) clearly description of CRC diagnoses and the sources of cases and controls. The major exclusion criteria were as follows: 1) no control group; 2) overlapping or republished studies; 3) no usable information reported; and 4) cases or controls suffered from other cancers or other colorectal diseases.

Classification of NAT2 Acetylation Status

Eligible studies were classified into two types— "phenotype" or "genotype" studies— because the methods for measuring NAT2 acetylation status is different-measuring phenotypes by using metabolic response to a particular compound or measuring alleles directly, and we did not combine these studies for analysis. In our study, phenotype frequencies were summarized as slow and rapid status. In genotype studies, rapid acetylators were defined as carriers of homozygous or heterozygous for rapid acetylator alleles; those individuals who had two slow acetylation alleles were classified as slow acetylators, consistent with the definition in most studies.

Data Extraction and Analysis

One of the authors extracted and summarized the following information from each article: first author, publication year, country of origin, study type, study population, number of cases and controls, and numbers of cases and controls of different acetylation status, phenotyping and genotyping technique, location of tumors, matching, exposure assessment, and results of studies. This was checked by a second independent investigator to avoid input errors. Any disagreement was resolved by discussion; a third investigator adjudicated the disagreements if they could not come to an agreement.

Statistical Analysis

A meta-analysis was performed separately for phenotype and genotype studies. The strength of the associations between the NAT2 polymorphism and CRC susceptibility was estimated by odds ratio (OR) with 95% confidence intervals (CI). Heterogeneity was analyzed among the studies using the Cochran’s Q test and I² test. Fixed effects model was used when I² was less than 30%. Otherwise, the random effects model was used (I² >30%). We constructed a funnel plot to test the influence of publication bias. Sensitivity analysis was performed by deselecting studies with extreme findings to test the robustness of the results. Statistical analysis was performed using the Review Manager 5.1. P<0.05 was considered statistically significant.

Results

Study Characteristics

Fig. 1 shows the literature selection process. Overall, 51 studies of NAT2 acetylator status and CRC risk were eligible for our final analyses. They were published between 1986 and 2011. The size of study population ranged from 72 to 3587 individuals (14666 cases and 20037 controls). Of the included studies, 2 studies evaluated NAT2 acetylator status by phenotyping and genotyping separately, 6 studies by phenotyping only, and 43 studies by genotyping only. Characteristics of the included studies in this meta-analysis are presented in Tables 1 and 2.

Main Results

Phenotype Studies. Of the 8 phenotype studies, 4 studies identified acetylation phenotype via administration of sulfamethazine, 1 via administration of p-aminobenzoic acid (PABA), 4-aminobiphenyl (ABP), 2-aminofluorene (AF), and β-naphthylamine (BNA), and other 3 used the caffeine test. For the meta-analysis, the test for heterogeneity was statistically significant (I²=60%, P=0.01). Figs. 2 and 3 show the summary odds ratio (rapid acetylator, OR, 1.32; 95% CI, 0.92–1.89; P=0.14; slow acetylator, OR, 0.76; 95% CI, 0.53–1.09; P=0.14) for the combined rapid or slow acetylator phenotype studies separately, using the random-effect model. It is noteworthy that a plot of the rapid or slow acetylator status and CRC risk showed a trend toward a less significant association in the studies.
Of the 45 genotyping studies, 14 studies were carried out in Asian countries, 16 in European countries, 14 in American countries, and 1 in Australia. In some studies, the authors classified individuals into 3 categories (slow, intermediate, and rapid acetylators), and in our meta-analysis, intermediate acetylators were reclassified as fast acetylators.

For the meta-analysis, ORs were calculated from the reported frequencies of genotype by NAT2 status. Overall, the combined results based on all studies indicated that no significantly elevated CRC risk was associated with fast or slow NAT2 genotypes between cases and controls (rapid acetylator, OR, 1.01; 95% CI, 0.94–1.08, \( P = 0.86 \); slow acetylator, OR, 0.99; 95% CI, 0.93–1.06; \( P = 0.86 \), and there

**Table 1. Characteristics of Studies Included in the Meta-Analysis for Phenotype**

| Author and Year | Country | Study Type | No. of Cases | No. of Controls | Rapid Cases | Rapid Controls | Slow Cases | Slow Controls | Method for Phenotype Determination | Matching |
|-----------------|---------|------------|--------------|----------------|-------------|----------------|------------|---------------|----------------------------------|----------|
| Lang et al. (7), 1986 | USA | Case-control | 43 | 41 | 23 | 13 | 20 | 28 | Sulfamethazine | Age |
| Ilett et al. (8), 1987 | Australia | Case-control | 49 | 86 | 28 | 26 | 21 | 60 | Sulfamethazine | Age, sex, and racial origin |
| Wohlleb et al. (9), 1990 | USA | Case-control | 43 | 41 | 23 | 13 | 20 | 28 | Sulfamethazine | – |
| Kirlin et al. (10), 1991 | USA | Case-control | 25 | 12 | 12 | 9 | 13 | 3 | PABA, ABP, AF, and BNA | – |
| Ladero et al. (11), 1991 | Spain | Case-control | 109 | 96 | 49 | 40 | 60 | 56 | Sulfamethazine | Age |
| Lang et al. (12), 1994 | USA | Case-control | 34 | 205 | 14 | 92 | 20 | 113 | Caffeine test | – |
| Le Marchand et al. (13), 2001 | USA | Case-control | 348 | 466 | 272 | 346 | 76 | 120 | Caffeine test | Sex, ethnicity, age |
| Ishibe et al. (14), 2002 | USA | Case-control | 140 | 211 | 65 | 106 | 75 | 105 | Caffeine test | Gender and age in 5-year intervals |

PABA, \( p \)-aminobenzoic acid; ABP, 4-aminobiphenyl; AF, 2-aminofluorene; BNA, \( \beta \)-naphthylamine.

**Genotype Studies**

Of the 45 genotyping studies, 14 studies were carried out in Asian countries, 16 in European countries, 14 in American countries, and 1 in Australia. In some studies, the authors classified individuals into 3 categories (slow, intermediate, and rapid acetylators), and in our meta-analysis, intermediate acetylators were reclassified as fast acetylators.
Table 2. Characteristics of Studies Included in the Meta-Analysis for Genotype

| Author and Year | Country | Study Type | No. of Cases (M/F) | No. of Controls (M/F) | Rapid Cases (M/F) | Rapid Controls (M/F) | Slow Cases (M/F) | Slow Controls (M/F) | Location of the Tumors | Matching | Exposure Assessment |
|-----------------|---------|------------|--------------------|-----------------------|-------------------|----------------------|------------------|---------------------|------------------------|----------|---------------------|
| 1 2 3           | USA     | Case-control | 44                 | 28                    | 20                 | 13                   | 24               | 15                  | –                      | –        | –                   |
| Rodriguez et al. (15), 1993 | Japan | Case-control | 36                 | 36                    | 33                 | 3                    | 33               | 3                   | –                      | –        | Age                 |
| Shibuta et al. (17), 1994 | Japan | Case-control | 234                | 329                   | 208                | 298                  | 26               | 31                  | Colon and rectum       | –        | –                   |
| Bell et al. (18), 1995 | UK     | Case-control | 202                | 112                   | 96                 | 50                   | 106              | 62                  | –                      | Age      | Meat consumption and cigarette smoking |
| Spurr et al. (19), 1995 | UK     | Case-control | 103                | 96                    | 32                 | 34                   | 71               | 62                  | –                      | –        | –                   |
| Hubbard et al. (20), 1997 | UK     | Case-control | 275                | 343                   | 100                | 140                  | 317              | 203                 | –                      | –        | –                   |
| Welfare et al. (21), 1997 | UK     | Case-control | 174 (102/72)       | 174 (102/72)          | 73 (41/32)         | 74 (41/33)           | 101 (61/40)      | 100 (61/39)         | Right side and left side of colon | –        | –                   |
| Chen et al. (22), 1998 | USA    | Nested Case-control | 212                | 221                   | 81                 | 96                   | 131              | 125                 | –                      | Age ±1 year and smoking | Red meat intake |
| Gil et al. (23), 1998 | Portugal | Case-control | 114                | 201                   | 66                 | 81                   | 48               | 120                 | –                      | –        | –                   |
| Lee et al. (24), 1998 | Singapore | Case-control | 216                | 187                   | 156                | 134                  | 60               | 53                  | Right and left side of colon, sigmoid and rectum | –        | –                   |
| Kampman et al. (25), 1999 | USA    | Case-control | 1624 (912/712)     | 1963 (1036/927)       | 694 (576/318)     | 807 (433/374)        | 930 (536/394)   | 1156 (603/553)      | –                      | Sex and 5-year age group | Meat consumption |
| Yoshioka et al. (26), 1999 | Japan | Case-control | 106                | 100                   | 101                | 93                   | 95               | 7                   | –                      | –        | –                   |
| Agüínez et al. (27), 2000 | Spain  | Nested Case-control | 120                | 258                   | 60                 | 119                  | 60               | 139                 | Non-sigmoid colon, Sigmoid colon, Rectum | –        | –                   |
| Katoh et al. (28), 2000 | Japan  | Case-control | 103                | 122                   | 98                 | 115                  | 5                | 7                   | –                      | –        | –                   |
| Butler et al. (29), 2001 | Australia | Case-control | 209                | 200                   | 60                 | 57                   | 149              | 143                 | –                      | Gender   | –                   |
| Le Marchand et al. (13), 2001 | USA    | Case-control | 543                | 654                   | 419                | 497                  | 124              | 157                 | –                      | Sex, ethnicity, and age (2 years) | Diet, smoking, exercise, medical history, and occupational history |
| Ishibe et al. (14), 2002 | USA    | Case-control | 143                | 208                   | 64                 | 98                   | 79               | 110                 | Gender and age in 5-year intervals | –        | Meat consumption |
Table 2. Characteristics of Studies Included in the Meta-Analysis for Genotype (Continuation)

| 1 | 2         | 3         | 4      | 5      | 6      | 7      | 8      | 9      | 10                   | 11                            | 12                        |
|---|-----------|-----------|--------|--------|--------|--------|--------|--------|----------------------|-------------------------------|----------------------------|
|   | Tiemersma et al. (30), 2002 | Netherlands | Nested Case-control | 102   | 537   | 43     | 237   | 59     | 300     | Gender, age (5-year intervals) | Meat consumption and cigarette smoking |
|   | Barrett et al. (31), 2003 | UK        | Case-control | 490   | 592   | 186    | 243   | 304   | 349     | Age- and sex-matched | Meat consumption and cigarette smoking |
|   | Slattery et al. (32), 2003 | USA       | Case-control | 766 (451/315) | 990 (561/429) | 357 (204/153) | 470 (255/215) | 409 (247/162) | 520 (306/214) | Sex and by 5-year age groups | Meat consumption and cigarette smoking |
|   | Van der Hel et al. (33), 2003* | Netherlands | Case-control | 258   | 857   | 112    | 362   | 146   | 495     | Colon and rectum | – | Cigarette smoking |
|   | He et al. (34), 2004 | China      | Case-control | 83    | 237   | 65     | 169   | 18    | 68      | – | – | – |
|   | Kiss et al. (35), 2004 | Hungary    | Case-control | 500   | 500   | 233    | 182   | 267   | 318     | – | Age, sex, smoking habits, and red meat consumption | Meat consumption and cigarette smoking |
|   | Chan et al. (36), 2005* | USA        | Nested Case-control | 183   | 443   | 76     | 176   | 107   | 267     | – | Year of birth, month/year of blood collection | Meat consumption and cigarette smoking |
|   | Chen et al. (37), 2005 | China      | Case-control | 139   | 343   | 119    | 293   | 20    | 50      | – | – | – |
|   | Landi et al. (38), 2005 | Spain      | Case-control | 360   | 308   | 168    | 146   | 192   | 162     | – | – | – |
|   | Borlak and Reamon-Bueettner (39), 2006 | Germany | Case-control | 92    | 243   | 40     | 91    | 52    | 152     | – | Healthy unrelated Caucasian | – |
|   | Lilla et al. (40), 2006 | Germany    | Case-control | 503   | 601   | 208    | 227   | 295   | 374     | – | Sex, 5-year age groups, and county of residence | Meat consumption and cigarette smoking |
|   | Mosleh et al. (41), 2006 | USA        | Case-control | 685   | 693   | 272    | 317   | 413   | 376     | – | Gender and age | Cigarette smoking |
|   | Pistorius et al. (42), 2006 | Germany | Case-control | 226   | 107   | 83     | 48    | 143   | 59      | – | – | – |
|   | Huang et al. (43), 2007 | China (Taiwan) | Case-control | 244 (128/116) | 299 (146/153) | 197 (100/97) | 220 (112/108) | 47 (28/19) | 79 (34/45) | – | Population | – |
|   | Jiang (44) 2007 | China      | Case-control | 168   | 204   | 96     | 135   | 72    | 69      | Proximal and distal | – | – |
|   | Luo et al. (45), 2007 | China      | Case-control | 83    | 83    | 65     | 63    | 18    | 20      | – | Gender, nation, occupation, living place, age (5-year intervals) | – |
|   | Mahid et al. (46), 2007 | USA        | Case-control | 122   | 222   | 54     | 96    | 68    | 126     | – | – | – |
|   | Yeh et al. (47), 2007 | China (Taiwan) | Case-control | 715   | 730   | 558    | 576   | 157   | 154     | – | Age- and sex-matched | – |
Table 2. Characteristics of Studies Included in the Meta-Analysis for Genotype (Continuation)

|   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|----|----|----|
| Yoshida et al. (48), 2007 | Japan | Case-control | 66 | 121 | 64 | 112 | 2 | 9 | – | – | Cigarette smoking |
| Butler et al. (49), 2008 | USA | Case-control | 500 | 830 | 273 | 405 | 227 | 425 | – | Race, age, and sex |
| Cotterchio et al. (50), 2008 | Canada | Case-control | 832 | 1247 | 374 | 511 | 458 | 736 | – | Sex-matched and age group-matched |
| Sørensen et al. (51), 2008 | Denmark | Nested Case-control | 377 | 768 | 166 | 323 | 211 | 445 | – | Gender and age |
| Kobayashi et al. (52), 2009 | Japan | Case-control | 105 | 225 | 93 | 201 | 12 | 24 | – | Gender, age (within 3 years), and area of residence |
| Nöthlings et al. (53), 2009 | USA | Nested Case-control | 992 | 1493 | 656 | 996 | 336 | 497 | – | Sex, ethnicity/race, and age |
| Zupa et al. (54), 2009 | Italy | Case-control | 92 (51/41) | 121 (56/65) | 42 (26/16) | 71 (33/38) | 50 (25/25) | 50 (23/27) | – | – | – |
| Peng et al. (55), 2010 | China | Case-control | 286 | 286 | 230 | 257 | 56 | 29 | – | Gender, nation, living place, age (3-year intervals) |
| Silva et al. (56), 2011 | Brazil | Case-control | 147 (90/56) | 212 (85/127) | 59 (25/34) | 102 (33/69) | 88 (46/42) | 110 (52/58) | – | Gender and age |
| Wang et al. (57), 2011 | USA | Case-control | 301 | 355 | 20 | 35 | 281 | 320 | – | Unaffected siblings and cousins in the family |

*The individuals are all females.*
### Meta-analysis of NAT2 Rapid Acetylator Status and CRC Susceptibility Based on NAT2 Phenotypes

| Study                          | Case | Control | Weight, % | Odds Ratio M-H, Random, 95% CI |
|-------------------------------|------|---------|-----------|--------------------------------|
| Ilett et al. (8), 1987        | 28   | 49      | 26        | 86                             |
| Ishibe et al. (14), 2002      | 65   | 140     | 106       | 211                            |
| Kirlin et al. (10), 1991      | 12   | 25      | 9         | 12                             |
| Ladero et al. (11), 1991      | 49   | 109     | 40        | 96                             |
| Lang et al. (7), 1986         | 23   | 43      | 13        | 41                             |
| Lang et al. (12), 1994        | 34   | 34      | 92        | 205                            |
| Le Marchand et al. (13), 2001 | 272  | 348     | 346       | 466                            |
| Wohlleb et al. (9), 1990      | 23   | 43      | 13        | 41                             |
| **Total (95% CI)**            | 791  | 1158    | 100       | 1.32 (0.92, 1.89)               |

Total events 486 645

Heterogeneity: \( \chi^2 = 17.69, df = 7 \) \( P = 0.01; F = 60% \)

Test for overall effect: \( Z = 1.49 \) \( P = 0.14 \)

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### Meta-analysis of NAT2 Slow Acetylator Status and CRC Susceptibility Based on NAT2 Phenotypes

| Study                          | Case | Control | Weight, % | Odds Ratio M-H, Random, 95% CI |
|-------------------------------|------|---------|-----------|--------------------------------|
| Ilett et al. (8), 1987        | 21   | 49      | 60        | 86                             |
| Ishibe et al. (14), 2002      | 75   | 140     | 105       | 211                            |
| Kirlin et al. (10), 1991      | 13   | 25      | 3         | 12                             |
| Ladero et al. (11), 1991      | 60   | 109     | 56        | 96                             |
| Lang et al. (7), 1986         | 20   | 43      | 28        | 41                             |
| Lang et al. (12), 1994        | 20   | 34      | 113       | 205                            |
| Le Marchand et al. (13), 2001 | 76   | 348     | 120       | 466                            |
| Wohlleb et al. (9), 1990      | 20   | 43      | 28        | 41                             |
| **Total (95% CI)**            | 791  | 1158    | 100       | 0.76 (0.53, 1.09)               |

Total events 305 513

Heterogeneity: \( \chi^2 = 17.69, df = 7 \) \( P = 0.01; F = 60% \)

Test for overall effect: \( Z = 1.49 \) \( P = 0.14 \)

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**Interactions**

**Smoking.** In terms of the main effect of NAT2 polymorphisms on CRC susceptibility associated with smoking, 6 of the 45 genotype studies analyzed the effect in detail by using a variety of exposure variables. Van der Hel et al. (33) and Silva et al. (56) showed significant evidence for the modification of NAT2 and CRC by smoking. Van der Hel et al. reported that rapid NAT2 acetylation in combination with smoking significantly increased the risk of CRC; meanwhile, Silva et al. indicated that cigarette smoking increased the risk of CRC among slow NAT2 acetylators. Lilla et al. (40) reported that exposure to environmental tobacco smoke was
Subtotal (95% CI) 13875 18879 100 1.01 (0.94, 1.08)

Test for overall effect: Z=0.09 (P=0.93)

Total events 7270 9804

Heterogeneity: $\chi^2=0.02$, $df=44$ ($P=0.005$); $I^2=39%$

Test for overall effect: Z=0.18 ($P=0.86$)

Test for subgroup differences: $\chi^2=50.5$, $df=3$ ($P=0.92$); $I^2=0%$

Fig. 4. Meta-analysis of NAT2 rapid acetylator status and CRC susceptibility based on NAT2 genotypes. Studies are stratified by regions.
### NAT2 and Colorectal Cancer

Studies are stratified by regions.

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**Fig. 5.** Meta-analysis of NAT2 slow acetylator status and CRC susceptibility based on NAT2 genotypes.
associated with an increased risk of CRC among NAT2 fast acetylators, but the elevated CRC risk associated with active smoking was not significantly modified by NAT2 genotype. Slattery et al. (32) found that current smokers who were fast acetylators were at slightly lower risk than current smokers who were slow acetylators; the risk was slightly less than would be expected on an additive scale. Chan et al. (36) reported that the interactions between genotype and either early or total lifetime smoking failed to achieve a statistical significance. Moreover, Yoshida et al. (48) found that the distribution of NAT2 genotypes was not associated with CRC risk in ever-smokers.

In order to evaluate the combined ORs of these studies, smoking status was reclassified as never or ever smoking since the definition of cutoff points for pack-years in these studies was a bit different. The combined results showed no significant evidence for the modification of CRC risk associated with NAT2 status by cumulative smoking exposure (Table 5), which agreed with the conclusion of a meta-analysis conducted by Raimondi et al. (59).

### Meat Consumption

In an ecological study among 27 countries by Ognjanovic et al. (60), the authors concluded that in combination with meat intake, some proportion of the international variability in CRC incidence may be attributable to genetic susceptibility to heterocyclic amines, as determined by NAT2 genotype.

Of the 45 studies included in our meta-analysis, 15 investigated the interactions between NAT2 acetylator status and meat consumption. Of these 15 genotype studies that measured meat intake (13, 21, 22, 25, 30–32, 36, 40, 49–53, 56), 13 investigated the hypothesized interaction of meat intake and NAT2 acetylator genotype. Welfare et al. (21), Chen et al. (22), Kampman et al. (25), Chan et al. (36), Lilla et al. (40), and Silva et al. (56) showed significant evidence for the modification of NAT2 and CRC by meat consumption. Welfare et al. reported that fast acetylators consuming fried meat more than twice a week were at risk of CRC (21). Chen et al. observed a stronger association between red meat intake and cancer risk among NAT2 rapid acetylators, especially among men aged 60 years and more (22). Kampman et al. reported that the overall mutagen index for red and white meat together was significantly positively associated with colon cancer risk among intermediate and rapid acetylators (25). Chan et al. indicated that women with rapid acetylator genotypes experienced a greater risk associated with intake of ≥0.5 serving of beef, pork, or lamb as a main dish per day compared to intake of less meat (36). Lilla et al. reported that the frequent consumption of red meat significantly increased CRC risk for NAT2 fast acetylators (40). Silva et al. found

| Gender | No. of Studies | No. of Cases | No. of Controls | NAT2 Status | OR  | 95% CI        | P   | Heterogeneity | I² | P     | Model |
|--------|----------------|-------------|----------------|-------------|-----|--------------|-----|---------------|----|-------|-------|
| Male   | 7              | 2118        | 2392           | Fast        | 0.95| 0.84–1.08    | 0.46| 0%            | 0.46| 0.96  | Fixed |
| Female | 9              | 2085        | 3397           | Fast        | 1.04| 0.88–1.24    | 0.61| 43%           | 0.08| Random |

| Tumor Sites | No. of Studies | No. of Cases | No. of Controls | NAT2 Status | OR  | 95% CI        | P   | Heterogeneity | I² | P     | Model |
|-------------|----------------|-------------|----------------|-------------|-----|--------------|-----|---------------|----|-------|-------|
| Proximal    | 6              | 678         | 2009           | Fast        | 1.05| 0.86–1.28    | 0.62| 0%            | 0.68| Fixed |
| Distal      | 5              | 471         | 1805           | Fast        | 0.98| 0.77–1.25    | 0.86| 14%           | 0.32| Fixed |

| Smoking     | No. of Studies | No. of Cases | No. of Controls | NAT2 Status | OR  | 95% CI        | P   | Heterogeneity | I² | P     | Model |
|-------------|----------------|-------------|----------------|-------------|-----|--------------|-----|---------------|----|-------|-------|
| Never       | 5              | 682         | 1394           | Fast        | 1.05| 0.87–1.28    | 0.59| 0%            | 0.44| Fixed |
| Ever        | 6              | 827         | 1265           | Fast        | 1.03| 0.80–1.34    | 0.80| 40%           | 0.14| Random |
that among NAT2 fast acetylators, meat consumption more than 3 times a week increased the risk of CRC (56). In contrast, Le Marchand et al. (13), Tiemersma et al. (30), Barrett et al. (31), Sørensen et al. (51), Butler et al. (49), Nöthlings et al. (53), and Kobayashi et al. (52) did not report any apparent effect of interaction between NAT2 genotypes and meat intake on CRC risk.

Because the categorizations and criteria of meat consumption varied, there were no matching data for combinations, and we did not evaluate the combined ORs of these studies in this meta-analysis.

**Sensitivity Analysis and Publication Bias**

Sensitivity analysis was performed subsequently, and it showed similar results when deleting a single study involved in the meta-analysis each time, indicating that our results were statistically robust.

A funnel plot was performed to evaluate the publication bias of the literature. There does not appear to be an obvious publication bias among all the genotype studies extracted to this meta-analysis, for the shape of the funnel plot is symmetry, similar to an invert funnel (Fig. 6). However, in the phenotype studies, there may be a publication bias because the plot was asymmetrical (Fig. 7).

**Discussion**

NAT2 is involved in the metabolism of various potential carcinogens, such as HCAs and PAHs, and it has been hypothesized that NAT2 genetic polymorphism may contribute to risk of CRC. A series of studies have been published, but no clear consensus has been reached.

In 2002, Ye and Parry (61) conducted a meta-analysis using the published data from 20 case-control studies. They reported that the pooling of studies based on phenotyping methods indicated that the overall odds ratio of colon cancer risk associated with rapid acetylator was 1.51 (95% CI, 1.07–2.12). However, the calculated overall odds ratio of colon cancer risk associated with rapid acetylator from the studies based on genotyping was 1.03 (95% CI, 0.94–1.12), consistent with what was observed in this larger analysis. Pooling studies were also conducted on specific tumor sites and ethnic groups. The results showed that the effect of rapid acetylator on colon cancer risk was not obviously different. Therefore, the authors concluded that NAT2 alone was not an important risk factor for colon cancer, and NAT2 rapid acetylation status had no specific effect on the risk of developing colon cancer.

In the same year, de Jong et al. (62) also performed a meta-analysis to detect low-penetrance genes and their involvement in CRC susceptibility. The pooled analysis for phenotype studies revealed a positive association between fast acetylatorship and CRC, but genotype studies detected neither an association between CRC and presumed fast acetylatorship overall nor in subgroup analyses for ethnicity, gender, and tumor localization.

Three years later, Chen et al. (63) conducted a meta-analysis to clarify the influence of genetic polymorphisms on CRC. They found that NAT2 rapid acetylator phenotype (pooled OR, 1.15), but not NAT2 rapid acetylator genotype (pooled OR, 1.05), had a significantly increased risk of CRC ($P<0.05$).

Why does the pooled analysis of the phenotype-based studies conducted by Ye and Parry tend to be positive and that by de Jong et al. and Chen et al. negative? It is likely that methodological differences, such as different criteria of including a study for analysis, may underlie the somewhat different observations across the meta-analysis studies. For example, Ye and Parry, and de Jong et al. reported different results, which are likely due to the fact that Ye and Parry included additional studies by Wohlleb et al. (64) and Lang et al. (1994), and de Jong et al. included additional studies by Robers-Thomson et al. (65), which contained the patients with colorectal adenomatous polyps, and by Lang et al. (1986), though both studies of Ye and Parry, and de Jong et al. included the same 2 studies (8, 11). In the meta-analysis of Chen et al., a study (66) inves-

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Fig. 6. Funnel plot of genotype studies

Fig. 7. Funnel plot of phenotype studies
tigating NAT (not only NAT2) polymorphism and gastrointestinal carcinoma (containing gastric carcinoma) and also 2 studies based on genotype (17, 25) were included. Comparing to the study of Ye and Parry, our meta-analysis included 4 more studies (10, 12–14) and still found a less significant association between the rapid or slow acetylator status and CRC risk.

Furthermore, phenotype is an expression of the actual ability to metabolize the relevant chemicals. There is some evidence that the alteration of acetylation phenotype was influenced by a number of the following factors: 1) disease status; 2) liver and renal functions; 3) selection or participation bias of case and/or controls and analytical method used; and 4) overlapping activity of NAT1, and in addition, misclassification may also be important because different xenobiotics and methods were used to assess NAT2 activity. Therefore, it is likely that genotype studies more accurately reflect the risk attributable to NAT2 acetylation status, which was shown by the consistent results of genotype studies in the present 4 meta-analyses.

Our study was built upon these previous meta-analyses with a more comprehensive and thorough assessment of NAT2 polymorphism and CRC susceptibility and included some new studies published after 2005. Importantly, we also did a pooled analysis of raw data from a large sample size (phenotype studies, 791 cases and 1158 controls; genotype studies, 13 875 cases and 18 879 controls) to corroborate the meta-analysis. The pooling of phenotype studies showed no significant association between the NAT2 acetylator status and CRC risk (rapid acetylator, OR, 1.32; 95% CI, 0.92–1.89, \( P = 0.14 \); slow acetylator, OR, 0.76; 95% CI 0.53–1.09; \( P = 0.14 \)). The combined ORs for rapid and slow acetylator status and CRC risk in genotype studies were 1.01 (95% CI, 0.94–1.08, \( P = 0.86 \)) and 0.99 (95% CI, 0.93–1.06, \( P = 0.86 \)), respectively. In the subgroup analysis by regions, no increased risks were found in Asians, Europeans, Americans, or Australians. Pooling studies were also conducted on the groups of gender and specific tumor sites, but results showed no significant association in genotype distribution between CRC and control as well. It is possible that the results would be more confidence in the meta-analysis because of the larger numbers of cases and controls.

It is widely recognized that not only the main effect of a gene, but also the influence of gene–environmental or gene–diet interactions on cancer risk are important.

An interaction between NAT2 genetic polymorphism and smoking in cancer risk received great attention in some pieces of research. NAT2 is a phase II metabolizing enzyme detoxifying arylamines, some of which are derived from tobacco smoke (67). The action of NATs on these carcinogens can generate electrophilic ions capable of inducing DNA point mutations, so smoking may interact with NAT2 polymorphism. However, the results of epidemiologic studies were incompatible as described previously, and it may be partly explained by the complexity of tobacco smoke constituents, variation in metabolism of smoking, and differences in a study design. In a meta-analysis conducted by Raimondi et al. (59), the authors made a pooling and found a nonsignificant positive interaction between NAT2 genetic polymorphism and smoking for CRC risk, consistent with our results.

Another factor that has been investigated as a potential modifier of the NAT2 and CRC association is meat consumption. The consumption of meat, especially cooked at high temperature, is associated with exposure to HCAs. It has been shown that after absorption, they need to be bioactivated or detoxicated by N-acetyltransferase enzymes or enzymes of other family, such as cytochrome P450 (CYP), glutathione S-transferase (GST), and sulfotransferase (SULT), before they can damage DNA (68). Therefore, the effect modification of the association between meat consumption and CRC risk by NAT2 polymorphisms has been suggested. However, the associations were not consistent across studies. The role of NAT2 polymorphisms in the effect modification of environmental carcinogens should be assessed in well-designed, large-scale epidemiological studies with comprehensive information on risk factors for better understanding the etiologic role of dietary factors.

Regarding NAT2, the results of our meta-analysis of the genotype studies failed to show a significant association between NAT2 polymorphism and CRC risk. Molecular biologically, because the products of several genes interact, NAT2 polymorphisms may not be associated with CRC alone, and an association with CRC is still possible in combination with polymorphisms of other genes. For two of these combinations, an association with CRC was shown with the combined high-risk genotypes of CYP1A2 and NAT2 (12) and of GSTT1 and NAT2 (69). Only with specific knowledge of whether other genes are involved, it will be possible to recognize epidemiologically the exact estimate of risk conferred via one particular gene. Future studies should also measure the interaction of NAT2 and other genes in studies involving large numbers of patients and controls.

Several limitations of this meta-analysis should be interpreted with caution. Firstly, some included studies and stratified analyses were limited by the relatively small sample size. Secondly, our results were based on unadjusted estimates, and a more precise analysis would have been performed if all

Medicina (Kaunas) 2012;48(3)
individual raw data had been available. Thirdly, gene polymorphisms could modify the association between smoking and CRC only in specific categories of smokers such as long-term smokers (70), and other factors such as age at initiation of smoking and years since smoking cessation for former smokers could play a role. In our analysis, smoking status was reclassified as never or ever smoking, and it might be that this classification was not accurate and did not reflect the real association between NAT2 polymorphism and smoking in colorectal cancer. Finally, as in most meta-analyses, publication bias must be considered because only published studies were included in the meta-analysis. Following the construction of a funnel plot (Fig. 7), we conclude that there is some degree of publication bias in the phenotype studies. Therefore, we cannot exclude this probability in our meta-analysis, and such a situation may lead to incorrect conclusions.

In spite of these limitations, our meta-analysis had some strengths. First, the sufficient number of cases and controls were pooled from multiple studies, which significantly increased the statistical power of our analysis. Second, the symmetry of the funnel plot among all the genotype studies (Fig. 6) suggests that in these publications, bias is less likely to have appeared, indicating that the pooled results of genotype studies may be unbiased. Third, when comparing with previous meta-analyses (61–63), we considered not only association between NAT2 polymorphism and CRC susceptibility by phenotype and genotype studies separately and stratified to subgroup analyses for regions, gender, and tumor localization, but also paid attention to the impact of NAT2 and environmental factors, such as smoking and meat consumption, on CRC. We could therefore give a more complete picture on the role of NAT2 polymorphisms contributing to CRC risk.

Conclusions
Findings from this meta-analysis and pooled analysis indicate that there is no overall association between NAT2 polymorphism and CRC susceptibility. It is of great important to conduct large-scale studies using standardized unbiased phenotyping or genotyping methods, homogeneous CRC patients, and well-matched controls. Moreover, future studies evaluating smoking and meat intake should try to collect and use standardized exposure measures, which would greatly help summarize the results of related studies.

Statement of Conflicts of Interest
The authors state no conflict of interest.

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