N-Acetyltransferase Polymorphism and Risk of Colorectal Adenoma and Cancer: A Pooled Analysis of Variations from 59 Studies

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Abstract

Background: There have been an increasing number of studies with evidence suggesting that the N-acetyltransferase 1 (NAT1) and N-acetyltransferase 2 (NAT2) genotypes may be implicated in the development of colorectal cancer (CRC) and colorectal adenoma (CRA). So far the published data on this association has remained controversial, however. We performed a meta-analysis of case-cohort and case-control studies using a subset of the published data, with an aim to derive a better understanding of the underlying relationship.

Methods/Principal Findings: A literature search was performed using Medline database for relevant studies published through October 31, 2011. A total of 39 publications were selected for this meta-analysis, including 11,724 cases and 16,215 controls for CRC, and 3,701 cases and 5,149 controls for CRA. In our pooled analysis of all these studies, the results of our meta-analysis suggested that the NAT1 genotype was not significantly associated with an elevated CRC risk (OR 0.99, 95% CI 0.91–1.07). We also found that individuals with the rapid NAT2 genotype did have an elevated risk of CRC (OR 1.07, 95% CI 1.01–1.13). There was no evidence for an association between the NAT1 and 2 rapid genotype and an elevated CRA risk (NAT1: OR 1.14, 95% CI 0.99–1.29; NAT2: OR 0.94, 95% CI 0.86–1.03).

Conclusion: This meta-analysis suggests that individuals with NAT2 genotype had an elevated risk of CRC. There was no evidence for the association between NAT1 and 2 rapid genotype and CRA risk.

Introduction

Meat consumption has been linked to an increased risk of colorectal cancer (CRC) in many epidemiological studies [1,2]. Potent mutagens such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are formed during the high-temperature cooking of meat. The chemical structure of the HCA can be detoxified by the phase II enzymes N-acetyltransferase 1 and 2 (NAT1 and NAT2). The alteration of NAT1 and NAT2 acetylator status may decrease enzymatic activity and thus lead to a decreased efficiency in detoxification in the body, further resulting in an elevated risk of cancer.

So far, 36 NAT2 genetic variants have been identified in human, of which NAT2*A is the most common allele associated with rapid acetylation [3]. Meanwhile, NAT2*A1A, NAT2*A2A-G, NAT2*A3A and NAT2*A8 are also classified as rapid alleles, while the rest of the alleles are considered as slow alleles. Four relatively common polymorphic alleles exist for NAT1: designated as NAT1*A3, NAT1*A4, NAT1*A10, and NAT1*A11, with NAT1*A4 being the most common allele and NAT1*A10 the putative rapid allele. Subjects with more than one rapid allele were classified under NAT1 rapid acetylation, while others were under NAT1 slow acetylation.

Previous studies have investigated the relationship between the NAT1 and NAT2 genotype and predisposition to CRC and CRA [4–43]. The results were, however, inconsistent and even contradictory. Each individual study may have been underpowered to detect the effect of NAT1 and NAT2 genotype on the susceptibility of CRC and CRA. We therefore performed this meta-analysis of all eligible studies to derive a more scientifically convincing association of the NAT1 and NAT2 genotype with CRC and CRA.

Methods

Study eligibility, criteria, and literature searches

Computerised searches in MEDLINE were performed using the following search terms “NAT1”, “NAT2”, “genotype”, and
“colorectal cancer” or “colorectal adenoma” (the last search update was October 31, 2011). As studies with the same population by different investigators or overlapping data by the same authors were found, the most recent or complete articles with the largest numbers of subjects were included. Abstracts written in non-English language were not considered. Our initial search and the process of study selection is summarised in Figure 1.

Inclusion criteria
All human-associated studies were included if they met the following criteria: (1) evaluate the association between NAT1 and NAT2 genotype and the risk of CRC and CRA; (2) CRC and CRA cases must have been diagnosed by histological examination; (3) studies with full-text article.

Quality assessment
Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist (shown in Figure 2). Of the fourteen items in the checklist, ten items were relevant to this review and were used [44].

Data extraction
Data were extracted from each study by two reviewers independently according to the prespecified selection criteria (shown in Table 1). Supplementary information was obtained, when required, by contacting the lead author of the study. Contact was made by mail. In total, the lead authors of four studies [45–48] were contacted, but none replied. The following characteristics were collected for each study: first author’s name, ethnicity, source of case and control groups (hospital patient, healthy individual, population control, and random individual).

Statistical methods
Statistical analyses were done with Stata, version 11.0. Heterogeneity among studies was checked by the random-effects model (the DerSimonian and Laird method) if there was significant heterogeneity. A P-value of more than the nominal level of 0.05 for the Q statistic indicated a lack of heterogeneity across studies, allowing the use of the fixed-effects model (the Mantel-Haenszel method). Subgroup analyses were performed by type of study, genotype (NAT1 and NAT2), ethnicity, and source of control. Funnel plot asymmetry was assessed by the method of Egger’s linear regression test. The significance of the intercept was determined by the t test suggested by Egger (P<0.05 was considered representative of statistically significant publication bias).

Results
Eligible studies and meta-analysis database
As summarised in Table 1, 39 publications were selected for this meta-analysis, including 48 studies of the colorectal cancer (11,724
Based on meta-analysis from 34 studies, a significant increased risk of colorectal cancer was observed for those individuals with rapid acetylator polymorphisms in NAT2 (OR 1.07, 95% CI 1.01–1.13). When stratified by ethnicity, elevated risk of CRC was also observed among Caucasian populations (OR 1.09, 95% CI 1.02–1.16). There was no evidence for the association between the rapid genotype and CRC risk among Asian and African populations. And in a stratified analysis by source of control, individuals carrying the NAT2 rapid genotype were not significantly associated with increased CRC risk. There was no statistically heterogeneity among these studies in overall comparisons (P = 0.06, I^2 = 29.3%).

The associations of CRA risks with NAT1 and NAT2 genotype are also shown in Table 2. There was no evidence for the association between NAT1 and 2 rapid genotype and CRA risk (NAT1: OR 1.14, 95% CI 0.99–1.29; NAT2: OR 0.94, 95% CI 0.86–1.03). Similarly, no associations were found for the stratified analysis by ethnicity.

**Discussion**

Allelic polymorphism of the NAT2 enzyme has been studied for a long time, first detected phenotypically, based on enzyme activity distribution in healthy subjects, and later these activity differences were bound to an allelic polymorphism [49]. NAT1 was originally believed to be monomorphic, because of the unimodal distribution of its activity in the studied populations. Numerous studies have investigated the relationship between NAT1 and NAT2 genotypes and CRC or CRA susceptibility. The results vary widely and are often discordant likely because of ethnic and geographic differences of the enrolled subjects. In order to resolve this conflict, this meta-analysis was performed to derive a more precise estimation of the association.

Variations in the frequency of NAT1 and NAT2 genotype among different ethnic groups have been reported. Our results showed that frequency of the NAT1 rapid acetylation phenotype was 65.4% in Asian populations, which was significantly higher than that in European populations (35.8%). And for NAT2 phenotype, the rapid acetylation phenotype frequency was 79.8% in Asians and 42.4% in Europeans. In the stratified analysis by ethnicity, elevated risk was found for Caucasian. But there was no evidence for the association between NAT1 and NAT2 genotype and CRC risk among Asian populations.

There is epidemiologic evidence for differential effects of acetylation with CRA risk by ethnicity. For example, Probst-Hensch et al. reported an inverse association between NAT2 rapid genotypes and colorectal adenomas among African Americans, but an increased risk among whites [50]. It has been suggested that the individual single nucleotide polymorphisms may occur uniquely within specific ethnic populations resulting in allele frequencies and could account for racial differences in disease susceptibility [51]. For a long time, genetic susceptibility to cancer has been attributed to xenobiotic exposure. However, this view has changed with the advances in molecular biology. It is now known that exposure to xenobiotics and the development of cancer vary among individuals because of variations that occur at the molecular level which, in turn, are under genetic control [52]. In recent studies, lifestyle habits including alcohol and tobacco use and dietary habits (meat intake) have been associated with gene mutations in an attempt to obtain more consistent results regarding cancer risk factors and prognosis [53]. Although currently available data are controversial due to ethnic differences and differences in lifestyle, this has been the best approach to better understand carcinogenesis at the molecular level.

Several studies have also investigated the association between NAT1 and NAT2 genotypes and CRC risk, as reviewed in 2000 [4]. Contrary to the negative result of most articles, some findings suggest that NAT2 gene variants associated with more rapid
### Table 1. Characteristics of studies included in the meta-analysis.

| Study               | Place of study | Gene    | Ethnicity       | Case  | Case comment                                                                 | Control | Design |
|---------------------|----------------|---------|-----------------|-------|-------------------------------------------------------------------------------|---------|--------|
| Bell et al. 1995    | UK             | NAT1, 2 | Caucasian       | 202   | CRC cases with adenocarcinoma of colon or rectum from the North Staffordshire Hospital between 1990–1994 | HP      |        |
| Probst-Hensch et al. 1996 | USA           | NAT1, 2 | Mixed           | 441   | CRA cases from two Southern California Kaiser Permanente Medical Centers between 1991 and 1993 | PB      |        |
| Welfare et al. 1997 | UK             | NAT2    | Caucasian       | 174   | CRC cases in the Newcastle and North Tyneside health districts over a 9 month period | PB      |        |
| Chen et al. 1998    | USA            | NAT1, 2 | Caucasian (98%) | 212   | Male confirmed of CRC cases from the Physicians’ Health Study                 | HI      |        |
| Hubbard et al. 1998 | UK             | NAT2    | Caucasian       | 245   | CRC sample collected from three local hospitals between 1988 and 217 1993      | HI      |        |
| Gil and Lehner et al. 1998 | Portugal     | NAT2    | Caucasian       | 114   | CRC cases from the Lisbon area or South/Central Portugal during the 201 period 1994 to 1996 | PB      |        |
| Lee et al. 1998     | Singapore      | NAT2    | Asian           | 216   | CRC cases recruited from the National University Hospital and Singapore General Hospital | HI      |        |
| Kampman et al. 1999 | USA            | NAT2    | Caucasian       | 1,624 | CRC cases with the primary colon carcinoma diagnosed between 1991 to 1994     | PB      |        |
| Potter et al. 1999  | USA            | NAT2    | Caucasian       | 527   | CRA cases from an NCI-funded program project between 1991 and 633 1994        | PB      |        |
| Katoh et al. 2000   | Japan          | NAT1, 2 | Asian           | 103   | CRC cases with colorectal adenocarcinoma from Kitakyushu City during 1991 to 1995 | RI      |        |
| Agündez et al. 2000 | Spain          | NAT2    | Caucasian       | 120   | CRC cases with carcinoma of colon or rectum from 1997 to 1999                | HI      |        |
| Ishibe et al. 2002  | USA            | NAT1, 2 | Mixed           | 146   | CRA cases from a clinic–based case–control study                             | HP      |        |
| Tiemersma et al. 2002 | Netherlands   | NAT1, 2 | Caucasian       | 102   | CRC cases from Netherlands Cancer Registry (NCR) and three regional cancer registries between 1987 to 1998 | RI      |        |
| Barrett et al. 2003 | Sweden         | NAT2    | Caucasian       | 490   | CRC cases recruited from three centres: Dundee, Leeds and York in 592 the period 1997–2000 | PB      |        |
| Van der Hel et al. 2003 | Netherlands | NAT1, 2 | Caucasian       | 258   | Female with diagnosis of CRC cases recruited from 1987 to 1996                | PB      |        |
| Kiss et al. 2004    | Hungary        | NAT2    | Caucasian       | 500   | CRC cases from Centre Hospital of Ministry of Internal Affairs and from the area of Baranya and Vas Country | PB      |        |
| Tiemersma et al. 2004 | Netherlands   | NAT1, 2 | Caucasian       | 431   | CRA cases recruited among patients at the eight hospitals in the Netherlands between 1997 and 2000 | HI      |        |
| He et al. 2005      | China          | NAT2    | Asian           | 83    | CRC cases recruited from the Department of Surgery at Hebei No. 4237 Hospital | HI      |        |
| Chan et al. 2005    | USA            | NAT2    | Caucasian       | 183   | 183 female cases with CRC from the Nurses’ Health Study from 1976-443 in 11 US states | HI      |        |
| Landi et al. 2005   | Spain          | NAT1, 2 | Caucasian       | 360   | CRC cases from the University Hospital in Barcelona from 1996 to 1998         | HI      |        |
| Chen et al. 2005    | China          | NAT1, 2 | Asian           | 139   | CRC cases from the population census in Zhejiang province from 1899 to 1990   | HI      |        |
| Moslehi et al. 2006 | USA            | NAT2    | Mixed           | 685   | CRA cases from screening–arm participants of the PLCO Trial between 1993 and 1999 | PB      |        |
| Study                  | Place of study | Gene | Ethnicity | Case | Case comment                                                                 | Control | Design |
|-----------------------|----------------|------|-----------|------|-------------------------------------------------------------------------------|---------|--------|
| Lilla et al. 2006     | Germany        | NAT1, 2 | Caucasian | 505  | CRC cases from 22 hospitals in the Rhine-Neckar-Odenwald region 604 between 2003 and 2004 | PB      |        |
| Borlak et al. 2006    | Germany        | NAT2  | Caucasian | 92   | CRC cases (colon) provided by the the Imperial Cancer Research Fund Laboratory of the Ninewell’s Hospital | HI      |        |
| Pistorius et al. 2006 | Germany        | NAT2  | Caucasian | 209  | Patients with diagnosis of sporadic or familial CRC cases who met at least one criterion of the Bethesda guidelines | HI      |        |
| Huang et al. 2007     | China          | NAT2  | Asian     | 244  | Sporadic CRC cases recruited from the Chung Shan Medical University Hospital from 2000 to 2005 | PB      |        |
| Mahid et al. 2007     | USA            | NAT1, 2 | Caucasian | 122  | Sporadic CRC cases from the University of Louisville colorectal surgery unit | RI      |        |
| Yoshida et al. 2007   | Japan          | NAT2  | Asian     | 66   | CRC cases from the Kobe Medical Center and Rosai Hospital between 2003 and 2005 | RI      |        |
| Butler et al. 2008    | USA            | NAT1, 2 | Mixed     | 507  | 217 African cases and 290 Caucasian cases with adenocarcinoma of colon cancer between 1996 and 2000 | PB      |        |
| Shin et al. 2008      | USA            | NAT1, 2 | Mixed     | 557  | CRA cases from Tennessee Colorectal Polyp Study (TCP)                          | HP      |        |
| Stjørensen et al. 2008| Denmark        | NAT2  | Caucasian | 377  | CRC cases from a Danish prospective study from 1993 to 2003                   | PB      |        |
| Cotterchio et al. 2008| Canada         | NAT2  | Caucasian | 832  | CRC cases from the OFCCR between 1997 and 2000                               | PB      |        |
| Yeh et al. 2009       | China          | NAT1, 2 | Asian     | 727  | CRC cases recruited from the Chang Gung Memorial Hospital between 1995 and 1999 | HI      |        |
| Nothlings et al. 2009 | USA            | NAT1, 2 | Mixed     | 1,009| CRC cases from the Multiethnic Cohort Study between 1993 and 1996              | PB      |        |
| Zupa et al. 2009      | Italy          | NAT2  | Caucasian | 92   | CRC cases of colon cancer from the Centro di Riferimento Oncologico di Basilicata | HI      |        |
| Wang et al. 2010      | USA            | NAT2  | Mixed     | 914  | CRA cases from Hawaii during 1996 to 2007 and CRC cases from Hawaii during 1994 to 1999 | HP      |        |
| Da Silva et al. 2010  | Brazil         | NAT2  | Mixed     | 147  | CRC cases from Department of Gastroenterology, University Hospital between 2008 and 2009 | HI      |        |
| Cleary et al. 2010    | Canada         | NAT1  | Caucasian | 1,174| CRC cases from the OFCCR between 1997 and 2000                               | PB      |        |

HB, hospital–based patient; PB, population-based control; HI, healthy individual; RI, random individual.
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Acetylation activity may be related to increased risk of colorectal cancer [20]. This could be explained by the reaction of meat consumption and cigarette smoking on individuals with high genetic susceptibility. It was reported that NAT2 rapid acetylator genotypes may contribute to CRC risk of individuals with high consumption of red meats, not to that of active smokers [28]. However, a meta-analysis with 20 publications cited that NAT2 rapid acetylation status has no specific effect on the risk of developing colon cancer [54]. The discrepancy could be attributed to the potential problem of misclassification for meat intake and smoking history. There were some other studies on the combined effect of NAT1 or NAT2 and meat intake. However, they did not categorise on how meat was consumed [38], and present information for meat consumption in a uniform standard [28, 35, 39]. Possible misclassification in exposure measurement and heterogeneity in definition of meat intake or tobacco use may partly explain the high inconsistency of the findings.

The present study has several limitations that need consideration. First, we only considered two metabolic enzymes (NAT1 and NAT2). Because additional enzymes are involved in the bioactivation and detoxification of heterocyclic amine, they may also play a role in modifying CRC or CRA risk, this may increase the misclassification of measured variables. Second, only three studies evaluated associations between NAT1 or NAT2 genotype and CRC risk in histologic subgroup, such as associations among cases in the Duke stage [5, 14, 28]. Thirdly, our meta-analysis was based on unadjusted OR estimates because not all published studies were presented with adjusted ORs [15, 42] or when they did, the ORs were not adjusted by the same potential confounders [16, 22, 27]. The magnitude of the observed association for NAT2 with CRC risk is modest, possibly owing to the unadjusted

Table 2. Stratified analysis of the NAT1, NAT2 genotype on colorectal cancer and adenoma risk.

| Type of study                  | No | Sample (cas/con) | Test of association | Test of heterogeneity |
|-------------------------------|----|-----------------|---------------------|----------------------|
|                               |    |                 | OR 95% CI P Result | Q P I² (%)           |
| Colorectal cancer             |    |                 |                     |                      |
| NAT1 acetylator               | 14 | 5,177/7,475     | 0.99 0.91–1.07 0.74 | – 15.03 0.31 13.50 |
| Ethnicity                     |    |                 |                     |                      |
| African                       | 1  | 208/299         | 0.95 0.85–1.07 0.40 | – – –               |
| Asian                         | 3  | 963/1,198       | 1.10 0.91–1.34 0.32 | – 0.26 0.88 0.00    |
| Caucasian                     | 9  | 3,162/4,633     | 1.01 0.92–1.12 0.80 | – 10.15 0.26 21.20 |
| Mixed                         | 1  | 844/1,345       | 0.94 0.87–1.01 0.09 | – – –               |
| Source of control             |    |                 |                     |                      |
| Healthy individual            | 3  | 1,072/1,297     | 1.08 0.90–1.29 0.42 | – 0.64 0.73 0.00    |
| Hospital patient              | 2  | 561/433         | 1.44 1.06–1.94 0.02 | + 2.23 0.14 55.10   |
| Population control            | 6  | 3,216/4,864     | 0.94 0.86–1.03 0.19 | – 3.28 0.66 0.00    |
| Random individual             | 3  | 328/881         | 0.91 0.69–1.19 0.48 | – 0.69 0.71 0.00    |
| NAT2 acetylator               | 34 | 10,509/14,964   | 1.07 1.01–1.13 0.01 | + 46.70 0.06 29.30  |
| Ethnicity                     |    |                 |                     |                      |
| African                       | 1  | 215/307         | 1.01 0.88–1.16 0.91 | – – –               |
| Asian                         | 7  | 1,566/2,039     | 1.12 0.94–1.33 0.20 | – 5.64 0.47 0.00    |
| Caucasian                     | 23 | 7,096/10,307    | 1.09 1.02–1.16 0.01 | + 36.04 0.03 39.00  |
| Mixed                         | 3  | 1,632/2,311     | 0.96 0.84–1.10 0.56 | – 2.05 0.36 2.60    |
| Source of control             |    |                 |                     |                      |
| Healthy individual            | 12 | 2,270/2,969     | 0.93 0.82–1.05 0.25 | – 11.74 0.38 6.30   |
| Hospital patient              | 4  | 1,283/1,469     | 1.04 0.88–1.23 0.66 | – 0.34 0.95 0.00    |
| Population control            | 14 | 6,608/9,525     | 1.14 1.03–1.26 0.01 | + 26.28 0.02 50.50  |
| Random individual             | 4  | 393/1,001       | 1.06 0.79–1.41 0.72 | – 1.46 0.69 0.00    |
| Colorectal adenoma            |    |                 |                     |                      |
| Genotype                      |    |                 |                     |                      |
| NAT1                          | 4  | 1,553/2,587     | 1.14 0.99–1.29 0.06 | – 1.29 0.73 0.00    |
| NAT2                          | 7  | 3,683/5,109     | 0.94 0.86–1.03 0.18 | – 9.83 0.13 39.00   |
| Ethnicity                     |    |                 |                     |                      |
| Caucasian                     | 3  | 1,381/1,496     | 1.07 0.92–1.25 0.36 | – 2.21 0.33 9.40    |
| Mixed                         | 8  | 3,855/6,200     | 0.98 0.90–1.06 0.55 | – 13.12 0.07 46.60  |
| Source of control             |    |                 |                     |                      |
| Hospital patient              | 7  | 3,142/5,402     | 1.02 0.93–1.11 0.72 | – 10.46 0.11 42.60  |
| Population control            | 4  | 2,094/2,294     | 0.96 0.86–1.09 0.54 | – 5.57 0.14 46.10   |

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Acetylation activity may be related to increased risk of colorectal cancer [20]. This could be explained by the reaction of meat consumption and cigarette smoking on individuals with high genetic susceptibility. It was reported that NAT2 rapid acetylator genotypes may contribute to CRC risk of individuals with high consumption of red meats, not to that of active smokers [28]. However, a meta-analysis with 20 publications cited that NAT2 rapid acetylation status has no specific effect on the risk of developing colon cancer [34]. The discrepancy could be attributed to the potential problem of misclassification for meat intake and smoking history. There were some other studies on the combined effect of NAT1 or NAT2 and meat intake. However, they did not categorise on how meat was consumed [38], and present information for meat consumption in a uniform standard [28, 35, 39]. Possible misclassification in exposure measurement and heterogeneity in definition of meat intake or tobacco use may partly explain the high inconsistency of the findings.
Figure 3. Begg’s funnel plot for publication bias test: Rapid versus slow. Each point represents a separate study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line: mean effect size. A: Funnel plot analysis for odds ratios for NAT1 genotype in overall CRC studies; B: Funnel plot analysis for odds ratios for NAT2 genotype in overall CRC studies; C: Funnel plot analysis for odds ratios for NAT1 and NAT2 genotype in overall CRA studies.

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estimate by age and sex in the pooled adjusted analysis. Given these results, our conclusions should be interpreted cautiously.

In conclusion, our meta-analysis suggests that individuals with the rapid NAT2 genotype had elevated risk of CRC. There was no evidence for the association between NAT1 and 2 rapid genotype and CRA risk. Our study significantly increased the statistical power of the analysis based on the studies for CRC and CRA risk. Further studies on estimating the effect of gene-gene and gene-environment interactions may eventually lead to a better and more comprehensive understanding of the association between the NAT1 and NAT2 genotype and CRC and CRA risk.

Author Contributions
Conceived and designed the experiments: YZ. DD. Performed the experiments: DD XV YC. Analyzed the data: JL. DD R. Luo. Contributed reagents/materials/analysis tools: JL. YZ. R. Li. Wrote the paper: JL. YZ. R. Luo.

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