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Original Article

NAT1 polymorphisms and cancer risk: a systematic review and meta-analysis

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Abstract: Purpose: To investigate the association between the *N*-acetyltransferase 1 (*NAT1*) slow and rapid acetylation phenotypes with cancer risk based on a meta-analysis. Methods: Previously published case-control studies were retrieved from PubMed, Embase, and Web of Science. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined to assess the relationship between *NAT1* polymorphisms and cancer risk. Results: A total of 73 studies (24874 cases and 30226 controls) were included in this meta-analysis. No significant association was identified between *NAT1* polymorphisms (slow acetylation versus rapid acetylation genotypes: OR = 0.978, 95% CI = 0.927-1.030, P < 0.001 for heterogeneity, I^2 = 45.5%) and cancer risk, whereas a significantly reduced risk of pancreatic cancer was identified in individuals with *NAT1* slow acetylation genotype (OR = 0.856, 95% CI = 0.733-0.999, P =0.509 for heterogeneity, I^2 = 0). When the *NAT1* slow acetylation genotype was analysed on the basis of stratified analyses of ethnicity, a significantly reduced risk of head and neck cancers was found among Asian (OR=0.281, 95% CI = 0.127-0.622). When the *NAT1* slow acetylation genotype was analysed on the basis of stratified analyses of source of control, only significantly reduced risks of colorectal cancer (OR = 0.882, 95% CI = 0.798-0.974, P = 0.212 for heterogeneity, I^2 = 22.9) and pancreatic cancer (OR=0.856, 95% CI = 0.733-0.999, P = 0.509 for heterogeneity, I^2 = 0) were found among hospital-based studies. Conclusions: No significant association between the *NAT1* polymorphisms and the risk of cancer was found except for pancreatic cancer.

Keywords: N-acetyltransferase 1, polymorphism, cancer, meta-analysis

Introduction

Cancer, also known as malignant neoplasm, is a major public health problem worldwide. Approximately 12.7 million cancer cases and 7.6 million deaths caused by were reported by GLOBOCAN 2008 [1]. Carcinogenesis is a multistep process in which numerous genetic and environmental factors are involved [2]. It has been shown that host genetic factors contribute to carcinogenesis through modification of gene structure and protein expression [3, 4]. Recent studies suggest that variants of genes encoding metabolic enzymes are significantly associated with the development of a number of cancers.

The *NAT* gene on chromosome 8p21.3-23.1, which encodes *N*-acetyltransferases (*NAT*; E.C.2.3.1.5) isozymes *NAT1* (*N*-acetyltransferase 1) and NAT2 (*N*-acetyltransferase 2) [5] and phase II xenobiotic metabolizing enzyme, plays an essential role in detoxifying carcinogens, and their reactive intermediates are also involved in *N*-acetylation and *O*-acetylation of aromatic and heterocyclic amine carcinogens [6]. There are many systematic reviews on the association of *NAT2* polymorphism and the risk of cancer. A meta-analysis conducted by Zhong [7] indicated that no association was found between *NAT2* acetylation status and gastric cancer risk. No significant association was found in overall analysis between *NAT2* acetylation status and lung cancer risk by Cui's meta-analysis [8], either. A meta-analysis conducted by Gong [9] found that a statistically significant association between *NAT2* polymorphism and

prostate cancer appeared in Asians, but not in Caucasians. And a pooled analysis conducted by Liu [10] found that suggested that individuals with NAT2 genotype had an elevated risk of colorectal adenoma risk.

To date, 28 human *NAT1* variants have been identified (http://louisville.edu/medschool/pharmacology/consensushuman-arylamine-n-acetyltransferase-gene-nomenclature/). The *NAT1*4* genotype has historically been designated as "wild type" and is commonly used a reference for studying *NAT1* polymorphisms. In the past decade, numerous epidemiological studies investigating the association between *NAT1* polymorphisms and cancer risk have been reported, however, the results of some studies are conflicting. For example, a case–control study conducted in Norway by Zienolddiny *et al*. [11] found that the fast acetylator phenotype of *NAT1* was significantly associated with lung cancer. However, negative association between them has also been reported [12].

In the present study, we conducted a meta-analysis to systematically study the association between *NAT1* polymorphisms and cancer risk based on published studies.

Materials and methods

Selection of published studies

A systematic search in the PubMed, Embase and Web of Science databases was conducted to retrieve studies published until July 1, 2014 using the following MeSH terms and keywords: '*NAT1*' or '*N*-acetyltransferase 1', 'polymorphism' or 'variant', and 'cancer' or 'carcinoma'. The references of retrieved studies were also scanned to identify eligible studies. Studies included in the present meta-analysis have to meet the following criteria: (i) articles investigating the association between *NAT1* polymorphisms and cancer risk; (ii) case-control studies; (iii) available genotype frequency for computing odds ratios (ORs) with 95% confidence intervals (CIs); (iv) studies with full-text article. Criteria for excluding studies were (i) only case population; (ii) outcome comparison not available or not able to be determined; (iii) duplicated publications; (iv) benign tumor or precancerous lesions.

Data extraction

Two investigators (Zhang KY and Gao LJ independently screened the titles, abstracts and full texts using a standardized extraction form. Agreement was reached to resolve conflicting evaluation based on consensus and discussion. For each study, the following results were collected: first author's name, year of publication, country of origin, ethnicity, cancer type, genotyping method, source of controls (population-based [PB] or hospital-based [HB] controls), total number of cases and controls, and genotype distributions in cases and controls. No minimum number of patients was defined in the present meta-analysis. In accordance with most studies, individuals with at least one of the high-activity *NAT1* alleles (*NAT1*10, NAT1*21, NAT1*24, and NAT1*25*) were defined as rapid acetylators, whereas individuals carrying two low-activity *NAT1* alleles(others except the high-activity alleles) were considered as slow acetylators.

Statistical analysis

Statistical analyses were performed using the STATA software (version 12.0; Stata Corporation, College Station, Texas). Statistical significance was evaluated using two-tailed test and a *P* value less than 0.05 was considered as statistical significance unless stated otherwise. Hardy-Weinberg equilibrium (HWE) in controls was assessed by chi-squared test and a *P* value less than 0.05 was considered as significant disequilibrium. If HWE disequilibrium was identified ($P < 0.05$), or equilibrium evaluation was not possible, sensitivity analysis was performed. The strength of the association between *NAT1* polymorphisms and cancer risk was evaluated on the basis of ORs with 95% confidence intervals (CIs). The chi-square-based Q statistic was used to test heterogeneities among the studies included in the present meta-analysis [13]. A fixed-effect model with Mantel–Haenszel method was used to calculate the pooled odds ratios if Q-test *P* value was ≥ 0.1 [14]. Otherwise, a random-effect model with inverse variance method was used. The risks (ORs) of cancer associated with the *NAT1* slow/rapid acetylation polymorphisms were estimated for each study. One-way sensitivity analysis was performed to

Table 1. Characteristics of the studies included in the meta-analysis

First Author	Year	Country	Ethnicity	Cancer type	Genotyping Method	Source of control	Case	Control
lung cancer								
Abdel-Rahman	1998	USA	Mixed	lung cancer	PCR-RFLP	HB	45	47
Bouchardy, C.	1998	France	Caucasian	lung cancer	PCR-RFLP	HB	150	172
Ishibe	1998	USA	Mixed	lung cancer	PCR-RFLP	HB	174	319
Wikman, H	2001	Germany	Caucasian	lung cancer	PCR-RFLP	HB	392	351
Zienolddiny, S.	2008	Norway	Caucasian	lung cancer	Sequecing	PB	390	186
colorectal cancer								
Eichholzer	2012	Switzerland	Caucasian	colorectal cancer	MassArray	PB	399	776
Cleary	2010	Canada	Caucasian	colorectal cancer	TaqMan	HB	1159	1284
Yeh	2009	China	Asian	colorectal cancer	PCR–RFLP	HB	722	733
Nothlings	2009	USA	Mixed	colorectal cancer	TaqMan/Sequence Detection System	PB	844	1345
Sorensen	2008	Denmark	Caucasian	colorectal cancer	TaqMan/Sequence Detection System	HB	377	766
Butler	2008	USA	others	colorectal cancer	PCR–RFLP/(AS)-PCR	HB	208	299
Butler	2008	USA	Caucasian	colorectal cancer	PCR–RFLP/(AS)-PCR	HB	282	528
Mahid	2007	USA	Mixed	colorectal cancer	TaqMan	HB	123	223
Lilla	2006	Germany	Caucasian	colorectal cancer	Fluorescence-based melting curve	PB	605	604
Landi	2005	Italy	Caucasian	colorectal cancer	Sequence Detection System	HB	359	321
Chen	2006	China	Asian	colorectal cancer	PCR–RFLP	PB	138	343
Kiss	2004	Hungary	Caucasian	colorectal cancer	PCR–RFLP	HB	500	500
Van Der Hel	2003	Netherlands	Caucasian	colorectal cancer	PCR–RFLP	PB	218	804
Zhang	2002	China	Asian	colorectal cancer	PCR–RFLP	HB	104	101
Tiemersma	2002	Netherlands	Caucasian	colorectal cancer	Allele-specific hybridization	PB	102	536
Le Marchand	2001	USA	Mixed	colorectal cancer	PCR–RFLP	PB	539	649
Katoh	2000	Japan	Asian	colorectal cancer	PCR–RFLP/(AS)-PCR	HB	103	122
Kampman	1999	USA	Mixed	colorectal cancer	Oligonucleotide ligation assay	PB	1624	1963
Chen	1998	USA	Mixed	colorectal cancer	PCR–RFLP	PB	212	221
Bell	1995	UK	Caucasian	colorectal cancer	PCR–RFLP	HB	202	112
Moslehi	2006	USA	Mixed	colorectal cancer	TaqMan	PB	636	636
Ishibe	2002	USA	Mixed	colorectal cancer	PCR–RFLP	HB	132	192
Probst-Hensch	1996	USA	Mixed	colorectal cancer	PCR–RFLP	HB	441	484
head and neck cancer								
Demokan	2010	Turkey	others	head and neck cancer	PCR–RFLP	HB	95	93
Fronhoffs	2001	Fronhoffs	Caucasian	head and neck cancer	PCR	HB	291	300
Olshan	2000	USA	Mixed	head and neck cancer	PCR–RFLP	HB	171	193

Majumder	2012	India	others	head and neck cancer	TaqMan	HB	299	381
Katoh	1998	Japan	Asian	head and neck cancer	PCR–RFLP	HB	62	122
pancreatic cancer								
Suzuki	2008	USA	Mixed	pancreatic cancer	PCR–RFLP	HB	649	585
Li	2006	USA	Mixed	pancreatic cancer	TaqMan	HB	304	322
Jiao	2007	USA	Caucasian	pancreatic cancer	TaqMan	HB	501	548
non-Hodgkin's lymphoma								
Chiu	2005	USA	Mixed	non-Hodgkin's lymphoma	PCR–RFLP	PB	267	543
Kilfoy	2010	USA	Mixed	non-Hodgkin's lymphoma	TaqMan	PB	453	522
Morton	2006	USA	Mixed	non-Hodgkin's lymphoma	TaqMan	PB	916	746
Aschebrook-Kilfoy	2012	USA	Mixed	non-Hodgkin's lymphoma	PCR–RFLP	PB	328	447
Kerridge	2002	Australia	Caucasian	non-Hodgkin's lymphoma	PCR–RFLP	HB	164	193
bladder cancer								
Koutros	2011	USA	Caucasian	bladder cancer	TaqMan	PB	247	324
Covolo	2008	Italy	Caucasian	bladder cancer	PCR–RFLP	HB	197	211
McGrath	2006	USA	Caucasian	bladder cancer	TaqMan	PB	193	479
Gu	2005	USA	Caucasian	bladder cancer	PCR–RFLP	HB	490	491
Garcia-Closas	2005	Spain	Caucasian	bladder cancer	TaqMan	HB	965	942
Hung, R	2004	Italy	Caucasian	bladder cancer	PCR–RFLP	HB	201	214
Schroeder	2003	USA	Mixed	bladder cancer	PCR–RFLP	HB	234	207
Stern	2002	USA	Mixed	bladder cancer	PCR–RFLP	HB	225	200
Cascorbi	2001	Germany	Caucasian	bladder cancer	PCR–RFLP	HB	425	343
Hsieh	1999	China	Asian	bladder cancer	PCR–RFLP	HB	65	171
Taylor	1998	USA	Mixed	bladder cancer	PCR–RFLP	HB	230	203
Okkels	1997	Denmark	Caucasian	bladder cancer	PCR–RFLP	HB	248	223
prostate cancer								
Sharma	2010	Canada	Mixed	prostate cancer	TaqMan	PB	1685	1642
Sharma	2010	Canada	Caucasian	prostate cancer	TaqMan	PB	421	421
Kidd	2011	USA	Caucasian	prostate cancer	mass spectrometry	PB	200	184
Iguchi	2009	USA	Caucasian	prostate cancer	TaqMan	PB	179	170
Hein	2002	USA	Caucasian	prostate cancer	PCR–RFLP	HB	47	121
Costa	2005	Portugal	Caucasian	prostate cancer	PCR–RFLP	PB	127	145
Rovito	2005	USA	Caucasian	prostate cancer	TaqMan	PB	139	146
Fukutome	1999	Japan	Asian	prostate cancer	PCR–RFLP	HB	101	97
gastri cancer								
Wideroff	2007	USA	Caucasian	gastri cancer	TaqMan	PB	116	211
Katoh	2000	Japan	Asian	gastri cancer	PCR–RFLP/(AS)-PCR	HB	140	122

BOISSY	2000	USA	Caucasian	gastri cancer	PCR-RFLP	HB	94	112
Lang	2003	Poland	Caucasian	gastri cancer	PCR-RFLP	HB	292	410
breast cancer								
Van Der Hel	2003	Netherlands	Caucasian	breast cancer	PCR-RFLP	PB	228	264
Lee	2003	Korea	Asian	breast cancer	TaqMan	PB	245	275
Krajinovic	2001	Canada	Caucasian	breast cancer	PCR allele-specific-oligonucleotide (ASO) hybridization assays	HB	125	182
Millikan	2000	USA	Mixed	breast cancer	PCR-RFLP	HB	490	469
other cancers								
Muller	2008	Germany	others	acute myeloid leukemia	TaqMan	HB	132	208
Krajinovic	2000	Canada	Caucasian	acute myeloid leukemia	PCR-RFLP	HB	155	306
Wideroff	2007	USA	Caucasian	Esophageal adenocarcinoma	TaqMan	PB	67	211
Zhang	2005	China	Asian	hepatocellular carcinoma	PCR-RFLP	HB	96	173
Yu	2000	China	Asian	hepatocellular carcinoma	PCR-RFLP	HB	151	211
Lincz	2004	Australia	Caucasian	multiple myeloma	PCR-RFLP	HB	90	198

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PB: population-based case control study; HB: hospital-based case control.

Table 2. Pooled ORs and 95% CIs of stratified meta-analysis

Variables	N	OR	95% CIs	I^2 (%)	P for Heterogeneity
Total	76	0.978	0.927-1.030	45.5	< 0.001
Cancer type					
Lung cancer	5	0.867	0.592-1.269	73.3	0.005
Colorectal cancer	23	0.961	0.880-1.050	54.8	0.001
Head and neck cancer	5	0.826	0.595-1.146	63.5	0.027
Pancreatic cancer	3	**0.856**	**0.733-0.999**	0	0.509
Non-Hodgkin's lymph	5	1.007	0.892-1.136	0	0.863
Bladder cancer	12	1.068	0.929-1.227	47.2	0.035
Prostate cancer	8	1.019	0.892-1.164	9.3	0.358
Gastri cancer	4	0.913	0.532-1.567	81.0	0.001
Breast cancer	5	0.967	0.826-1.132	0	0.791
other cancers	6	1.102	0.906-1.339	0	0.641
Source of control					
PB	28	0.978	0.927-1.030	27.0	0.096
HB	48	0.941	0.872-1.016	51.6	< 0.001
Ethnicity					
Caucasian	39	0.981	0.906-1.061	49.3	< 0.001
Asian	11	0.887	0.730-1.076	44.6	0.054
Mixed	22	0.996	0.918-1.080	46.6	0.009
Others	4	1.028	0.843-1.253	0	0.532

N: involved studies' number; OR, odds ratio; PB: population-based case control study; HB: hospital-based case control. Random model was chosen for data pooling when *P*-value < 0.10 and /or I^2 > 50%; otherwise fixed model was used; The numbers in bold indicated statistically significant values.

assess the stability of the results. Specifically, each study was sequentially removed from the meta-analysis to evaluate its influence on pooled ORs. Begg and Mazumdar [15] adjusted rank correlation test and the Egger regression asymmetry test [16] were used to identify publication bias.

Results

Characteristics of the studies

A total of 207 articles were retrieved from PubMed, Embase, and Web of Science. Among them, 76 case-control studies including 24874 cases and 30226 controls in73 articles met the inclusion criteria. Three articles reported two independent studies that were considered separately. The characteristics of each study were listed in **Table 1**. In general, there were 5 lung cancer studies [17-20], 23 colorectal cancer studies [21-41], 5 head and neck cancer studies [42-46], 3 pancreatic cancer studies [47-49], 5 non-Hodgkin's lymphoma studies [50-54], 12 bladder cancer studies [55-66], 8 prostate cancer studies [67-73], 4 gastric cancer studies [34, 74, 75], 5 breast cancer studies [76-80] and 6 other cancers studies [74, 81-85]. Thirty-nine, 11, 22, and 4 studies were on Caucasian, Asian, and Mixed population, and other population, respectively. There were 48 hospital-based studies and 28 population-based studies.

Meta-analysis

The strength of the association between *NAT1* polymorphisms (slow acetylation versus rapid acetylation genotypes) and the susceptibility to cancers were shown in **Table 2**. Overall, the *NAT1* acetylation phenotype was not significantly associated with cancer risk compared with the *NAT1* rapid acetylation phenotype. The forest plot of overall comparison between slow and rapid acetylation genotypes was shown in **Figure 1**. The pooled OR was 0.978 (95% CI = 0.927-1.030, *P* < 0.001 for heterogeneity, I^2 = 45.5%). Substantial heterogeneity was identified among these studies.

In the subgroup analyses by ethnicity, no significant risks were found in Caucasian (OR = 0.981, 95% CI = 0.906-1.061, *P* < 0.001 for heterogeneity, I^2 = 49.3%), Asian (OR = 0.887, 95% CI = 0.730-1.076, P < 0.001 for heterogeneity, I^2 = 44.6%), Mixed population(OR = 0.996, 95% CI = 0.918-1.080, *P* < 0.001 for heterogeneity, I^2 = 46.6%) and Others (OR = 1.028, 95% CI = 0.843-1.253, *P* = 0.532 for heterogeneity, I^2 = 0). In addition, no significantly increased risk was detected in different source of controls (for hospital-based studies: OR = 0.941, 95% CI = 0.872-1.016, *P* < 0.001 for heterogeneity, I^2 = 51.6%); for population-based studies: OR = 0.978, 95% CI = 0.927-1.030, P = 0.096 for heterogeneity, I^2 = 27.0%). In stratified analyses by cancer types, significant associations were found only for pancreatic cancer (OR = 0.856, 95% CI = 0.733-0.999, P = 0.509 for heterogeneity, I^2 = 0) (**Table 2**).

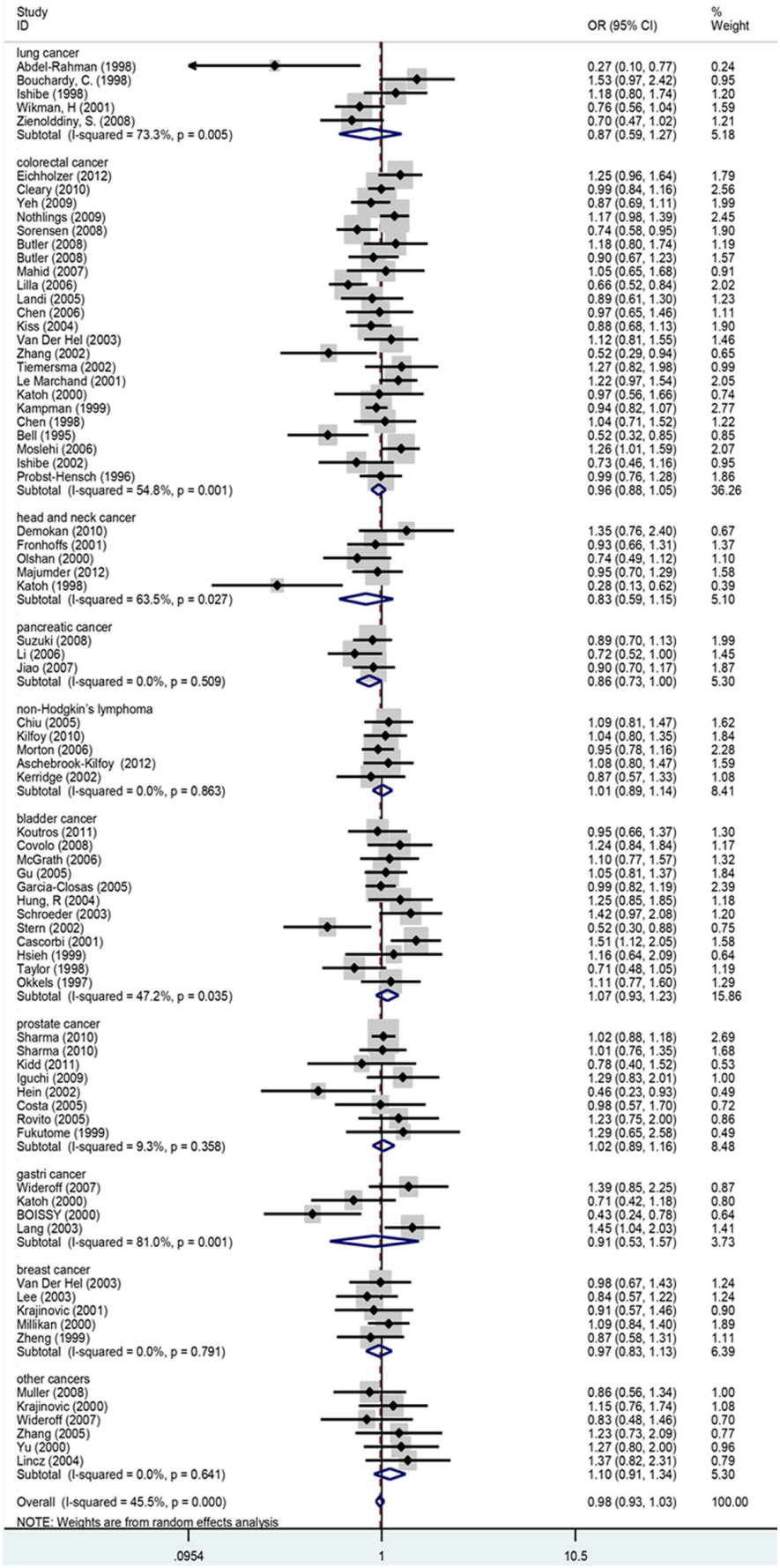
Study ID
OR (95% CI)
% Weight
lung cancer
Abdel-Rahman (1998) 0.27 (0.10, 0.77) 0.24
Bouchardy, C. (1998) 1.53 (0.97, 2.42) 0.95
Ishibe (1998) 1.18 (0.80, 1.74) 1.20
Wikman, H (2001) 0.76 (0.56, 1.04) 1.59
Zienolddiny, S. (2008) 0.70 (0.47, 1.02) 1.21
Subtotal (I-squared = 73.3%, p = 0.005) 0.87 (0.59, 1.27) 5.18
colorectal cancer
Eichholzer (2012) 1.25 (0.96, 1.64) 1.79
Cleary (2010) 0.99 (0.84, 1.16) 2.56
Yeh (2009) 0.87 (0.69, 1.11) 1.99
Nothlings (2009) 1.17 (0.98, 1.39) 2.45
Sorensen (2008) 0.74 (0.58, 0.95) 1.90
Butler (2008) 1.18 (0.80, 1.74) 1.19
Butler (2008) 0.90 (0.67, 1.23) 1.57
Mahid (2007) 1.05 (0.65, 1.68) 0.91
Lilla (2006) 0.66 (0.52, 0.84) 2.02
Landi (2005) 0.89 (0.61, 1.30) 1.23
Chen (2006) 0.97 (0.65, 1.46) 1.11
Kiss (2004) 0.88 (0.68, 1.13) 1.90
Van Der Hel (2003) 1.12 (0.81, 1.55) 1.46
Zhang (2002) 0.52 (0.29, 0.94) 0.65
Tiemersma (2002) 1.27 (0.82, 1.98) 0.99
Le Marchand (2001) 1.22 (0.97, 1.54) 2.05
Katoh (2000) 0.97 (0.56, 1.66) 0.74
Kampman (1999) 0.94 (0.82, 1.07) 2.77
Chen (1998) 1.04 (0.71, 1.52) 1.22
Bell (1995) 0.52 (0.32, 0.85) 0.85
Moslehi (2006) 1.26 (1.01, 1.59) 2.07
Ishibe (2002) 0.73 (0.46, 1.16) 0.95
Probst-Hensch (1996) 0.99 (0.76, 1.28) 1.86
Subtotal (I-squared = 54.8%, p = 0.001) 0.96 (0.88, 1.05) 36.26
head and neck cancer
Demokan (2010) 1.35 (0.76, 2.40) 0.67
Fronhoffs (2001) 0.93 (0.66, 1.31) 1.37
Olshan (2000) 0.74 (0.49, 1.12) 1.10
Majumder (2012) 0.95 (0.70, 1.29) 1.58
Katoh (1998) 0.28 (0.13, 0.62) 0.39
Subtotal (I-squared = 63.5%, p = 0.027) 0.83 (0.59, 1.15) 5.10
pancreatic cancer
Suzuki (2008) 0.89 (0.70, 1.13) 1.99
Li (2006) 0.72 (0.52, 1.00) 1.45
Jiao (2007) 0.90 (0.70, 1.17) 1.87
Subtotal (I-squared = 0.0%, p = 0.509) 0.86 (0.73, 1.00) 5.30
non-Hodgkin's lymphoma
Chiu (2005) 1.09 (0.81, 1.47) 1.62
Kilfoy (2010) 1.04 (0.80, 1.35) 1.84
Morton (2006) 0.95 (0.78, 1.16) 2.28
Aschebrook-Kilfoy (2012) 1.08 (0.80, 1.47) 1.59
Kerridge (2002) 0.87 (0.57, 1.33) 1.08
Subtotal (I-squared = 0.0%, p = 0.863) 1.01 (0.89, 1.14) 8.41
bladder cancer
Koutros (2011) 0.95 (0.66, 1.37) 1.30
Covolo (2008) 1.24 (0.84, 1.84) 1.17
McGrath (2006) 1.10 (0.77, 1.57) 1.32
Gu (2005) 1.05 (0.81, 1.37) 1.84
Garcia-Closas (2005) 0.99 (0.82, 1.19) 2.39
Hung, R (2004) 1.25 (0.85, 1.85) 1.18
Schroeder (2003) 1.42 (0.97, 2.08) 1.20
Stern (2002) 0.52 (0.30, 0.88) 0.75
Cascorbi (2001) 1.51 (1.12, 2.05) 1.58
Hsieh (1999) 1.16 (0.64, 2.09) 0.64
Taylor (1998) 0.71 (0.48, 1.05) 1.19
Okkels (1997) 1.11 (0.77, 1.60) 1.29
Subtotal (I-squared = 47.2%, p = 0.035) 1.07 (0.93, 1.23) 15.86
prostate cancer
Sharma (2010) 1.02 (0.88, 1.18) 2.69
Sharma (2010) 1.01 (0.76, 1.35) 1.68
Kidd (2011) 0.78 (0.40, 1.52) 0.53
Iguchi (2009) 1.29 (0.83, 2.01) 1.00
Hein (2002) 0.46 (0.23, 0.93) 0.49
Costa (2005) 0.98 (0.57, 1.70) 0.72
Rovito (2005) 1.23 (0.75, 2.00) 0.86
Fukutome (1999) 1.29 (0.65, 2.58) 0.49
Subtotal (I-squared = 9.3%, p = 0.358) 1.02 (0.89, 1.16) 8.48
gastri cancer
Wideroff (2007) 1.39 (0.85, 2.25) 0.87
Katoh (2000) 0.71 (0.42, 1.18) 0.80
BOISSY (2000) 0.43 (0.24, 0.78) 0.64
Lang (2003) 1.45 (1.04, 2.03) 1.41
Subtotal (I-squared = 81.0%, p = 0.001) 0.91 (0.53, 1.57) 3.73
breast cancer
Van Der Hel (2003) 0.98 (0.67, 1.43) 1.24
Lee (2003) 0.84 (0.57, 1.22) 1.24
Krajinovic (2001) 0.91 (0.57, 1.46) 0.90
Millikan (2000) 1.09 (0.84, 1.40) 1.89
Zheng (1999) 0.87 (0.58, 1.31) 1.11
Subtotal (I-squared = 0.0%, p = 0.791) 0.97 (0.83, 1.13) 6.39
other cancers
Muller (2008) 0.86 (0.56, 1.34) 1.00
Krajinovic (2000) 1.15 (0.76, 1.74) 1.08
Wideroff (2007) 0.83 (0.48, 1.46) 0.70
Zhang (2005) 1.23 (0.73, 2.09) 0.77
Yu (2000) 1.27 (0.80, 2.00) 0.96
Lincz (2004) 1.37 (0.82, 2.31) 0.79
Subtotal (I-squared = 0.0%, p = 0.641) 1.10 (0.91, 1.34) 5.30
Overall (I-squared = 45.5%, p = 0.000) 0.98 (0.93, 1.03) 100.00
NOTE: Weights are from random effects analysis
.0954
1
10.5

Figure 1. Meta-analysis of the association between *NAT1* polymorphisms (slow and rapid acetylation genotypes) and susceptibility to cancer. The sizes of the symbols are proportional to the study.

Table 3. Stratified analyses of NAT1 polymorphisms on cancer risk by ethnicity

Variables	N	OR	95% CIs	I^2 (%)	P for Heterogeneity
Total	76	0.978	0.927-1.030	45.5	< 0.001
Caucasian					
Lung cancer	3	0.912	0.592-1.404	74.5	0.020
Colorectal cancer	10	0.899	0.773-1.044	63.8	0.003
Head and neck cancer	1	0.927	0.656-1.309	_	_
Pancreatic cancer	1	0.905	0.700-1.169	_	_
Non-Hodgkin's lymph	1	0.874	0.575-1.328	_	_
Bladder cancer	8	***1.104***	***0.993-1.227***	1.5	0.418
Prostate cancer	6	1.003	0.834-1.207	30.8	0.204
Gastric cancer	3	0.985	0.498-1.948	84.6	0.002
Breast cancer	3	0.925	0.728-1.174	0	0.916
other cancers	6	1.102	0.906-1.339	0	0.641
Asian					
Colorectal cancer	4	0.855	0.699-1.046	9.8	0.344
Head and neck cancer	1	**0.281**	**0.127-0.622**	_	_
Bladder cancer	1	1.156	0.641-2.086	_	_
Prostate cancer	1	1.294	0.648-2.584	_	_
Gastric cancer	1	0.708	0.423-1.184	_	_
Breast cancer	1	0.836	0.575-1.216	_	_
Mixed					
Lung cancer	2	0.616	0.147-2.578	85.1	0.010
Colorectal cancer	8	1.065	0.954-1.188	36.7	0.136
Head and neck cancer	1	0.742	0.491-1.122	_	_
Pancreatic cancer	2	0.829	0.683-1.006	6.6	0.301
Non-Hodgkin's lymph	4	1.020	0.899-1.157	0	0.846
Bladder cancer	3	0.822	0.461-1.466	81.6	0.004
Prostate cancer	1	1.019	0.884-1.176	_	_
Breast cancer	1	1.086	0.843- 1.399	_	_
others					
Colorectal cancer	1	1.183	0.803- 1.742	_	_
Head and neck cancer	2	1.034	0.770- 1.388	9.2	0.294

N: involved studies' number; OR, odds ratio; PB: population-based case control study; HB: hospital-based case control. Random model was chosen for data pooling when *P*-value < 0.10 and /or I^2 > 50%; otherwise fixed model was used; The numbers in bold indicated statistically significant values.

We also performed analyses based on different cancer types in different ethnicities. The results showed that significantly reduced risk of slow acetylation genotype of head and neck cancers was found in Asian (OR = 0.281, 95% CI = 0.127-0.622). However, no significant association between *NAT1* polymorphisms and risks of other types of cancers was detected in both Asian and Caucasian (**Table 3**). In addition, we conducted analyses based on different cancer types among source of control and found significantly reduced risks of both colorectal cancer (OR = 0.882, 95% CI = 0.798-0.974, P = 0.212 for heterogeneity, I^2 = 22.9) and pancreatic cancer (OR = 0.856, 95% CI = 0.733-0.999, P = 0.509 for heterogeneity, I^2 = 0) among hospital-based population. Similarly, no significant association between *NAT1* polymorphisms and the risks of other different types of cancers was found in both hospital-based studies and population-based studies (**Table 4**).

Heterogeneity and sensitivity analyses

Significant heterogeneities was detected between studies. Then the source of heterogeneity was evaluated by cancer types (lung cancer, colorectal cancer, head and neck cancer, pancreatic cancer, non-Hodgkin's lymphoma, bladder cancer, prostate cancer, gastric cancer, breast cancer and other types of cancers), ethnicity (Caucasian, Asian, Mixed and Others) and source of controls (population-based and hospital-based case controls). The results suggested that cancer types (χ^2 = 42.158, df = 9, P < 0.001) and ethnicity (χ^2 = 36.737, df = 3, P < 0.001), but not the source of controls (χ^2 = 0.615, df = 1, P = 0.433) contributed substantially to heterogeneity. Sensitivity analysis through sequentially removal of individual study demonstrated that no study significantly affected the overall OR (the 95% CIs always overlap one unit).

Table 4. Stratified analyses of *NAT1* polymorphisms on cancer risk by source of control

Variables	N	OR	95% CIs	Tau-squared	I^2 (%)	P for Heterogeneity
Total	76	0.978	0.927-1.030	0.0215	45.5	< 0.001
PB						
Lung cancer	1	0.695	0.474-1.020	0.1279	_	_
Colorectal cancer	10	1.063	0.929-1.217	0.0225	65.0	0.002
Non-Hodgkin's lymph	4	1.020	0.899-1.157		0	0.846
Bladder cancer	2	1.022	0.792-1.318	0.0265	0	0.587
Prostate cancer	6	1.035	0.923-1.161	0	0	0.818
Gastric cancer	1	1.385	0.853-2.249	0.2425	_	_
Breast cancer	3	0.896	0.717-1.118	0	0	0.832
other cancers	1	0.834	0.476-1.459	_	_	_
HB						
Lung cancer	4	0.911	0.564-1.471	0.0074	76.7	0.005
Colorectal cancer	13	**0.882**	**0.798- 0.974**	0.0334	22.9	0.212
Head and neck cancer	5	0.826	0.595-1.146	0.0836	63.5	0.027
Pancreatic cancer	3	**0.856**	**0.733-0.999**	0	0	0.509
Non-Hodgkin's lymph	1	0.874	0.575-1.328	0	_	_
Bladder cancer	10	1.075	0.911-1.269	0.0152	55.9	0.015
Prostate cancer	2	0.784	0.483-1.272	0	76.4	0.040
Gastric cancer	3	0.786	0.379-1.629		85.9	0.001
Breast cancer	2	1.044	0.835-1.306		0	0.517
other cancers	5	1.146	0.930-1.411		0	0.641

N: involved studies' number; OR, odds ratio; PB: population-based case control study; HB: hospital-based case control. Random model was chosen for data pooling when *P*-value < 0.10 and /or I^2 > 50%; otherwise fixed model was used; The numbers in bold indicated statistically significant values.

Publication bias

As shown in **Figures 2** and **3**, the symmetrical funnel plots suggested no publication bias (*P* = 0.260). The Egger's test further supported no publication bias in the present meta-analysis (*P* = 0.150).

Discussion

To date, many epidemiological studies have evaluated the association of *NAT1* polymorphism with the risk of cancer such as (lung cancer [11, 17-19], colorectal cancer [22-27], head and neck cancer [43, 45, 46], pancreatic cancer [47-49] non-Hodgkin's lymphoma [50-52], bladder cancer [55-59], prostate cancer [67, 69, 70], gastric cancer [34, 74, 75], breast cancer [76-79], but the results remain contradictory. Meta-analysis is a powerful method for the evaluation of effect size of numerous independent epidemiological studies based on statistical analysis, providing more reliable results than single study. To the best of our knowledge, this study is the first meta-analysis to date including the largest and most comprehensive assessments of the relationship between the *NAT1* polymorphisms and cancer risk. No significant association between the *NAT1* polymorphisms and cancer risk was identified in the present meta-analysis of 73 case-control studies including 24874 and 30226 control cases. In the stratified analysis by cancer types, no significant associations were found among studies on lung cancer, colorectal cancer, head and neck cancer, non-Hodgkin's lymphoma, bladder cancer, prostate cancer, gastric cancer and breast cancer. However, we observed an increase risk in pancreatic cancer among the *NAT1* rapid acetylator compared to the slow one. Our results are consistent with five previously pooled analysis on colorectal cancer [86, 87], prostate cancer [88] and bladder cancer [89, 90], in which no significant association was found between *NAT1* polymorphisms and cancer risk. Inconsistent results among different studies on various cancers may be explained by the distinct role of *NAT1* in different cell types and tissues. However, no signifi-

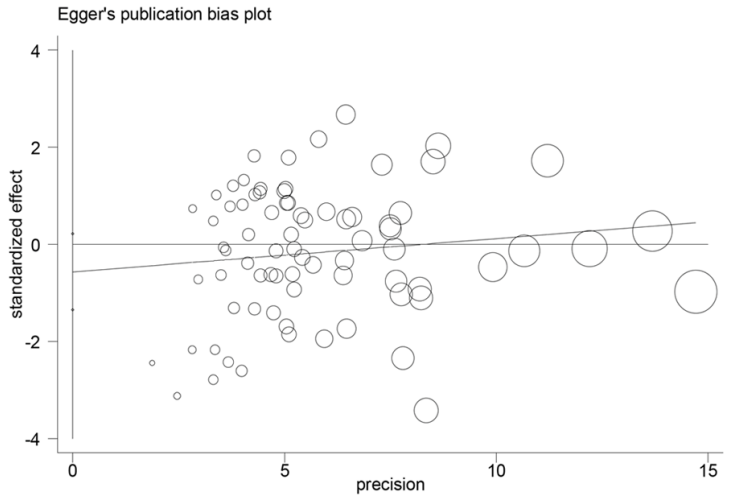

Figure 2. No significant publication bias was found based on the Begg's funnel plots. Each point represents an individual study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line, mean effect size.

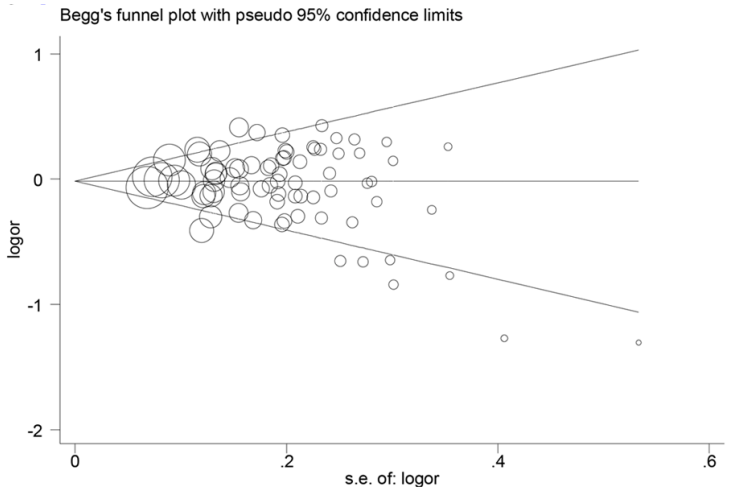

Figure 3. No significant publication bias was found on the basis of Egger's funnel plots. Each point represents an individual study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line, mean effect size.

cant association between the *NAT1* phenotypes and cancer risk was detected in the present meta-analysis even when stratifying for race and study design.

Interestingly, analyses based on various cancer types in different ethnicities revealed that a significantly reduced risk of a head and neck cancer study among Asian (OR = 0.281, 95% CI = 0.127-0.622) was found. However, given the limited sample size, the result should be carefully interpreted and further validation in larger well-designed studies are highlighted. To date, numerous studies have been conducted to detect the overall effects of *NAT1* polymorphisms on cancer susceptibilities. However, many studies generated conflicting results. Although negative association between *NAT1* polymorphisms and cancer risk [12] has been reported, two independent studies [18, 19] have observed a significant association of the *NAT1* polymorphism with lung cancer risk. However these studies should be interpreted cautiously because these do not agree on the *NAT1* risk genotype. Given that chemical compounds in tobacco are inactivated by phase II enzymes, it has been proposed that head and neck cancer risk could be modified by *NAT* genotypes. Head and neck cancer are strongly associated with smoking, and a few studies have explored the role of *NAT1* polymorphisms in the risk of developing head and neck cancer in smokers. However, these findings are inconsistent. Either a decreased risk in carriers with the variant *NAT1**10 [91] or a lack of association between *NAT1* polymorphisms and the risk of head and neck cancer have been reported [43]. The *NAT1**10 variant was associated with increased risk of breast cancer among women who consumed well-done meat [78]. The other study, however, reported that no significant association of *NAT* polymorphisms and breast cancer risk was identified [92]. First, ethnic differences of *NAT1* polymorphisms may contribute to the discrepancy of these results. In addition, the influence of genetic variants may be masked by other as-yet-unidentified causal genes involved in carcinogenesis, because gene-to-gene and gene-to-environment interactions have been of great interest to evaluate the exact roles of genetic polymorphisms in carcinogenesis. However, lack of the original data limited our further evaluation of potential gene-to-gene and gene-to-

environment interactions and to validate the influence of ethnic differences on the effects of functional polymorphism on cancer risk.

In addition, analysis based on cancer types stratified by the source of controls indicated only significantly reduced risk of colorectal cancer and pancreatic cancer in studies using hospital-based controls. However, these hospital-based studies may have biases because certain benign diseases that have different risk of developing malignancy can be included in such controls and they are not the best representative of general population. Thus, the use of a proper and representative cancer-free control subjects is critically important for reducing study biases in such case-control studies.

The present meta-analysis has some limitations. First, lack of the original data of the reviewed studies limited our evaluation on the potential both gene-gene and gene-environment interactions. Second, the controls were not uniformly defined. Some studies employed a healthy population as the reference group, whereas others used hospital patients without gastric cancer as the reference group. Thus, the controls may not always truly represent the underlying source populations. In addition, our meta-analysis was based on unadjusted OR estimates because not all published studies were presented with adjusted ORs. ORs were provided in some other studies, however, the ORs were not adjusted by the same potential confounders. Fourth, we only considered the *NAT1* metabolic enzyme. Because NAT2 enzyme is involved in the bioactivation and detoxification of heterocyclic amine, it may also play a role in modifying cancer risk, this may increase the misclassification of measured variables. Therefore, these results should be interpreted cautiously.

In summary, the present meta-analysis suggests no significant association between *NAT1* slow genotype and cancer risk except for pancreatic cancer. However, we observed a reduce risk in pancreatic cancer among the *NAT1* slow acetylators. Further studies evaluating the effects of gene-gene and gene-environment interactions may eventually lead to a better and more comprehensive understanding of the association between *NAT1* genotypes and cancer risk.

Disclosure of conflict of interest

None.

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