RESEARCH ARTICLE

NAD(P)H: Quinone Oxidoreductase 1 (NQO1) C609T Gene Polymorphism Association with Digestive Tract Cancer: A Meta-analysis

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Abstract

NAD(P)H: quinone oxidoreductase 1 (NQO1) C609T gene polymorphisms have been reported to influence the risk for digestive tract cancer (DTC) in many studies; however, the results remain controversial and ambiguous. We therefore carried out a meta-analysis of published case-control studies to derive a more precise estimation of any associations. Electronic searches were conducted on links between this variant and DTC in several databases through April 2012. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of associations in fixed or random effect models. Heterogeneity and publication bias were also assessed. A total of 21 case-control studies were identified, including 6,198 cases and 7,583 controls. Overall, there was a statistically significant association between the NQO1 C609T polymorphism and DTC risk (TT vs. CC: OR=1.224, 95%CI=1.055-1.421; TT/CT vs. CC: OR=1.195, 95%CI=1.073-1.330; TT vs. CT/CC: OR=1.183, 95%CI=1.029-1.359; T vs. C: OR=1.180, 95%CI=1.080-1.290). When stratified for tumor location, the results based on all studies showed the variant allele 609T might have a significantly increased risk of upper digest tract cancer (UGIC), but not colorectal cancer. In the subgroup analysis by ethnicity, we observed a significantly risk for DTC in Caucasians. For esophageal and gastric cancer, a significantly risk was found in both populations, and for colorectal, a weak risk was observed in Caucasians, but not Asians. This meta-analysis suggested that the NQO1 C609T polymorphism may increase the risk of DTC, especially in the upper gastric tract.

Keywords: Digestive tract cancer - polymorphism - NQO1 - meta-analysis

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Introduction

Digestive tract cancers are the most common malignant tumors worldwide, with three million new cases each year (Parkin et al., 2005; Kanavos, 2006), of which Esophageal carcinoma is the sixth leading cause of cancer death in the world (Enzinger et al., 2003), Gastric cancer is the fourth commonest cancer and the second commonest cause of cancer death, globally (Ferlay et al., 2008), colorectal cancer is also the third most common cancer in males and the second in females (Jemal et al., 2011). Despite advances in surgery and chemotherapy, it still has a higher mortality rates. The mechanism of DTC is still unclear. The carcinogenesis of DTC is a complex, multi-factorial, and multistep event, in which many factors are implicated, such as genetic factors, cigarette smoking, heavy alcohol drinking, and poor dietary pattern (Compare et al., 2010). Except for these shared risk factors, different primary sites of DTC cancers have different risk factors and thus different etiologies. For example, Helicobacter pylori infection is involved in gastric cancer (Asombang et al., 2012), Barrett's esophagus is a key risk factor for esophageal carcinoma (Racette et al., 2011). In recent years, genetic factors are increasingly recognized as major contributors to DTC, also including single nucleotide polymorphisms (SNPs) (Chen et al., 2010).

NAD(P)H: Quinone Oxidoreductase 1 (NQO1), known as diphtheria toxin diaphorase (DT-diaaphorase), is a cytosolic flavoenzyme and its gene is located on chromosome 16q22. Many single nucleotide polymorphisms in this gene are thought to influence expression of the encoding proteins and/or activity of encoding proteins thereby predisposing to disease (Nebert et al., 2002). A common single nucleotide polymorphism at position 609 of the NQO1 promoter region has been described in years. (dsSNP ID: rs1800566) (Traver et al., 1997). NQO1 has been described as an anticancer enzyme and detoxicant, but the variant allele will reduce enzymatic activity according to in vitro studies (Siegel et al., 1999). So many epidemiological studies have been done to evaluate the association between NQO1 C609T polymorphism and cancers. The relationships between NQO1 C609T polymorphism and lung, bladder and colorectal cancers have been comprehensively studied by

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Table 1. Characteristics of the Studies Included in the Meta-analysis

Author	Year	Population	Source of control	Sample size		Type of cancer	Genotyping method	*P* value for HWE
				Cases	controls			
Sarbia M(1)	2003	Germany	population	61	252	Esophageal cancer	PCR-RFLP	0.87308
Zhang(1)	2003	China	hospital	193	141	Esophageal cancer	PCR-RFLP	0.95644
Zhang(2)	2003	Germany	hospital	257	252	Esophageal cancer	PCR-RFLP	0.87308
Von Rahden BH	2004	Germany	hospital	140	260	Esophageal cancer	PCR-RFLP	0.38345
Marjani HA	2010	Iran	hospital	93	50	Esophageal cancer	PCR-RFLP	0.76727
Hamajima N(1)	2002	Japan	hospital	102	399	Esophageal cancer	PCR-CTPP	0.52442
Zhang	2003	China	hospital	193	141	Esophageal cancer	PCR-RFLP	0.95644
Sarbia M(2)	2003	Germany	population	120	252	Gastric cancer	PCR-RFLP	0.87308
Sarbia M(3)	2003	Germany	population	203	252	Gastric cancer	PCR-RFLP	0.52442
Hamajima N(2)	2002	Japan	hospital	143	399	Gastric cancer	PCR-CTPP	0.592629
Malik MA	2011	Kashmir	population	108	195	Gastric cancer	PCR-RFLP	0.69113
Li	2004	China	hospital	124	165	Gastric cancer	PCR-RFLP	0.86125
Mitrou PN	2007	UK	population	894	946	Colorectal cancer	PCR-RFLP	0.18828
Nisa H	2010	Japan	population	685	778	Colorectal cancer	PCR-RFLP	0.56676
Tijhuis MJ	2008	Netherland	population	740	698	Colorectal cancer	PCR-RFLP	0.96596
Harth V	2000	Germany	population	323	205	Colorectal cancer	PCR-RFLP	0.52442
Hamajima N(3)	2002	Japan	hospital	146	399	Colorectal cancer	PCR-RFLP	0.98214
Hlavata I	2010	Czech	population	495	495	Colorectal cancer	TaqMan	0.96603
Northwood EL	2010	UK	population	317	296	Colorectal cancer	TaqMan	0.96603
Van der Logt EM	2006	Netherland	population	371	415	Colorectal cancer	PCR-RFLP	0.9978
Sachse C	2002	UK	population	490	593	Colorectal cancer	PCR-RFLP	0.84023

F, fixed-effect model; R, random-effect model; DTC, digestive tract cancer

meta-analyses (Chao et al., 2006).

To date, a considerable number of studies have been conducted to investigate the association between NQO1 gene polymorphism and DTC susceptibility in humans. However, the results remain controversial and ambiguous. So, we performed this meta-analysis to get a more precise estimation of the association.

Materials and Methods

Publication search

Articles were identified by an electronic search on Medline, Embase, China National Knowledge Infrastructure (CNKI) and the Cochrane Library using the following keywords: "quinone oxidoreductace" OR "NQO1" OR "DT-diaphorase" OR "DTD" OR "quinone reductase" OR " NAD(P)H dehydrogenase(quinone)" AND "esophageal" OR "gastric" OR "colorectal" and "CRC"(last search: April 2012). Eligible studies were retrieved and examined carefully. Review articles were hand-searched to find additional eligible studies. The studies included must meet the following criteria: (1) evaluation of the NQO1 C609T polymorphism and DTC cancer risk; (2) case-control study; (3) at least two comparison groups (DTC group vs. control group).

Data extraction

Two authors (CLZ and FX) independently extracted data and entered them in a customized database. Reviews, nonoriginal articles, and studies on DTC cell lines and animal models were excluded from our meta-analysis. Discrepancies about inclusion of studies and interpretation of data were resolved by discussion, consensus, and arbitration by (CHL or QH). The following data were collected from each study: first author' name, year of publication, ethnicity, country of origin, sources of controls, genotyping method, Hardy-Weinberg equilibrium(HWE), and number of different genotypes in cases and controls.

Statistical methods

Statistical analyses were performed by STATA 10.0 (STATA Corp., College Station, TX). Crude ORs with 95%CIs were used to assess the strength of association between the NQO1 C609T polymorphism and DTC cancer risk. We evaluated the risk of the codominant model (TT VS. CC), the dominant model (TT/CT vs. CC), the recessive model (TT vs. TA/AA) and allele model (T vs. C), respectively. Heterogeneity assumption was checked by the chi-square based Q test and was regarded to indicate significance for $P<0.05$ (Cochran, 1954). The fixed model would be used if the test of heterogeneity was not significant; otherwise the random-effect model would be used (Mantel et al., 1959; DerSimonian et al., 1986). Heterogeneity among studies was assessed by I2 statistic interpreted as the proportion of total variation contributed by variation between studies. Sensitivity analysis was carried out by including and excluding studies not in HWE (Thakkinstian et al., 2005). An estimate of potential publication bias was evaluated by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggested a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, if $P<0.05$, the publication bias was statistically significant. Subgroup analyses were performed by the location of tumor, ethnicities and sources of controls.

Results

Characteristics of included studies

Totally, 34 papers were identified after an initial

Table 2. Meta-analysis of the association between the NQO1 (609C/T) polymorphism and the risk of DTC

Type of cancer	Number of studies	Comparison	Test of association				Test of heterogeneity			Publication bias	
			OR	95% CI	*P* value	Model	Q	*P* value	I^2	*P* value (Egger's)	*P* value (Begg's)
DTC	21	TT vs. CC	1.224	1.055-1.421	0.008	F	28.59	0.096	30.10%	0.075	0.176
		TT/CT vs. CC	1.195	1.073-1.330	0.001	R	39.23	0.006	49.00%	0.156	0.212
		TT vs. CC/CT	1.183	1.029-1.359	0.018	F	27.35	0.126	26.90%	0.11	0.072
		T vs. C	1.18	1.080-1.290	0	R	41.72	0.003	52.10%	0.18	0.289
Esophageal cancer	7	TT vs. CC	1.69	1.240-2.304	0.001	F	9.96	0.126	39.80%	0.764	0.81
		TT/CT vs. CC	1.299	1.085-1.555	0.004	F	12.55	0.051	52.20%	0.368	0.953
		TT vs. CC/CT	1.532	1.159-2.025	0.003	F	10.42	0.108	42.40%	0.764	0.773
		T vs. C	1.289	1.051-1.581	0.015	R	13.17	0.041	54.20%	0.368	0.964
Gastric cancer	5	TT vs. CC	1.599	1.131-2.261	0.008	F	4.27	0.371	6.30%	0.142	0.227
		TT/CT vs. CC	1.361	1.118-1.658	0.002	F	9.16	0.057	56.30%	1	0.775
		TT vs. CC/CT	1.474	1.075-2.020	0.016	F	4.56	0.335	12.30%	0.327	0.279
		T vs. C	1.331	1.145-1.546	0	F	7.02	0.135	43.00%	0.114	0.071
Colorectal cancer	9	TT vs. CC	0.99	0.814-1.205	0.924	F	4.1	0.848	0.00%	0.404	0.309
		TT/CT vs. CC	1.104	1.014-1.202	0.023	F	11.98	0.152	33.20%	0.677	0.826
		TT vs. CC/CT	0.976	0.809-1.177	0.796	F	3.89	0.876	0.00%	0.532	0.518
		T vs. C	1.068	0.995-1.147	0.07	F	11.02	0.201	27.40%	0.835	0.852

F, fixed-effect model; R, random-effect model; DTC, digestive tract cancer

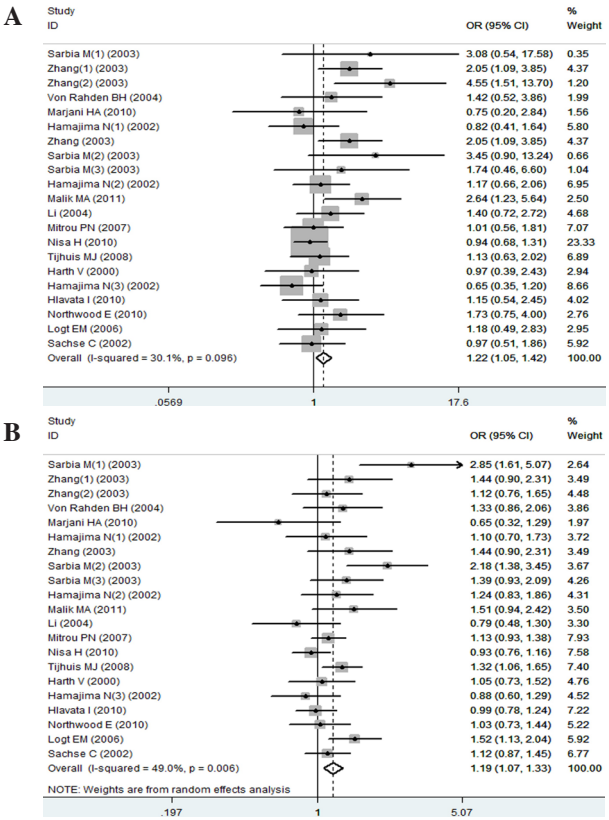

Figure 1. A. Overall Meta-analysis for NQO1 C609T Polymorphism (TT vs. CC) and Digestive Tract Cancer Risk; B. Overall Meta-analysis for NQO1 C609T Polymorphism (TT/CT vs. CC) and Digestive Tract Cancer Risk

search. Based on the exclusion and inclusion criteria in original manuscript, after reading the titles or abstract, 18 studies didn't meet the criteria (6 were not about the gene polymorphisms and DTC risk, 3 were not case-control study, 3 didn't get sufficient information, 1 was a meta-analysis, 1 was not consistent with HWE, and 4 were repeatable studies). So, 16 studies were retrieved for detailed assessment. Of the 16 papers, two of these studies discussed different DTC (Hamajima et al., 2002; Sarbla et al., 2003) and one discussed different subpopulations (Zhang et al., 2003), which we treated independently. Thus, a total of 21 case-control studies (Among these studies, esophageal cancer (n=7) (Hamajima et al., 2002; Sarbla et al., 2003; Zhang et al., 2003; Zhang et al., 2003; vov Rahden et al., 2005; Marjani et al., 2010), gastric cancer (n=5) (Hamajima et al., 2002; Hamajima et al., 2002; Sarbla et al., 2003; Li et al., 2004; Malik et al., 2011), CRC (n=9) (Harth et al., 2000; Harth et al., 2000; Sachse et al., 2002; Hamajima et al., 2002; van der Logt et al., 2006; Mitrou et al., 2007; Tijhuis et al., 2008; Nisa et al., 2010; Hlavata et al., 2010; Northwood et al., 2010) including 6,198 DTC patients and 7,583 controls were included in our meta-analysis. Twelve studies were conducted in Caucasian, and nine in Asian. The characteristics of the studies were showed in Table 1.

Main results of meta-analysis

NQO1 C609T gene polymorphism and DTC: Overall, a total of 21 case-control studies including 6,198 DTC cases and 7,583 healthy controls were in the meta-analysis. A significant heterogeneity was observed in TT/CT vs. CC and T vs. C contrasts (Table 2), and we conducted analyses using the random-effect model .The combined result based on all studies showed that there was statistically significant link between NQO1 C609T polymorphism and DTC risk (TT vs. CC: OR=1.224, 95%CI=1.055-1.421; TT/CT vs. CC: OR=1.195, 95%CI=1.073-1.330; TT vs. CT/CC: OR=1.183, 95%CI=1.029-1.359; T vs. C: OR=1.180, 95%CI=1.080-1.290) (Table 2, Figure 1, 2). In the analysis of ethnic groups, the results showed that T allele carriers had a significantly increased risk of DTC in Caucasians (TT vs. CC: OR=1.318, 95%CI=1.039-1.672), but not Asians (TT vs. CC: OR=1.241, 95%CI=0.913-1.688) (Table 3).

NQO1 C609T gene polymorphism and esophageal cancer: In all, seven studies containing 1,039 esophageal cancer patients and 1,495 healthy controls assessed the association of NQO1 C609T gene polymorphism and esophageal cancer risk. A significant heterogeneity was

Table 3. Meta-analysis of the Association Between the NQO1 (609C/T) Polymorphism and DTC in Subgroup

Subgroup analyses(n)	TT vs. CC			TT/CT vs. CC			TT vs. CC/CT			T vs. C		
	OR(95%CI)	P_h	I^2	OR(95%CI	P_h	I^2	OR(95%CI)	P_h	I^2	OR(95%CI)	P_h	I^2
DTC												
Caucasian(n=12)	1.318(1.039-1.672)	0.455	0.00%	1.269(1.109-1.452)	0.014	53.80%	1.248(0.986-1.580)	0.487	0.00%	1.232(1.105-1.374)	0.041	45.80%
Asian(n=9)	1.241(0.913-1.688)	0.027	53.80%	1.046(0.919-1.191)	0.175	30.50%	1.201(0.913-1.581)	0.033	52.20%	1.105(0.954-1.279)	0.023	55.00%
Esophageal cancer												
Caucasian(n=3)	2.648(1.375-5.101)	0.295	18.10%	1.557(0.938-2.584)	0.027	72.30%	2.473(1.301-4.698)	0.236	30.70%	1.459(1.169-1.822)	0.13	51.00%
Asian(n=4)	1.480(1.039-2.107)	0.122	48.20%	1.191(0.927-1.529)	0.23	30.30%	1.367(1.001-1.866)	0.122	48.30%	1.190(1.004-1.411)	0.086	55.70%
Gastric cancer												
Caucasian(n=2)	2.401(0.931-6.195)	0.477	0.00%	1.692(1.250-2.290)	0.147	52.40%	2.051(0.800-5.259)	0.582	0.00%	1.582(1.216-2.059)	0.166	47.90%
Asian(n=3)	1.503(1.035-2.182)	0.234	31.10%	1.164(0.898-1.508)	0.165	44.60%	1.412(1.009-1.975)	0.156	46.10%	1.226(1.021-1.471)	0.274	22.80%
Colorectal cancer												
Caucasian(n=7)	1.117(0.854-1.459)	0.963	0.00%	1.158(1.053-1.275)	0.295	17.70%	1.065(0.817-1.389)	0.94	0.00%	1.130(1.038-1.230)	0.588	0.00%
Asian(n=2)	0.862(0.646-1.151)	0.296	8.30%	0.921(0.764-1.109)	0.772	0.00%	0.894(0.684-1.167)	0.241	27.30%	0.933(0.818-1.065)	0.404	0.00%

P_h, *P*-value of Q test for heterogeneity test; DTC, digestive tract cancer

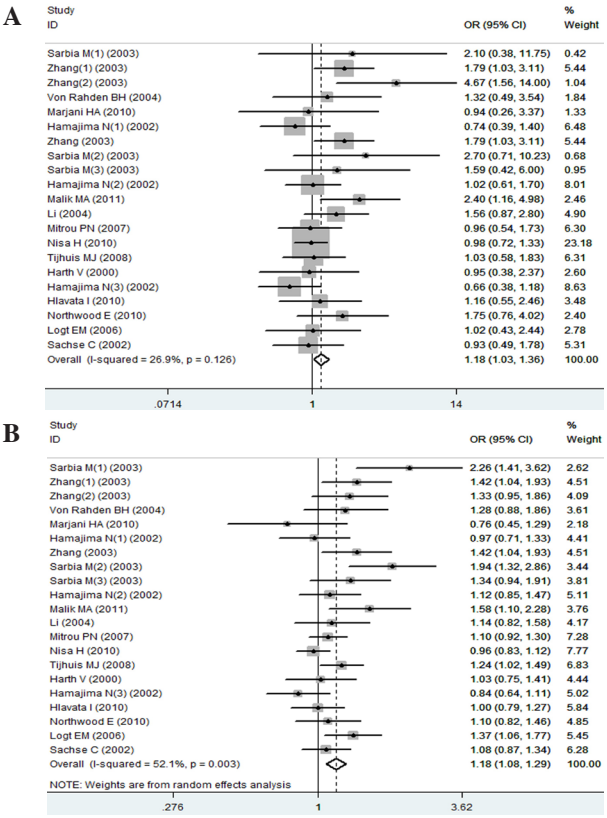

Figure 2. A. Overall Meta-analysis for NQO1 C609T Polymorphism (TT vs. CC/CT) and Digestive Tract Cancer Risk; B. Overall Meta-analysis for NQO1 C609T Polymorphism (T vs. C) and Digestive Tract Cancer Risk

observed only in the T vs. C contrast (*P*=0.041), and we conducted analyses using the random-effect model. There was statistically significant link between NQO1 C609T polymorphism and esophageal cancer risk (Table 2). In the analysis of ethnic groups, significant associations were observed in both groups. The detail information was shown in Table 3.

NQO1 C609T gene polymorphism and gastric cancer: Totally, five studies including 698 cases and 1,263 controls examined the effect of NQO1 C609T gene polymorphism on gastric cancer. No significant heterogeneity was observed in all contrasts of genotypes. Similarly, contrasts of genotypes also detected a significant association (Table 2). In the analysis of ethnic groups, significant associations were also observed in both groups (Table 3).

NQO1 C609T gene polymorphism and colorectal cancer: Nine studies which contained 4,461 cases and 4,825 controls investigated the possible relationship of NQO1 C609T gene polymorphism with colorectal cancer. No significant heterogeneity was observed, and we conducted analyses using the fixed-effect model. A significant association was observed only in the TT/CT vs. CC genotype. The comparisons of other genotypes did not detect any statistical associations (Table 2). In the subgroup analysis by ethnicity, a weak risk was found for Caucasians, but not Asians (Table 3).

Publication bias and sensitivity analysis

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plot did not reveal obvious asymmetry and the Egger's test suggested the absence of publication bias (*P*=0.176 for TT vs. CC; *P*=0.212 for TT/CT vs. CC; *P*=0.072 for TT vs. CC/CT; *P*=0.289 for T vs. C) (Table 2).

Discussion

NQO1 is an antioxidant enzyme, important in the detoxification of environmental carcinogens. A single nucleotide polymorphism(C→T) at position 609 of the NQO1 cDNA has been associated with susceptibility to tumors induced by chemical carcinogens. In this study, we performed a systematic review of association between the NQO1 C609T and risk for DTC based on 21 case-control studies for which information was available. Our meta-analysis provided evidence that TT/CT genotypes of NQO1 C609T were associated with a significantly increased risk for DTC. Many investigators also have reported similar observation in other cancers. A meta-analysis showed that the variant 609TT/CT genotypes were associated with an increased risk for lung, bladder and colorectal cancer, which was similar with our current finding (Chao et al., 2006).

However, in our meta-analysis, we found that the significant association between NQO1 C609T polymorphism and DTC risk might be mainly attributed to UGIC, but not colorectal cancer, especially in Asians. In previous meta-analysis study, Wang et al. (2012) and his colleagues' meta-analysis study also showed that the NQO1 gene 609 C> T polymorphism might contribute to esophageal cancer occurrence, especially in Eastern Asians, but in our study, no significantly different was observed in Caucasians or Asians. For colorectal cancer, no significant associations were found between NQO1

C609T polymorphism and colorectal cancer risk, but in the subgroup analysis by ethnicity; significant associations were observed for colorectal cancer in Caucasians, which was similar with previous meta-analysis study (Zhou et al., 2011; Chen et al., 2012). The reason may be that the different cancer sites had a dissimilar prevalence with a difference in clinical feature, prognosis and possibly in genetic and environmental epidemiology (Benedix et al., 2010); and the other reason may be the limited number of studies.

Another major finding of this study was that the association of NQO1 C609T polymorphism and DTC susceptibility may be not according to ethnicity, but there was a higher significance among Caucasians (Table 3), which was not similar with previous study. That showed a wide variation of the allele frequency had been observed across ethnic groups, the homozygous variant genotype was as rare as 2% in white population but as frequent as 20% in Asian populations (Kelsey et al., 1997). The reasons may be that the limited number of studies also made the results from subgroup analysis by ethnicity less reliable; in addition, the differences in genetic backgrounds and the environment they lived in may influence the association between the NQO1 C609T polymorphism and risk for DTC. Therefore, our results should be interpreted with caution.

It is worth mentioning that testing for deviations from HWE in controls is an important requirement in population genetic studies. HWE is based on five basic assumptions: 1) the population is large (i.e., there is no genetic drift); 2) there is no gene flow between populations, from migration or transfer of gametes; 3) mutations are negligible; 4) individuals are mating randomly; and 5) natural selection is not operating on the population. Deviation from HWE may point to genotyping error, racial heterogeneity, or selection bias (Trikalinos et al., 2006).

Similar to other systematic reviews and meta-analyses, some limitations of this meta-analysis should be acknowledged. First, lacking of the original data (the small sample size in some subgroup analyses) limited our further evaluation of potential interaction. Second, some controls were selected from hospital population; such people might have benign digestive tract diseases and correspond to a potentially incremental risk of DTC. Third, our meta-analysis was based on unadjusted estimates, while a more precise analysis could be conducted if the individual study data and records were available. Fourth, many environmental and genes factors may affect the risk of DTC; our finding may be due to the context of the gene with other factors.

In conclusion, these suggested that NQO1 C609T polymorphism may be associated with the risk of DTC in Caucasians and Asians, and this genetic variant may increase the risk of UGIC, but not colorectal cancers in Asians. More well-designed and unbiased prospective studies with larger sample size should be evaluated the associations.

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References

Asombang AW, Kelly P (2012). Gastric cancer in Africa: what do we know about incidence and risk factors? *Trans R Soc Trop Med Hyg*, **106**, 69-74.

Benedix F, Kube R, Meyer F, et al (2010). Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum*, **53**, 57-64.

Chao C, Zhang ZF, Berthiller J, Boffetta P, Hashibe M (2006). NAD(P)H:quinone oxidoreductase 1 (NQO1) Pro187Ser polymorphism and the risk of lung, bladder, and colorectal cancers: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, **15**, 979-87.

Chen B, Zhou Y, Yang P, Wu XT (2010). Glutathione S-transferase M1 gene polymorphism and gastric cancer risk: an updated analysis. *Arch Med Res,* **41**, 558-66.

Chen J, Lin Y, Zhang R, Huang ZJ, Pan XG (2012). Contribution of NAD(P)H quinone oxidoreductase 1 (NQO1) Pro187Ser polymorphism and risk of colorectal adenoma and colorectal cancer in Caucasians: a meta-analysis. *Arch Med Res*, **43**, 58-66.

Cochran WG (1954). The combination of estimates from different experiments. *Biometrics*, **10**, 101-29.

Compare D, Rocco A, Nardone G (2010). Risk factors in gastric cancer. *Eur Rev Med Pharmacol Sci*, **14**, 302-8.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials,* **7**, 177-88.

Enzinger PC, Mayer RJ (2003). Esophageal cancer. *N Engl J Med*, **349**, 2241-52.

Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.

Hamajima N, Matsuo K, Iwata H, et al (2002). NAD(P)H: quinone oxidoreductase 1(NQO1) C609T polymorphism and the risk of eight cancers for Japanese. *Int J Clin Oncol*, **7**, 103-8.

Harth V, Donat S, Ko Y, et al (2000). NAD(P)H quinone oxidoreductase 1 codon 609 polymorphism and its association to colorectal cancer. *Arch Toxicol*, **73**, 528-31.

Hlavata I, Vrana D, Smerhovsky Z, et al (2010). Association between exposure-relevant polymorphisms in CYP1B1, EPHX1, NQO1,GSTM1,GSTP1 and GSTT1 and risk of colorectal cancer in a Czech population. *Oncol Rep*, **24**, 1347-53.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Kanavos P (2006). The rising burden of cancer in the developing world. *Ann Oncol*, **17**, 15-23.

Kelsey KT, Ross D, Traver RD, et al (1997). Ethnic variation in the prevalence of a common NAD(P)H quinone oxidoreductase polymorphism and its implications for anti-cancer chemotherapy. *Br J Cancer*, **76**, 852-54.

Li Y, Zhang JH, Guo W, et al (2004). Polymorphism of NAD(P) H dehydrogenase (quinone)1 (NQO1) C609T and risk of esophageal neoplasm. *Zhonghua Liu Xing Bing Xue Za Zhi*, **25**, 731.

Malik MA, Zargar SA, Mittal B (2011). Role of NQO1 609C>T and NQO2-3423G>A polymorphisms in susceptibility to gastric cancer in Kashmir valley. *DNA Cell Bio*, **30**, 297-303.

Mantel N, Haenszel W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, **22**, 719-48.

Marjani HA, Biramijamal F, Rakhshani N, Hossein-Nezhad A, Malekzadeh R (2010). Investigation of NQO1 genetic polymorphism, NQO1 gene expression and PAH-DNA adducts in ESCC. A case-control study from Iran. *Genet Mol Res*, **9**, 239-49.

Mitrou PN, Watson MA, Loktionov AS, et al (2007). Role of NQO1C609T and EPHX1 gene polymorphisms in the association of smoking and alcohol with sporadic distal colorectal adenomas: results from UKFSS Study. *Carcinogenesis*, **28**, 875-82.

Nebert DW, Roe AL, Vandale SE, Bingham E, Oakley GG (2002). NAD(P)H: quinone oxidoreductase (NQO1) polymorphism, exposure to benzene, and predisposition to disease: a HuGE review. *Genet Med,* **4**, 62-70.

Nisa H, Kono S, Yin G, et al (2010). Cigarette smoking, genetic polymorphisms and colorectal cancer risk: the Fukuoka Colorectal Cancer study. *BMC Cancer*, **10**, 274.

Northwood EL, Elliott F, Forman D, et al (2010). Polymorphisms in xenobiotic metabolizing enzymes and diet influence colorectal adenoma risk. *Pharmacogenet Genomics*, **20**, 315-26.

Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Racette AL, Miller RT (2011). Esophageal carcinoma: matching patients with treatment methods. *JAAPA*, **24**, 28, 30-1.

Sachse C, Smith G, Wilkie MJ, et al (2002). A pharmacogenetic study to investigate the role of dietary carcinogens in the etiology of colorectal cancer. *Carcinogenesis*, **23**, 1839-49.

Sarbla M, Brrzer M, Siegel D, et al (2003). Association between NAD(P)H: Quinone oxidoreductase 1 (NQO1) inactivating C609T polymorphism and adenocarcinoma of the upper gastrointestinal tract. *Int J Cancer*, **107**, 381-6.

Siegel D, McGuinness SM, Winski SL, Ross D (1999). Genotype-phenotype relationships in studies of a polymorphism in NAD(P)H:quinone oxidoreductase 1. *Pharmacogenetics*, **9**, 113-21.

Thakkinstian A, McElduff P, D'Este C, Duffy D, Attia J (2005). A method for meta-analysis of molecular association studies. *Stat Med*, **24**, 1291-306.

Tijhuis MJ, Visker MH, Aarts JM, et al (2008). NQO1 and NFE212 polymorphisms, fruit and vegetable intake and smoking and the risk of colorectal adenomas in an endoscopy-based population. *Int J Cancer*, **122**, 1842-8.

Traver RD, Siegel D, Beall HD, et al (1997). Characterization of a polymorphism in NAD(P)H: quinone oxidoreductase (DT-diaphorase). *Br J Cancer*, **75**, 69-75.

Trikalinos TA, Salanti G, Khoury MJ, Ioannidis JP (2006). Impact of violations and deviations in Hardy–Weinberg equilibrium on postulated gene-disease associations. *Am J Epidemiol*, **163**, 300-9.

van der Logt EM, Bergevoet SM, Roelofs HM, et al (2006). Role of epoxide hydrolase, NAD(P)H: quinone oxidoreductase, cytochrome P450 2E1 or alcohol dehydrogenase genotypes in susceptibility to colorectal cancer. *Mutat Res*, **593**, 39-49.

vov Rahden BH, Stein HJ, Langer R, et al (2005). C609T Polymorphism of the NAD(P) H: Quinone oxidoreductase 1 gene does not significantly affect susceptibility for esophageal adenocarcinoma. *Int J Cancer*, **113**, 506-8.

Wang Z, Hu J, Zhong J (2012). Meta-analysis of the NAD(P)H: quinine oxidoreductase 1 gene 609 C>T polymorphism with esophageal cancer risk. *DNA Cell Biol*, **31**, 560-7.

Zhang J, Schulz WA, Li Y, et al (2003). Association of NAD(P)H: quinone oxidoreductase1 (NQO1) C609T polymorphism with esophageal squamous cell carcinoma in a German Caucasian and a northern Chinese population. *Carcinogenesi*, **24**, 905-9.

Zhang JH, Li Y, Wang R, et al (2003). The NAD(P)H: quinone oxidoreductase 1 C609T polymorphism and susceptibility to esophageal cancer. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, **20**, 544-6.

Zhou JY, Shi R, Yu HL, Zheng WL, Ma WL (2011). Association of NQO1 Pro187Ser polymorphism with the risks for colorectal cancer and colorectal adenoma: a meta-analysis. *Int J Colorectal Dis*, **27**, 1123-4.