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The *NQO1* polymorphism C609T (Pro187Ser) and cancer susceptibility: a comprehensive meta-analysis

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Background: Evidence is increasingly emerging about multiple roles for the NAD(P)H quinone oxidoreductase 1 enzyme in cancer. The C609T (rs1800566, Pro187Ser) null polymorphism of the *NQO1* gene contributes significantly to the variation in enzymatic activity across different populations. *NQO1* C609T polymorphism was thoroughly investigated with respect to cancer susceptibility. The results were inconsistent partly due to low sample sizes. The aim of the present work was to perform a meta-analysis to assess association for all common cancer sites separately and in combination.

Methods: Our meta-analysis involved 92 studies including 21 178 cases and 25 157 controls. Statistical analysis involved individual cancer sites and the combined cancer risk. Association was tested under different genetic models.

Results: We found a statistically significant association between the variant T allele and overall cancer risk in the worldwide population (for the TT *vs* CC model, OR = 1.18 (1.07–1.31), $P = 0.002$, $I^2 = 36\%$). Stratified analysis revealed that this association was largely attributed to the Caucasian ethnicity (for the TT *vs* CC model, OR = 1.28 (1.12–1.46), $P = 0.0002$, $I^2 = 1\%$). Stratification by tumour site showed significant association for bladder cancer in the worldwide population (for the TT *vs* CC model, OR = 1.70 (1.17–2.46), $P = 0.005$, $I^2 = 0\%$), and in the Asian population (for the TT *vs* CC model, 1.48 (1.14–1.93), $P = 0.003$, $I^2 = 16\%$). Positive association was also found for gastric cancer in the worldwide population under the dominant model (OR = 1.34 (1.09–1.65), $P = 0.006$, $I^2 = 15\%$).

Conclusion: Our results indicate that the C609T polymorphism of the *NQO1* gene is an important genetic risk factor in cancer.

Cancer is a leading cause of death worldwide. It is estimated that the burden of cancer will increase up to 22.2 million new cases diagnosed annually worldwide by 2030, which represents an increase by 75% compared with the statistics of 2008 (Bray *et al*, 2012).

It is now recognised that sporadic cancer is a complex and multifactorial disease involving the contribution and interaction of several genetic and environmental factors. In the recent years, polymorphisms in low-penetrance genes involved in anti-carcinogenic biochemical pathways have been a subject of thorough investigation in the context of identifying the genetic risk factors for cancer development.

The NAD(P)H quinone oxidoreductase 1 enzyme (EC 1.6.5.2), encoded by the *NQO1* gene, which is mapping to chromosomal location 16q22.1, was hypothesised to have a crucial role in the protection against oxidative stress and was shown to be a multifunctional antioxidant and an exceptionally versatile cytoprotector (Dinkova-Kostova and Talalay, 2010). Furthermore, recent studies indicated protective roles for NQO1 unrelated to its enzymatic activity and involved in apoptosis, as it was found to act as a stabiliser for the tumor suppressor protein p53 (Asher *et al*, 2002a). Figure 1 summarizes the multiple protective roles of NQO1 known so far.

Several polymorphisms were identified in the *NQO1* gene. However, by far the most commonly studied and the most

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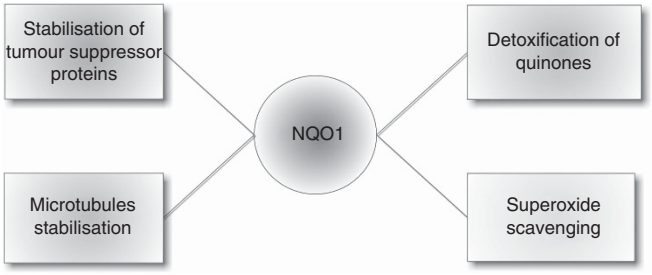

Figure 1. The multiple and general roles of NQO1 in the protection against the development of cancer.

biochemically influential polymorphism is the C609T polymor phism (dbSNP: rs1800566) at exon 6 of the gene, which results in a proline-to-serine amino-acid change at codon 187 of the protein. The *NQO1* C609T polymorphism was shown to have an established and strong impact on enzymatic activity of the expressed protein by extremely decreasing stability, as the variant enzyme is rapidly ubiquitinated and degraded by the proteasome (Siegel *et al*, 2001). Thus, it was found that homozygosity for the variant T allele results in virtually complete elimination of enzymatic activity (2–4% activity of the wild type), whereas heterozygosity yields decreased enzymatic activity by threefold compared with homozygosity for the wild-type allele (Kuehl *et al*, 1995; Siegel *et al*, 2001).

A large number of studies reported the investigation of the role of *NQO1* C609T polymorphism in the susceptibility for developing several types of cancer. However, the results were inconsistent rather than conclusive, possibly due to the small sample size in the majority of studies. Although a few number of meta-analyses were performed in an attempt to overcome the problem of low statistical power in individual studies, these meta-analyses considered individual cancer sites separately (Yuan *et al*, 2011; Liu and Zhang, 2011; Guo *et al*, 2012; Zhou *et al*, 2012). Recognised as a global and versatile antioxidant and cytoprotector ubiquitously expressed in all tissues, the gene for NQO1 is proposed to have common roles among all histopathologically different types of cancer arising in different sites or tissues. Therefore, it is biologically plausible to study the effects of polymorphisms in the *NQO1* gene with respect to overall cancer risk. The aim of the present study was to conduct a global meta-analysis to investigate the role of *NQO1* C609T polymorphism with respect to the overall cancer risk, and perform new or updated site-specific meta-analyses involving all common sites of cancer previously investigated in relation to the *NQO1* C609T polymorphism.

MATERIALS AND METHODS

Search strategy. The PubMed database was searched to identify case–control association studies involving cancer and *NQO1* C609T polymorphism. To ensure comprehensive searching, we used only general keywords: 'NQO1' or 'NADPH:quinone oxidoreductase 1' and 'Cancer' and 'polymorphism' without applying search filters. Articles were retrieved on 17 January 2013. Article searching was repeated independently by searching the Scopus database to compare with the PubMed search results and identify articles not indexed in PubMed. All articles were initially reviewed by abstract and title examination to select for relevant articles, which were subjected to further screening.

Study selection and inclusion/exclusion criteria. Relevant articles were subjected to the following predetermined inclusion criteria: (1) studies investigating the *NQO1* C609T polymorphism with respect to disease susceptibility. (2) Studies with case–control design. (3) Studies including full genotyping data (CC, CT, and TT counts in the case and control groups). (4) Genotype distribution of *NQO1* C609T in the control group is in Hardy–Weinberg equilibrium (HWE). (5) Studies involving adult cancer (childhood leukaemia studies were excluded). (6) Studies involving primary cancer (therapy-related cancer studies were excluded). (7) Studies published in English.

Data extraction. The following information about the eligible studies was extracted: first author name, year of publication, country of study, ethnicity of studied subjects, tumour site, full genotyping data for the case and control groups, and source of control groups (hospital- or population-based controls). When an article included several ethnic groups or cancer sites, each comparison was treated as a separate study. In a few studies where the racial descent of study subjects was not plainly stated, ethnicity was inferred on the basis of the largest ethnic group inhabiting the country of study.

Statistical analysis. We strictly followed published guidelines and recommendations for quality assessment in meta-analyses of genetic association studies (Stroup *et al*, 2000; Minelli *et al*, 2009). (1) We tested five different genetic models and avoided assuming only one 'wrong' genetic model. (2) Between-study heterogeneity and publication bias were thoroughly assessed. (3) Concordance with HWE was comprehensively tested for all studies. (4) Sensitivity analysis was performed to check for the impact of individual studies or subgroups of studies. (5) Meta-regression analysis was performed to identify any potential source of heterogeneity. (6) The random effects model was utilised to calculate odds ratios and 95% confidence intervals (CIs) whenever moderate-to-high heterogeneity was found.

We tested all relevant studies for concordance of the genotypic distribution of the *NQO1* C609T polymorphism in the control group with the HWE principle using the χ^2-test, and considered P-values < 0.05 as statistically significant. Association between the *NQO1* C609T polymorphism and cancer risk was investigated under different genetic models; namely, the dominant (CC *vs* CT + TT), recessive (CC + CT *vs* TT), homozygous codominant (TT *vs* CC), heterozygous codominant (CC *vs* CT) and allele contrast model (C *vs* T). The strength of association was assessed by calculating the odds ratios and 95% confidence intervals and the Z-test was used to evaluate statistical significance with P-values < 0.01 considered as statistically significant. Stratified analysis by cancer site, ethnicity, and minor allele frequency (MAF) in controls was conducted. Cancer sites with less than three studies were all grouped under a category termed 'other' in the overall population analysis. Studies involving mixed populations belonging to different ethnic groups were assigned the 'Mixed' ethnicity category.

Between-study heterogeneity was assessed using the Cochran's Q-test (Cochran, 1954) by calculating the $P_{\text{heterogeneity}}$ value, and was quantitated by calculating the I^2 statistic. A random effects model using the DerSimonian and Laird method was used to calculate the OR and 95% CI for comparisons with moderate-to-high heterogeneity ($I^2 > 25\%$). Otherwise, a fixed-effects model using the Mantel–Haenszel method was utilised (Petitti *et al*, 1994). Moreover, meta-regression analysis (Thompson and Sharp, 1999) was used to identify three possible sources of heterogeneity including ethnicity, tumour site, and MAF.

Sensitivity analysis was performed by sequential omission of individual studies (leave-one-out analysis) and tumour sites for various genetic models in the Asian, Caucasian, and overall population.

Publication bias was evaluated graphically using the Begg's funnel plot and statistically using the method of Egger's linear regression test (Egger *et al*, 1997).

Comprehensive Meta-Analysis (Version 2, Biostat, Englewood NJ, USA) and OpenMetaAnalyst (http://www.cebm.brown.edu/open_meta) were used for statistical analyses.

RESULTS

Characteristics of retrieved studies. Systematic screening was performed to identify relevant and eligible studies (Figure 2). PubMed search returned 251 articles (retrieved on 17 January 2013). Initial examination involving abstracts and titles lead to the exclusion of 130 non-relevant articles. Of the remaining 121 relevant articles, 15 articles were found to lack complete genotyping data, 8 articles were published in other languages than English, 12 articles involved childhood leukaemia, and 5 articles involved secondary cancer. As a result, 81 articles including 97 studies (comparisons) were found to be eligible (Table 1). Upon testing for concordance with the HWE principle, five studies were found to deviate from HWE and were excluded. Finally, a total of 76 articles involving 92 studies and 21 178 cases and 25 157 controls were included. Scopus searching did not return any additional eligible studies not indexed in PubMed. About 80% of studies involved either Caucasian or Asian populations. There were 50 studies on Caucasian populations, 24 on Asians, 6 studies on Indians, 4 studies on Arabs, 2 studies on African Americans, 2 studies on Turks, and single studies on Persian, Hawaiian, Hispanic, and mixed populations.

Quantitative synthesis. We observed significant variation of the T allele frequency across different ethnicities in healthy controls (Figure 3). Statistically significant association was found for the total population when all studied cancer sites were combined, and under all studied genetic models (Table 2), with the strongest association found under the TT *vs* CC model (OR = 1.18 (1.07–1.31), $P = 0.002$). On stratification by ethnicity, we found statistically significant associations for the Caucasian subgroup under all genetic models with the strongest association found under the TT *vs* CC model (OR = 1.28 (1.12–1.46), $P = 0.0002$). Stratification by cancer site revealed statistically significant associations for bladder cancer (for the TT *vs* CC model, OR = 1.48 (1.14–1.93), $P = 0.003$), and gastric cancer (for the dominant model, OR = 1.34 (1.09–1.65), $P = 0.006$) (Table 2).

We investigated the interaction between the two major ethnic groups (Caucasian and Asian) and cancer site with respect to the effects of *NQO1* C609T on cancer susceptibility (Table 3). Significant association was found for bladder cancer in Asians (for the TT *vs* CC model, OR = 1.70 (1.17–2.46), $P = 0.005$).

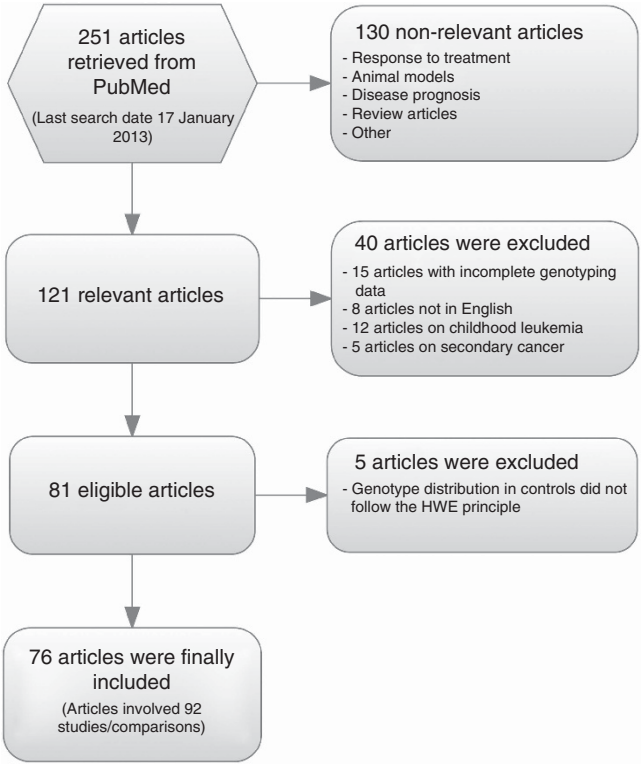

Figure 2. Flow chart demonstrating study selection steps.

Test of heterogeneity and meta-regression analysis. Heterogeneity tests for the total group involving combined cancer sites showed statistically significant ($P_{heterogeneity} < 0.05$) but quantitatively moderate heterogeneity with I^2 values < 50% (Table 2). However, when stratified by ethnicity, heterogeneity was found statistically insignificant and quantitatively low for the Caucasian subgoup (I^2 values < 25%), except for the heterozygous codominant model ($I^2 = 26\%$) (Table 2). Furthermore, the homozygous codominant (TT *vs* CC) and the recessive (TT *vs* CT + CC) models showed extremely low heterogeneity in Caucasians ($I^2 = 1\%$) indicating generally consistent findings among studies in these populations. By contrast, tests for the Asian subgroup showed statistically significant and quantitatively moderate-to-high heterogeneity, which pointed to the Asian ethnicity as an important source of heterogeneity. This was confirmed by meta-analysis regression (Table 4), which identified the Asian subgroup as a major source of heterogeneity relative to the Caucasian subgroup ($P = 0.03$). This was also supported by general examination of the forest plot (Figure 4) where it was evident that the majority of Caucasian studies yielded consistently odds ratios > 1 for the TT *vs* CC model (indicating increased risk for the TT homozygous genotype), whereas Asian studies yielded more scattered odds ratios. Additionally, when the MAF in controls were grouped into 'high' (> 35%) or 'low' (< 35%) categories, the 'high' MAF subgroup, which correlates with the Asian subgroup (Figure 3), was found to be a significant source of heterogeneity relative to the 'low' MAF subgroup ($P < 0.001$). MAF was also examined as a continuous variable and was confirmed to be a major source of heterogeneity as indicated by the regression plot (Figure 5) and *P*-value of < 0.001 (Table 4).

Sensitivity analysis. Single studies or single tumour sites were sequentially excluded from the meta-analysis to investigate the relative weights of individual studies or data sets. The odds ratios and *P*-values were not statistically altered indicating that the meta-analysis was generally robust.

Publication bias. Publication bias was assessed for the two most commonly investigated genetic models (homozygous codominant and allele contrast models). The shapes of funnel plots did not indicate any evidence of significant asymmetry (Figure 6). In addition, the Egger's test did not yield any evidence of publication bias ($t = 0.97$, $P = 0.33$, for TT *vs* CC, and $t = 0.28$, $P = 0.78$ for T *vs* C).

DISCUSSION

Our meta-analysis included 92 studies and involved 21 178 cases and 25 157 controls. Although all common cancer sites except for bladder and stomach cancers showed no statistically significant association, the combined analysis showed that the variant T allele of *NQO1* C609T polymorphism is strongly associated with overall cancer risk in the total population. Stratification by ethnicity revealed that association is significant for the Caucasian populations, which comprised the largest part of available studies

Table 1. Database of relevant studies in the meta-analysis

First author[a]/Year	Cancer site[b]	Country	Ethnicity[c]	Study design	Cases/ controls	Case (CC/CT/TT), *T*%	Control (CC/CT/TT), *T*%	HW *P*-value (control)
Singh *et al* (2011)	Breast	India	Indian	PB	200/200	(45/131/24), 0.45	(34/149/17), 0.46	0
Aston *et al* (2005)	Breast	USA	Caucasian	PB	564/1212	(369/177/18), 0.19	(824/347/41), 0.18	0.55
Hamajima *et al* (2002)	Breast	Japan	Asian	HB	237/640	(100/103/34), 0.36	(240/286/114), 0.40	0.17
Siegelmann-Danieli *et al* (2002)	Breast	USA	Caucasian	PB	346/235	(222/115/9), 0.19	(168/61/6), 0.16	0.87
Lajin *et al* (2013)	Breast	Syria	Arab	PB	122/139	(71/41/10), 0.25	(87/43/9), 0.22	0.25
Sarmanova *et al* (2004)	Breast	Czech	Caucasian	PB	238/310	(166/55/17), 0.19	(221/83/6), 0.15	0.58
Hong *et al* (2007)	Breast	USA	Caucasian	PB	496/495	(325/157/14), 0.19	(323/151/21), 0.19	0.53
Menzel *et al* (2004)	Breast	Austria	Caucasian	PB	218/424	(133/76/9), 0.22	(290/126/8), 0.17	0.18
Li *et al* (2005)	Head and neck	USA	Caucasian	HB	724/1226	(484/209/31), 0.19	(805/388/33), 0.19	0.09
Harth *et al* (2008)	Head and neck	Germany	Caucasian	HB	295/296	(199/84/12), 0.18	(197/87/12), 0.19	0.54
Soucek *et al* (2010)	Head and neck	Czech/Poland	Caucasian	HB	116/121	(92/21/3), 0.12	(83/35/3), 0.17	0.76
Begleiter *et al* (2005)	Head and neck	USA/Canada	Caucasian	HB	350/366	(245/94/11), 0.17	(249/106/11), 0.17	0.94
Benhamou *et al* (2001)	Head and neck	Finland	Caucasian	HB	250/172	(143/94/13), 0.24	(105/62/5), 0.21	0.24
Siraj *et al* (2008)	Head and neck	Saudi Arabia	Arab	PB	49/504	(30/18/1), 0.20	(295/177/32), 0.24	0.43
Park *et al* (2003)	Bladder	USA	Caucasian	HB	232/239	(142/82/8), 0.21	(163/66/10), 0.18	0.32
Schulz *et al* (1997)	Bladder	Germany	Caucasian	PB	99/260	(68/26/5), 0.18	(195/61/4), 0.13	0.76
Sanyal *et al* (2004)	Bladder	Sweden	Caucasian	PB	299/124	(206/85/8), 0.17	(83/34/7), 0.19	0.18
Terry *et al* (2005)	Bladder	USA	Caucasian	HB	235/214	(156/70/9), 0.19	(150/58/6), 0.16	0.89
Hung *et al* (2004)	Bladder	Italy	Caucasian	HB	201/214	(113/75/13), 0.25	(135/66/13), 0.21	0.21
Moore *et al* (2004)	Bladder	Argentina	Hispanic	PB	106/108	(62/35/9), 0.25	(61/40/7), 0.25	0.9
Pandith *et al* (2011)	Bladder	India	Indian	HB	104/120	(44/53/7), 0.32	(70/44/6), 0.23	0.79
Wang *et al* (2008)	Bladder	Taiwan	Asian	HB	300/300	(70/148/82), 0.52	(94/136/70), 0.46	0.13
Choi *et al* (2003)	Bladder	Korea	Asian	HB	177/170	(81/68/28), 0.35	(94/60/16), 0.27	0.17
Broberg *et al* (2005)	Bladder	Sweden	Caucasian	PB	61/156	(43/13/5), 0.19	(107/46/3), 0.17	0.44
Nishino *et al* (2008)	Cervical	Japan	Asian	HB	124/117	(76/26/22), 0.28	(69/29/19), 0.29	0
Niwa *et al* (2005)	Cervical	Japan	Asian	HB	131/320	(50/54/27), 0.41	(134/139/47), 0.36	0.27
Zhang *et al* (2003b)	Gastric	China	Asian	PB	124/165	(40/55/29), 0.46	(52/86/27), 0.42	0.39
Hamajima *et al* (2002)	Gastric	Japan	Asian	HB	143/640	(48/71/24), 0.42	(240/286/114), 0.40	0.08
Malik *et al* (2011)	Gastric	India	Indian	HB	107/195	(51/38/18), 0.35	(112/68/15), 0.25	0.31
Sarbia *et al* (2003)	Gastric	Germany	Caucasian	PB	320/252	(200/110/10), 0.20	(185/63/4), 0.14	0.6
Liu *et al* (2013)	Hepatocellular	China	Asian	HB	476/526	(138/220/118), 0.48	(191/235/100), 0.41	0.07
Akkiz *et al* (2010)	Hepatocellular	Turkey	Turk	HB	167/167	(86/71/10), 0.27	(96/62/9), 0.24	0.81
Goode *et al* (2011)	Ovarian	USA	Caucasian	HB	928/1035	(579/319/30), 0.20	(695/308/32), 0.18	0.76
Olson *et al* (2004)	Ovarian	USA	Caucasian	PB	123/182	(82/33/8), 0.20	(120/55/7), 0.19	0.82
Harth *et al* (2000)	Colorectal	Germany	Caucasian	PB	323/205	(209/102/12), 0.20	(135/62/8), 0.19	0.79
Sameer *et al* (2010)	Colorectal	India	Indian	HB	86/160	(53/29/4), 0.22	(116/39/5), 0.15	0.45
Nisa *et al* (2010)	Colorectal	Japan	Asian	PB	684/777	(259/336/89), 0.38	(282/392/103), 0.38	0.07
Hamajima *et al* (2002)	Colorectal	Japan	Asian	HB	146/640	(61/68/17), 0.35	(240/286/114), 0.40	0.08
Sachse *et al* (2002)	Colorectal	UK	Caucasian	PB	490/593	(316/157/17), 0.19	(398/173/22), 0.18	0.56
Begleiter *et al* (2006)	Colorectal	Canada	Caucasian	PB	298/349	(201/79/18), 0.19	(239/102/8), 0.17	0.45
van der Logt *et al* (2006)	Colorectal	Netherlands	Caucasian	PB	369/415	(225/134/10), 0.21	(292/112/11), 0.16	0.95
Hlavata *et al* (2010)	Colorectal	Czech	Caucasian	PB	495/495	(346/134/15), 0.17	(344/138/13), 0.17	0.85
von Rahden *et al* (2005)	Oesophageal	Germany	Caucasian	HB	140/260	(91/42/7), 0.20	(185/65/10), 0.16	0.17
Sarbia *et al* (2003)	Oesophageal	Germany	Caucasian	PB	61/252	(30/29/2), 0.27	(185/63/4), 0.14	0.6
Marjani *et al* (2010)	Oesophageal	Iran	Persian	HB	93/50	(51/35/7), 0.26	(22/24/4), 0.32	0.47
di Martino *et al* (2007)	Oesophageal	UK	Caucasian	HB	141/93	(96/43/2), 0.17	(55/33/5), 0.23	0.99
Zhang *et al* (2003a)	Oesophageal	Germany	Caucasian	PB	257/252	(183/56/18), 0.18	(185/63/4), 0.14	0.6
Zhang *et al* (2003a,b)	Oesophageal	China	Asian	PB	193/141	(51/92/50), 0.50	(48/70/23), 0.41	0.77
Umar *et al* (2012)	Oesophageal	India	Indian	HB	200/200	(92/93/15), 0.31	(93/86/21), 0.32	0.87
Malik *et al* (2012)	Oesophageal	India	Indian	HB	135/195	(68/43/24), 0.34	(112/68/15), 0.25	0.31
Hamajima *et al* (2002)	Oesophageal	Japan	Asian	HB	102/640	(37/52/13), 0.38	(240/286/114), 0.40	0.08
Sorensen *et al* (2005)	Lung	Denmark	Caucasian	PB	254/267	(162/83/9), 0.20	(176/80/11), 0.19	0.62
Yang *et al* (2007)	Lung	Korea	Asian	HB	314/347	(110/158/46), 0.4	(120/166/61), 0.41	0.78
Cote *et al* (2009)	Lung	USA	Caucasian	PB	387/405	(271/97/19), 0.17	(271/119/15), 0.18	0.67
Lin *et al* (2000)	Lung	China	Asian	HB	95/136	(12/63/20), 0.54	(41/73/22), 0.43	0.27
Lewis *et al* (2001)	Lung	UK	Caucasian	HB	82/145	(56/24/2), 0.17	(111/32/2), 0.12	0.86
Xu *et al* (2001)	Lung	USA	Caucasian	HB	780/1096	(513/246/21), 0.18	(715/341/40), 0.19	0.93

Table 1. (Continued)

First author[a]/Year	Cancer site[b]	Country	Ethnicity[c]	Study design	Cases/ controls	Case (CC/CT/TT), *T*%	Control (CC/CT/TT), *T*%	HW *P*-value (control)
Xu *et al* (2001)	Lung	USA	Mixed	HB	34/78	(18/14/2), 0.26	(20/41/17), 0.48	0.64
Yin *et al* (2001)	Lung	China	Asian	HB	84/84	(28/39/17), 0.43	(26/41/17), 0.45	0.91
Lin *et al* (2003)	Lung	Taiwan	Asian	HB	198/332	(57/141/0), 0.36	(95/237/0), 0.36	0
Hamajima *et al* (2002)	Lung	Japan	Asian	HB	192/640	(87/71/34), 0.36	(240/286/114), 0.40	0.26
Benhamou *et al* (2001)	Lung	Finland	Caucasian	HB	150/172	(85/55/10), 0.25	(105/62/5), 0.21	0.24
Alexandrie *et al* (2004)	Lung	Sweden	Caucasian	PB	524/530	(345/168/11), 0.18	(368/153/9), 0.16	0.12
Cote *et al* (2009)	Lung	USA	African-American	PB	113/121	(77/32/4), 0.18	(79/36/6), 0.20	0.48
Guo *et al* 2012	Lung	China	Asian	HB	681/597	(187/326/168), 0.49	(172/281/144), 0.48	0.17
Saldivar *et al* (2005)	Lung	USA	Caucasian	PB	683/683	(454/205/24), 0.19	(480/186/17), 0.16	0.84
Saldivar *et al* (2005)	Lung	USA	African-American	PB	36/36	(15/17/4), 0.35	(15/14/7), 0.39	0.28
Saldivar *et al* (2005)	Lung	USA	Caucasian	PB	107/107	(67/33/7), 0.22	(69/35/3), 0.19	0.56
Chen *et al* 1999	Lung	USA	Asian	PB	109/167	(54/48/7), 0.28	(64/78/25), 0.38	0.88
Chen *et al* 1999	Lung	USA	Caucasian	PB	135/171	(81/49/5), 0.22	(105/62/4), 0.20	0.14
Chen *et al* 1999	Lung	USA	Hawaiian	PB	83/102	(61/18/4), 0.16	(60/39/3), 0.22	0.26
Lan *et al* (2004)	Lung	China	Asian	PB	119/109	(37/57/25), 0.45	(32/54/23), 0.46	0.98
Chan *et al* (2005)	Lung	China	Asian	HB	75/162	(25/37/13), 0.42	(45/83/34), 0.47	0.71
Sunaga *et al* 2002	Lung	Japan	Asian	HB	198/152	(83/93/22), 0.35	(52/77/23), 0.40	0.53
Gra *et al* (2008)	Leukemia	Russia	Caucasian	PB	83/177	(52/28/3), 0.20	(119/52/6), 0.18	0.91
Hishida *et al* (2005)	Leukaemia	Japan	Asian	HB	51/476	(13/31/7), 0.44	(200/201/75), 0.37	0.04
Begleiter *et al* (2009)	Leukaemia	Canada	Caucasian	HB	323/299	(219/93/11), 0.18	(196/96/7), 0.18	0.23
Ouerhani *et al* (2013)	Leukaemia	Tunisia	Arab	PB	100/106	(46/45/9), 0.32	(66/32/8), 0.23	0.15
Voso *et al* (2007)	Leukaemia	Italy	Caucasian	PB	157/155	(101/48/8), 0.20	(108/40/7), 0.17	0.2
Seedhouse *et al* (2002)	Leukaemia	UK	Caucasian	PB	134/175	(95/30/9), 0.18	(110/53/12), 0.22	0.12
Kang *et al* (2008)	Multiple myeloma	Korea	Asian	PB	114/163	(37/70/7), 0.37	(50/80/33), 0.45	0.92
Lincz *et al* (2007)	Multiple myeloma	Australia	Caucasian	PB	100/201	(60/36/4), 0.22	(142/56/3), 0.15	0.34
Maggini *et al* (2008)	Multiple myeloma	Italy	Caucasian	PB	245/124	(149/82/14), 0.22	(77/40/7), 0.22	0.55
Schulz *et al* (1997)	Renal cell carcinoma	Germany	Caucasian	PB	131/260	(84/44/3), 0.19	(195/61/4), 0.13	0.76
Longuemaux *et al* (1999)	Renal cell carcinoma	France	Caucasian	HB	173/210	(102/60/11), 0.24	(136/66/8), 0.20	1
Hamajima *et al* (2002)	Lymphoma	Japan	Asian	HB	108/640	(40/51/17), 0.39	(240/286/114), 0.40	0.08
Gra *et al* (2008)	Lymphoma	Russia	Caucasian	PB	76/177	(54/20/2), 0.16	(119/52/6), 0.18	0.91
Kim *et al* (2009)	Lymphoma	Korea	Asian	HB	713/1689	(234/362/117), 0.42	(585/850/254), 0.40	0.054
Al-Dayel *et al* (2008)	Lymphoma	Saudi Arabia	Arab	PB	150/504	(94/37/19), 0.25	(295/177/32), 0.24	0.43
Bartsch *et al* (1998)	Pancreatic	USA/Europe	Caucasian	HB	81/76	(53/21/7), 0.22	(46/24/6), 0.24	0.27
Mohelnikova-Duchonova *et al* (2011)	Pancreatic	Czech	Caucasian	HB	235/265	(164/64/7), 0.17	(187/71/7), 0.16	0.93
Hamajima *et al* (2002)	Prostate	Japan	Asian	HB	56/640	(17/30/9), 0.43	(240/286/114), 0.40	0.08
Mandal *et al* (2012)	Prostate	India	Indian	HB	195/250	(105/67/23), 0.29	(164/72/14), 0.20	0.11
Steinbrecher *et al* (2010)	Prostate	Germany	Caucasian	PB	248/492	(163/80/5), 0.18	(333/133/26), 0.19	0.01
Ergen *et al* (2007)	Prostate	Turkey	Turk	HB	45/59	(23/17/5), 0.30	(23/26/10), 0.39	0.57
Stoehr *et al* (2012)	Prostate	Germany	Caucasian	HB	119/232	(76/37/6), 0.21	(166/60/6), 0.16	0.84
Steiner *et al* (1999)	Prostate	Germany	Caucasian	PB	54/100	(37/15/2), 0.18	(67/31/2), 0.18	0.46

Abbreviations: HB = hospital-based, PB = population-based.
[a]Reference are provided in the list of references. Five studies not in HW ($P<0.05$) were excluded from the meta-analysis.
[b]The head and neck cancer category includes oral, laryngeal, pharyngeal and thyroid cancers.
[c]The ethnicity 'Asian' was used to refer to populations inhabiting eastern Asia.

on the subject, but not for the Asian ethnicity, which was another largely represented ethnicity in the available studies. Furthermore, although heterogeneity for the total group was only moderate, as shown by I^2 values in Table 2, we identified the Asian ethnicity studies as the major source of heterogeneity observed. The high MAF (>35%), which strongly correlates with the Asian ethnicity, as can be seen in Figure 3, was also a major source of heterogeneity.

The C609T is one of very few known and common single-nucleotide polymorphisms that completely eliminate enzymatic activity, and its biological impact *in vivo* is undoubted. The NQO1 enzyme has been increasingly attracting attention in cancer and more roles unrelated to its classical metabolic functions (Figure 7) are being constantly discovered (Figure 1). First, the NQO1 enzyme has the classical role of catalysing the obligatory two-electron reduction of a broad range of exogenous and endogenous quinones to their respective hydroquinones, preventing the one-electron reduction of these compounds into semiquinones and a variety of reactive oxygen species (Iyanagi and Yamazaki, 1970; Bianchet *et al*, 2004). Second, NQO1 was shown to have an additional antioxidant effect by directly and independently scavenging superoxides (Siegel *et al*, 2004), a function that is

Table 2. Association between *NQO1* C609T polymorphism and cancer susceptibility based on tumour location and ethnicity under different genetic models

			TT *vs* CC			TC *vs* CC			TT *vs* TC + CC			TT + TC *vs* CC			T *vs* C		
	No. of studies	Cases/ controls	OR (95% CI), *P*	*P*-het	I^2	OR (95% CI), *P*	*P*-het	I^2	OR (95% CI), *P*	*P*-het	I^2	OR (95% CI), *P*	*P*-het	I^2	OR (95% CI), *P*	*P*-het	I^2
Site																	
Breast	7	2221/3455	1.19 (0.76–1.85), 0.45	0.02	59	1.10 (0.97–1.24), 0.13	0.36	9	1.16 (0.76–1.77), 0.5	0.03	57	1.10 (0.98–1.23), 0.11	0.25	23	1.09 (0.95–1.26), 0.2	0.08	47
Head and Neck	6	1784/2685	1.24 (0.88–1.74), 0.22	0.57	0	0.91 (0.79–1.04), 0.18	0.57	0	1.27 (0.91–1.78), 0.17	0.58	0	0.94 (0.82–1.07), 0.35	0.54	0	0.98 (0.88–1.10), 0.73	0.47	0
Bladder	10	1814/1905	**1.48 (1.14–1.93), <0.01**	0.30	16	**1.26 (1.08–1.46), <0.01**	0.47	0	1.29 (1.01–1.64), 0.12	0.28	17	**1.29 (1.12–1.48), <0.01**	0.51	0	**1.23 (1.10–1.38), <0.01**	0.58	0
Gastric	4	694/1252	1.55 (1.00–2.41), 0.05	0.23	31	1.25 (0.96–1.62), 0.09	0.25	27	1.49 (0.94–2.35), 0.09	0.14	44	**1.34 (1.09–1.65), <0.01**	0.32	15	1.29 (1.05–1.58), 0.02	0.16	42
Colorectal	8	2891/3634	0.99 (0.80–1.23), 0.95	0.23	25	1.08 (0.94–1.25), 0.29	0.13	37	0.99 (0.80–1.21), 0.91	0.24	24	1.08 (0.94–1.24), 0.28	0.12	39	1.06 (0.94–1.20), 0.33	0.08	44
Oesophageal	9	1322/2083	1.35 (0.81–2.26), 0.25	<0.01	63	1.12 (0.89–1.42), 0.34	0.04	50	1.29 (0.78–2.12), 0.32	<0.01	64	1.17 (0.93–1.49), 0.19	0.02	56	1.16 (0.94–1.44), 0.17	<0.01	67
Lung	22	5235/6307	0.96 (0.78–1.18), 0.7	0.06	35	0.97 (0.87–1.09), 0.64	0.04	38	0.96 (0.84–1.10), 0.57	0.42	3	0.97 (0.86–1.09), 0.57	<0.01	47	0.97 (0.89–1.07), 0.57	0.01	45
Leukaemia	5	797/912	1.21 (0.76–1.92), 0.41	0.92	0	1.10 (0.77–1.55), 0.61	0.04	60	1.17 (0.74–1.84), 0.5	0.98	0	1.10 (0.80–1.52), 0.54	0.06	56	1.08 (0.87–1.35), 0.48	0.17	38
Multiple myeloma	3	459/488	0.88 (0.25–3.11), 0.84	0.02	75	1.23 (0.92–1.64), 0.17	0.59	0	0.80 (0.22–2.92), 0.74	0.01	77	1.15 (0.87–1.52), 0.14	0.28	22	1.03 (0.68–1.58), 0.88	0.02	73
Lymphoma	4	1047/3010	1.17 (0.94–1.46), 0.17	0.35	9	0.94 (0.74–1.18), 0.58	0.21	33	1.19 (0.82–1.73), 0.36	0.14	45	1.02 (0.88–1.18), 0.08	0.60	0	1.04 (0.94–1.16), 0.43	0.80	0
Prostate	5	469/1281	1.48 (0.82–2.67), 0.19	0.18	36	1.25 (0.98–1.61), 0.08	0.40	2	1.34 (0.79–2.29), 0.28	0.22	30	1.26 (0.93–1.70), 0.14	0.20	33	1.19 (0.90–1.58), 0.23	0.08	52
Other	9	2445/3041	1.45 (1.16–1.81), <0.01	0.96	0	1.20 (1.07–1.35), <0.01	0.60	0	1.34 (1.09–1.65), <0.01	0.98	0	1.23 (1.10–1.38), <0.01	0.64	0	1.21 (1.10–1.32), <0.01	0.77	0
Ethnicity																	
Caucasian	50	13682/15613	**1.28 (1.13–1.46), <0.01**	0.45	1	**1.10 (1.03–1.17), <0.01**	0.05	26	**1.25 (1.11–1.42), <0.01**	0.46	1	**1.11 (1.06–1.17), <0.01**	0.08	23	**1.11 (1.06–1.16), <0.01**	0.11	20
Asian	24	5571/6645	1.02 (0.86–1.20), 0.851	<0.01	58	1.06 (0.93–1.20), 0.39	0.14	24	0.99 (0.87–1.14), 0.92	<0.01	47	1.04 (0.94–1.15), 0.47	0.01	44	1.01 (0.94–1.10), 0.73	<0.01	56
Other	18	1925/2899	1.26 (0.91–1.74), 0.158	0.03	43	1.04 (0.86–1.25), 0.72	<0.01	52	1.26 (0.94–1.69), 0.12	0.06	36	1.07 (0.88–1.30), 0.48	<0.01	57	1.08 (0.92–1.27), 0.35	<0.01	61
MAF in controls																	
<35	66	15669/18509	**1.35 (1.21–1.51), <0.01**	0.33	7	**1.10 (1.03–1.17), <0.01**	<0.01	32	**1.32 (1.18–1.47), <0.01**	0.34	6	**1.13 (1.07–1.20), <0.01**	0.01	30	**1.14 (1.08–1.19), <0.01**	0.01	30
>35	26	5509/6648	0.95 (0.80–1.13), 0.58	<0.01	58	1.02 (0.92–1.12), 0.71	0.08	29	0.95 (0.83–1.09), 0.49	<0.01	45	1.00 (0.89–1.11), 0.98	<0.01	48	0.98 (0.90–1.06), 0.6	<0.01	58
Total	92	21178/25157	**1.18 (1.07–1.31), 0.002**	<0.01	36	**1.08 (1.02–1.13), 0.005**	<0.01	32	**1.14 (1.04–1.25), 0.006**	<0.01	29	**1.10 (1.04–1.15), <0.001**	<0.01	38	**1.09 (1.04–1.13), <0.001**	<0.01	45

Abbreviations: CI = confidence interval; MAF = minor allele frequency; OR = odds ratio. Statistically significant associations ($P<0.01$) are shown in bold.

Table 3. Interaction between cancer site and ethnicity in the effects of NQO1 C609T on cancer susceptibility

			TT *vs* CC			TC *vs* CC			TT *vs* TC+CC			TT+TC *vs* CC			T *vs* C		
	No. of studies	Cases/ controls	OR (95% CI), *P*	*P*-het	I^2	OR (95% CI), *P*	*P*-het	I^2	OR (95% CI), *P*	*P*-het	I^2	OR (95% CI), *P*	*P*-het	I^2	OR (95% CI), *P*	*P*-het	I^2
Caucasian																	
Breast cancer	5	1862/2676	1.38 (0.75–2.52), 0.3	0.03	63	1.14 (0.99–1.30), 0.06	0.38	4	1.32 (0.72–2.44), 0.37	0.02	65	1.15 (1.01–1.30), 0.03	0.44	0	1.14 (1.00–1.31), 0.05	0.24	27
Head and neck	5	1735/2181	1.33 (0.94–1.89), 0.11	0.75	0	0.91 (0.79–1.04), 0.17	0.44	0	1.37 (0.97–1.94), 0.08	0.78	0	0.94 (0.82–1.08), 0.38	0.40	0	0.99 (0.88–1.11), 0.87	0.40	1
Bladder	6	1127/1207	1.32 (0.73–2.36), 0.36	0.11	44	1.19 (0.99–1.44), 0.07	0.58	0	1.26 (0.69–2.30), 0.45	0.09	48	1.20 (1.00–1.43), 0.05	0.69	0	1.16 (1.00–1.36), 0.05	0.57	0
Colorectal	5	1975/2057	1.25 (0.88–1.78), 0.2	0.41	0	1.12 (0.93–1.34), 0.24	0.15	41	1.21 (0.86–1.72), 0.27	0.33	14	1.13 (0.99–1.29), 0.06	0.27	23	1.12 (1.00–1.26), 0.05	0.44	0
Oesophageal	4	599/857	1.57 (0.49–5.01), 0.44	0.03	67	1.24 (0.74–2.09), 0.42	<0.01	77	1.47 (0.48–4.48), 0.5	0.03	65	1.29 (0.78–2.13), 0.32	<0.01	77	1.27 (0.82–1.94), 0.28	<0.01	77
Lung	9	3102/3576	1.19 (0.91–1.57), 0.21	0.52	0	1.06 (0.96–1.18), 0.26	0.71	0	1.18 (0.90–1.55), 0.24	0.53	0	1.07 (0.97–1.19), 0.16	0.68	0	1.07 (0.98–1.17), 0.12	0.59	0
Leukaemia	3	374/507	1.03 (0.56–1.91), 0.93	0.88	0	1.01 (0.66–1.55), 0.96	0.14	50	1.05 (0.57–1.93), 0.88	0.98	0	1.02 (0.69–1.51), 0.92	0.16	46	1.02 (0.76–1.37), 0.88	0.24	30
Other	13	2908/3413	1.38 (1.04–1.82), 0.02	0.96	0	1.17 (1.05–1.31), <0.01	0.26	19	1.33 (1.00–1.75), 0.05	0.98	0	1.19 (1.07–1.33), <0.01	0.25	19	1.17 (1.07–1.29), <0.01	0.35	9
Asian																	
Bladder	2	477/470	**1.70 (1.17–2.46), <0.01**	0.54	0	1.40 (1.04–1.88), 0.03	0.73	0	1.36 (0.99–1.87), 0.06	0.32	0	**1.49 (1.13–1.96), <0.01**	0.94	0	**1.33 (1.10–1.60), <0.01**	0.51	0
Gastric	2	267/805	1.18 (0.78–1.79), 0.44	0.52	0	1.06 (0.72–1.55), 0.78	0.24	27	1.17 (0.71–1.94), 0.54	0.18	44	1.10 (0.81–1.49), 0.53	0.52	0	1.09 (0.89–1.34), 0.41	0.75	0
Colorectal	2	830/1417	0.79 (0.51–1.24), 0.3	0.17	48	0.93 (0.77–1.13), 0.49	0.99	0	0.82 (0.52–1.28), 0.38	0.13	55	0.91 (0.76–1.09), 0.31	0.60	0	0.91 (0.77–1.07), 0.26	0.24	29
Oesophageal	2	295/781	1.24 (0.46–3.36), 0.67	0.03	79	1.20 (0.86–1.69), 0.28	0.89	0	1.11 (0.43–2.90), 0.83	0.02	81	1.21 (0.88–1.67), 0.24	0.34	0	1.14 (0.75–1.74), 0.54	0.05	73
Lung	9	1867/2394	0.87 (0.66–1.16), 0.35	0.05	48	0.94 (0.75–1.16), 0.55	0.04	50	0.93 (0.79–1.09), 0.35	0.50	0	0.92 (0.73–1.14), 0.42	0.02	56	0.93 (0.81–1.06), 0.27	0.05	49
Lymphoma	2	821/2329	1.10 (0.87–1.41), 0.42	0.46	0	1.07 (0.89–1.27), 0.49	0.98	0	1.06 (0.86–1.33), 0.58	0.41	0	1.04 (0.97–1.12), 0.41	0.79	0	1.05 (0.94–1.18), 0.39	0.54	0
Other	5	1014/2289	0.96 (0.56–1.65), 0.89	<0.01	78	1.12 (0.94–1.33), 0.21	0.36	8	0.89 (0.55–1.45), 0.65	<0.01	78	1.11 (0.87–1.14), 0.42	0.10	48	1.03 (0.81–1.30), 0.84	<0.01	74

Abbreviations: CI = confidence interval; OR = odds ratio. Statistically significant associations ($P<0.01$) are shown in bold.

Table 4. Meta-regression analysis identifying potential sources of heterogeneity under the homozygous codominant model (TT *vs* CC)

	n	Coefficient	Lower bound	Upper bound	*P*
Site					
Head and neck	6	Ref	—	—	—
Breast	7	−0.08	−0.64	0.48	0.78
Bladder	10	0.19	−0.36	0.74	0.50
Gastric	4	0.25	−0.38	0.88	0.43
Colorectal	8	−0.14	−0.69	0.40	0.60
Oesophageal	9	0.12	−0.44	0.69	0.68
Lung	22	−0.23	−0.72	0.25	0.35
Leukaemia	5	0.005	−0.68	0.69	0.99
Multiple myeloma	3	−0.49	−1.31	0.32	0.24
Lymphoma	4	−0.02	−0.62	0.58	0.95
Prostate	5	0.22	−0.46	0.90	0.52
Other	9	0.16	−0.38	0.70	0.57
Ethnicity					
Caucasian	50	Ref	—	—	—
Asian	24	−0.25	−0.47	−0.03	0.03
Other	18	0.015	−0.30	0.32	0.93
MAF (con)					
		−1.563	−2.436	−0.689	<0.001
Low (<35%)	66	Ref	—	—	—
High (>35%)	26	−0.35	−0.55	−0.15	<0.001

Abbreviations: MAF, minor allele frequency.

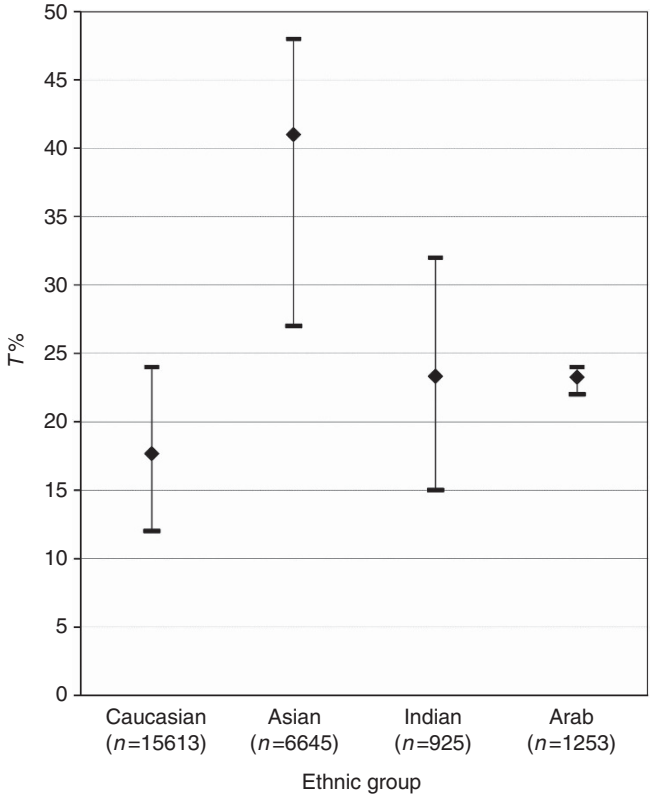

Figure 3. The mean and range of the MAF of *NQO1* C609T in controls in different ethnic groups.

shared with superoxide dismutase. Third, the NQO1 was found to maintain the integrity of microtubule cytoskeleton (Wignall *et al*, 2004), although the exact mechanism by which NQO1 functions in this respect is yet to be established. Fourth, the NQO1 enzyme was recently found to act as a stabiliser for several tumour suppressor proteins (p53, p73, and p33), and this stabilisation was shown to be especially prominent under conditions of oxidative stress (Asher *et al*, 2002a,b). As the C609T polymorphism principally affects the susceptibility of the enzyme to degradation *in vivo*, it affects all aspects of NQO1 function indistinguishably. The overall results of our meta-analysis showed that the variant T allele, which eliminates enzymatic activity, is a susceptibility allele that is compatible with the multiple NQO1 functions described above.

The largest role of NQO1 in cancer susceptibility is attributable to the interaction of the enzyme with environmental exposure. The high MAF of the C609T polymorphism of this 'environmental' enzyme in the Asian population (>35%) compared with the Caucasian population (<20%) suggests that the environmental exposure is widely different among the two populations. In other words, it can be inferred from the difference in MAF, on the basis of natural selection principles, that the rare allele carriers in the Asian populations are not as in disfavour as their counterparts in Caucasian populations. The variation in allele frequency of this polymorphism therefore highlights major environmental differences among the two populations and may in turn partly explain why a significant association was found in Caucasians but not in Asians. Another possible explanation is the widely different genetic structure between the two populations, as the overall effects of *NQO1* C609T polymorphism on cancer susceptibility might be overshadowed or compensated by variants in other metabolic genes (Hengstler *et al*, 1998; Persson *et al*, 1999; Zheng *et al*, 2011). We avoided stratification for other ethnicities due to the very limited number of available studies.

Although most individual studies on Caucasian populations statistically failed to establish an association, it can be seen from the forest plot (Figure 4) that the results of the overwhelming majority of individual studies in Caucasians consistently indicated that the rare allele was a susceptibility factor, as shown by odds ratios >1 for the majority of studies. The lack of statistical association despite the consistency in results among these studies might be due to the low MAF in these populations, as it is difficult from a statistical point of view to establish mild-to-moderate associations with low-frequency alleles because this requires extremely elevated sample sizes. Our meta-analysis may have overcome this problem of low statistical power by combining studies involving all common cancer sites. Combining all common cancer sites seems biologically plausible given the fact that the metabolic (Figure 7) and non-metabolic effects of this enzyme apply in all common cancer sites.

While evidence about the multiple protective roles of the NQO1 enzyme in cancer has been continuously emerging, it should be noted that NQO1 may have adverse effects in some cases. For example, it was found that the NQO1 may bioactivate procarcinogenic coumpounds such as certain nitroaromatic compounds and heterocyclic amines, present in tobacco smoke and certain processed foods (Benson, 1993; Chen *et al*, 1995; Ross *et al*, 2000). Determination of the nature of environmental exposure becomes more important in this context, as the variant T allele that eliminates enzymatic activity would be expected to exert protective effects under such conditions. Indeed, few studies reported protective effects for the TT homozygous genotype in Asian populations for lung cancer (Chen *et al*, 1999; Sunaga *et al*, 2002), and the nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), which was found to induce lung adenocarcinoma in rodents (Ohgaki *et al*, 1985; Hoffmann *et al*, 1996; Hecht, 1999), and is bioactivated by NQO1, was shown to exist in variable amounts in cigarettes of different brands/geographical origins (Gray *et al*, 2000). This may contribute to the heterogeneity of the effects of *NQO1* C609T polymorphism in lung cancer.

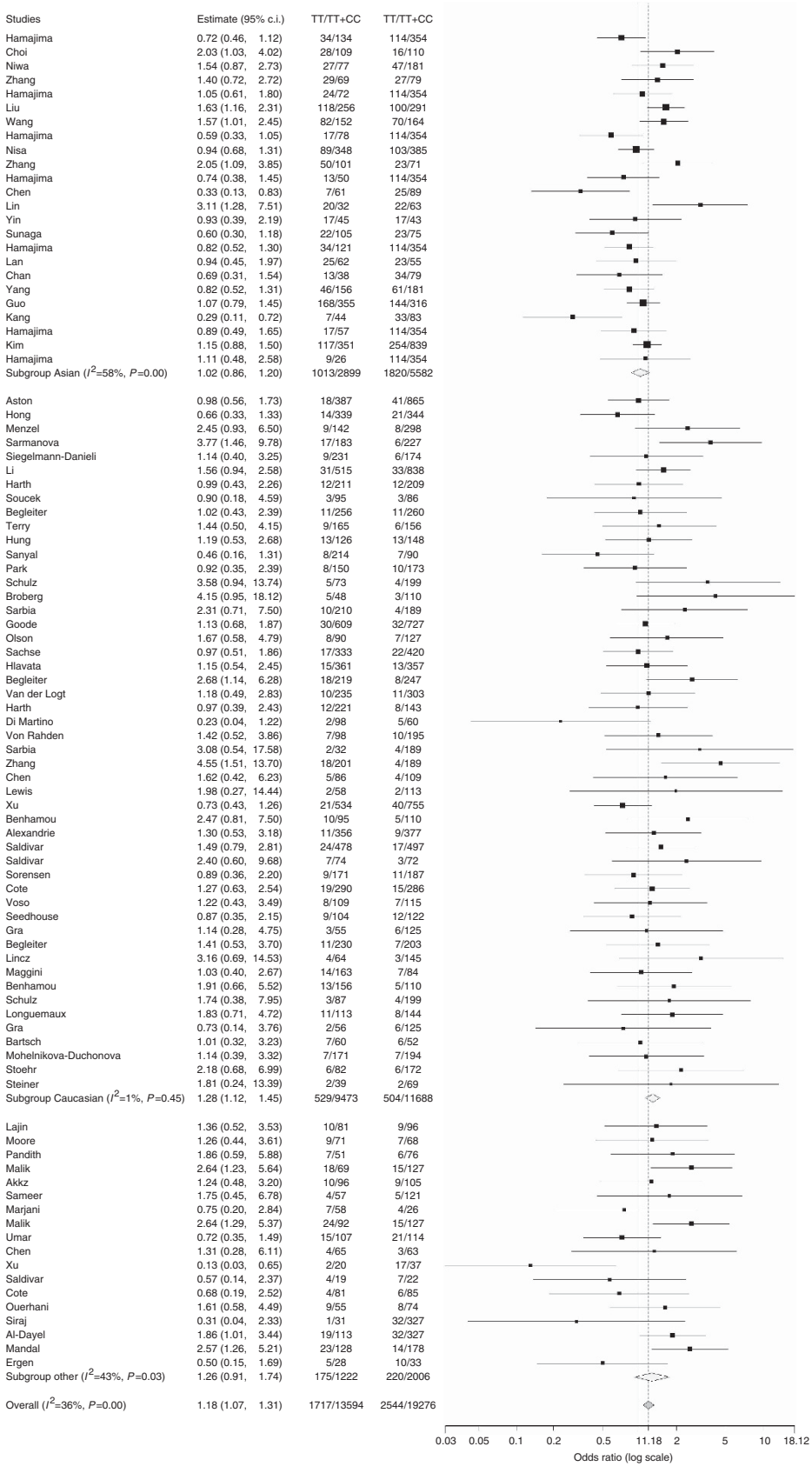

Figure 4. Forest plot of studies included in our meta-analysis under the homozygous codominant model (CC *vs* TT). The plot shows the odds ratios, 95% confidence intervals, I^2 values and $P_{Heterogeneity}$ values. Calculations are based on the random model.

The duality of NQO1 function in detoxifying and bioactivating carcinogens, the manifestation of which is obviously governed by specific environmental patterns, can explain the high heterogeneity observed in Asian populations in the present meta-analysis. The high environmental heterogeneity for the Asian subgroup may in turn explain the observed overall lack of association observed in

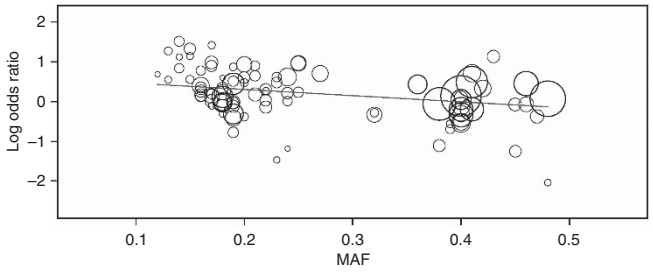

Figure 5. Meta-regression plot of the MAF of *NQO1* C609T in the control populations.

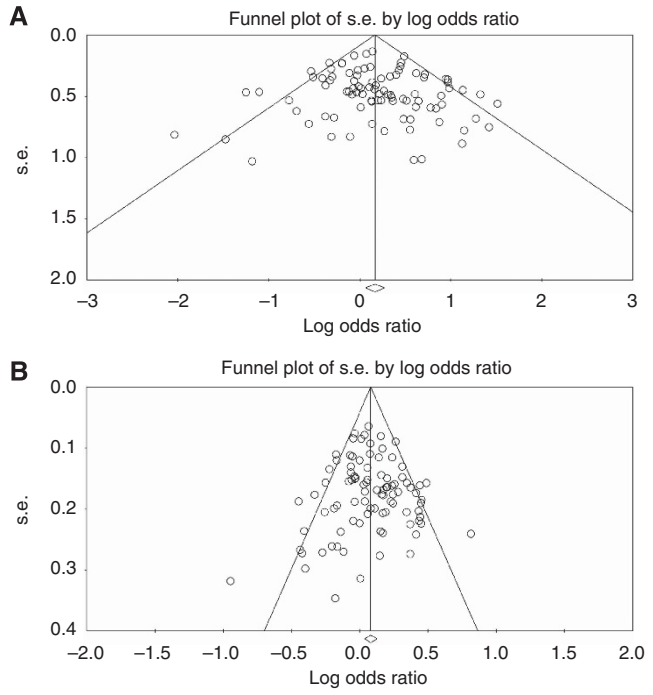

Figure 6. Funnel plots for the assessment of publication bias. Funnel plots assessing publication bias under the (**A**) homozygous codominant model (CC *vs* TT) and (**B**) allele contrast model (T *vs* C).

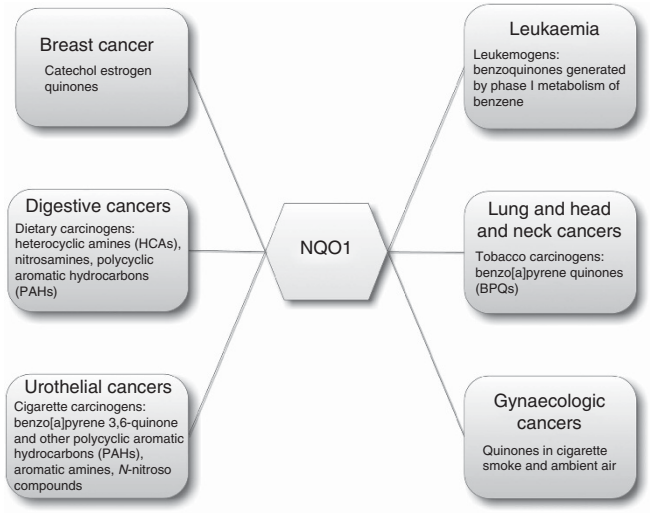

Figure 7. The multiple roles of NQO1 in the metabolism of established carcinogens.

our meta-analysis for this ethnicity. Our meta-analysis did not include studying the interaction between specific environmental factors and *NQO1* C609T polymorphism due to the lack of data in the published reports. More information about environmental exposure patterns in the Asian populations is important to resolve the source of heterogeneity observed in the present meta-analysis and assess the true effects of this polymorphism in these populations.

Although our results support firm conclusions about the association between the *NQO1* C609T polymorphism and total cancer risk and especially in the Caucasian subgroup, where very low heterogeneity and high consistency among studies were found, three major points are worth consideration in the present meta-analysis. First, the calculated odds ratios in the present meta-analysis were necessarily crude unadjusted odds ratios, as information about potential confounders, especially environmental exposure patterns, were rarely found in the individual studies. Second, our lack of association results with respect to certain individual cancer sites should be approached with caution because of the small sample sizes available in the published studies. Finally, the statistical problems of multiple testing in such comprehensive meta-analyses involving a very large number of statistical tests should be considered. Examination of Tables 2 and 3 shows that the total number of statistical tests performed was 165. However, we attempted to approach this issue rationally by only correcting for the number of genetic models tested through dividing the conventional cut-off *P*-value of 0.05 by the number of genetic models tested (five models). Hence, a cut-off *P*-value of 0.01 was considered. We did not correct for the number of cancer sites investigated, as we believe each cancer site should be tested independently, similarly to conducting individual meta-analyses involving single cancer sites. Although there has been some debate about the topic of correcting for multiple testing, we agree about the notion that exaggeration in correcting for multiple testing is as likely to harm scientific evidence as the lack of it, as it may negate true positive associations (Perneger, 1998; Krawczak *et al*, 2001).

CONCLUSION

The present comprehensive meta-analysis suggests the *NQO1* C609T polymorphism as an important genetic factor in the overall risk for developing cancer, especially in Caucasian populations. More case–control association studies are needed to support this finding in individual cancer sites and in various ethnic groups.

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