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Effects of *eNOS* gene polymorphisms on individual susceptibility to cancer: A meta-analysis

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ABSTRACT

Background: Whether endothelial nitric oxide synthase (*eNOS*) polymorphisms are implicated in cancer development remains controversial. Therefore, we performed this study to obtain a more conclusive result on associations between *eNOS* polymorphisms and cancer.

Methods: Literature retrieve was conducted in PubMed, Medline and Embase. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results: Forty-one studies were enrolled for analyses. Pooled overall analyses showed that rs1799983 (dominant model: $p = 0.01$; recessive model: $p = 0.007$; allele model: $p = 0.005$), rs2070744 (recessive model: $p = 0.004$) and rs869109213 (recessive model: $p < 0.0001$; allele model: $p = 0.02$) polymorphisms were all significantly associated with individual susceptibility to cancer. Further subgroup analyses revealed that rs2070744 and rs869109213 polymorphisms were only significantly associated with individual susceptibility to cancer in Caucasians, whereas the rs1799983 polymorphism was significantly associated with individual susceptibility to cancer in both Caucasians and Asians.

Conclusions: Our findings indicated that rs1799983, rs2070744 and rs869109213 polymorphisms may serve as genetic biomarkers of cancer in certain ethnicities.

1. Introduction

Cancer is a pivotal health problem all over the world [1]. In spite of enormous advances achieved in diagnosis and treatment over the past decades, it still accounts for over 22000 deaths every day [2]. Until now, the exact cause of cancer is still unknown. Although irregular life, smoking, heavy alcohol intake and chronic viral infection were already proved to be potential pathogenic factors of cancer by previous epidemiological investigations [3,4], the fact that a great inter-individual variability in disease susceptibility existed in these exposed to above mentioned carcinogenic factors suggested that genetic factors are also involved in cancer development.

Nitric oxide (NO) is a short-lived small molecule that could exert protection effects against free radicals, but at excessive concentrations, NO or its derivatives might cause DNA damage and lead to cancer development. Therefore, balance of NO level is critical for cancer prevention [5,6]. The endothelial nitric oxide synthase (eNOS), encoded by the *eNOS* gene located on chromosome 7q35-36, plays a pivotal role in regulating synthesis of NO [7], and previous studies showed that eNOS may also be implicated in cancer development. Firstly, eNOS expression levels were found to be significantly elevated in various cancerous tissues [8–11]. Secondly, it was evident that eNOS was also involved in multiple cancer-related events such as angiogenesis, invasion and metastasis [12–14]. Therefore, it is biologically plausible that *eNOS* polymorphisms, which may alter the expression level of *eNOS* and impact synthesize of NO, may serve as genetic biomarkers of cancer. So far, associations between *eNOS* polymorphisms and individual susceptibility to cancer remain controversial. Therefore, we performed the present meta-analysis to better explore potential roles of *eNOS* polymorphisms in cancer development.

2. Materials and methods

2.1. Literature search and inclusion criteria

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [15]. Potentially related literature (published before August 2018) were retrieved from PubMed, Medline and Embase using the following searching strategy: (endothelial nitric oxide synthase OR nitric oxide synthase type III OR eNOS OR NOS3) AND (polymorphism OR variant OR mutation OR genotype OR allele) AND (cancer OR tumor OR

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carcinoma OR neoplasm OR malignancy). Furthermore, the references of retrieved articles were also screened for other potentially relevant studies.

To test the research hypothesis of this meta-analysis, included studies must meet all the following criteria: (1) case-control study on associations between *eNOS* polymorphisms and individual susceptibility to cancer; (2) provide genotypic and/or allelic frequency of investigated *eNOS* polymorphisms in cases and controls; (3) full text in English or Chinese available. Studies were excluded if one of the following criteria was fulfilled: (1) not relevant to *eNOS* polymorphisms and cancer; (2) case reports or case series; (3) abstracts, reviews, comments, letters and conference presentations. For duplicate publications, we only included the study with the largest sample size for analyses.

2.2. Data extraction and quality assessment

The following data were extracted from included studies: (1) the name of the first author; (2) publication time; (3) country and ethnicity; (4) sample size; and (5) genotypic distributions of *eNOS* polymorphisms in cases and controls. Additionally, the probability value (p value) of Hardy-Weinberg equilibrium (HWE) was also calculated. When necessary, we wrote to the corresponding authors for extra information. We used the Newcastle-Ottawa scale (NOS) to assess the quality of eligible studies [16]. This scale has a score range of zero to nine, and studies with a score of more than seven were thought to be of high quality. Two reviewers conducted data extraction and quality assessment independently. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

2.3. Statistical analyses

All statistical analyses were conducted with Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate strength of associations between *eNOS* polymorphisms and individual susceptibility to cancer in all possible genetic models, and p values ≤ 0.05 were considered to be statistically significant. Between-study heterogeneities were evaluated with I^2 statistic. If I^2 was greater than fifty percent, random-effect models (REMs) would be used to pool the data. Otherwise, fixed-effect models (FEMs) would be employed for synthetic analyses [17,18]. Subgroup analyses were subsequently performed by ethnicity of participants, type of disease, sample size and whether the genotypic distributions of investigated polymorphisms violated HWE. Sensitivity analyses were conducted to examine the stability of synthetic results. Funnel plots were used to evaluate possible publication bias.

3. Results

3.1. Characteristics of included studies

We found 428 potential relevant articles. Among these articles, a total of 41 eligible studies were finally included for synthetic analyses (see Fig. 1) [19–59]. The NOS score of eligible articles ranged from 7 to 8, which indicated that all included studies were of high quality. Baseline characteristics of included studies were shown in Table 1.

3.2. Overall and subgroup analyses

To investigate potential associations between *eNOS* polymorphisms and individual susceptibility to cancer, thirty-five studies about rs1799983 polymorphism, nineteen studies about rs2070744 polymorphism and twenty-two studies about rs869109213 polymorphism were enrolled for analyses. Significant associations with individual susceptibility to cancer were detected for rs1799983 (dominant model: $p = 0.01$, OR = 0.85, 95%CI 0.75–0.96; recessive model: $p = 0.007$, OR = 1.31, 95%CI 1.08–1.59; allele model: $p = 0.005$, OR = 0.86, 95%CI 0.78–0.96), rs2070744 (recessive model: $p = 0.004$, OR = 1.47, 95%CI 1.13–1.92) and rs869109213 (recessive model: $p < 0.0001$, OR = 1.78, 95%CI 1.38–2.30; allele model: $p = 0.02$, OR = 0.84, 95%CI 0.72–0.98) polymorphisms in overall analyses.

Subgroup analyses according to ethnicity of participants revealed that rs2070744 and rs869109213 polymorphisms were only significantly associated with individual susceptibility to cancer in Caucasians, whereas the rs1799983 polymorphism was significantly associated with individual susceptibility to cancer in both Caucasians and Asians. When we stratified data based on type of disease, positive results were found for rs1799983 and rs2070744 polymorphisms in patients with prostate cancer, bladder cancer and breast cancer. Additionally, the rs869109213 polymorphism was also found to be significantly associated with the risk of prostate cancer. Furthermore, similar positive results were observed for rs1799983, rs2070744 and rs869109213 polymorphisms in stratified analyses by sample size and p value of HWE (see Table 2).

3.3. Sensitivity analyses

We performed sensitivity analyses by excluding studies that deviated from HWE. No alterations of results were detected in sensitivity analyses, which suggested that our findings were statistically reliable.

3.4. Publication biases

Publication biases were evaluated with funnel plots. We did not find obvious asymmetry of funnel plots in any comparisons, which indicated that our findings were unlikely to be impacted by severe publication biases (see Supplementary figure 1).

4. Discussion

To the best of our knowledge, this is so far the most comprehensive meta-analysis on associations between *eNOS* polymorphisms and cancer, and our pooled analyses demonstrated that rs1799983, rs2070744 and rs869109213 polymorphisms were all significantly associated with individual susceptibility to cancer. Further subgroup analyses revealed that rs2070744 and rs869109213 polymorphisms were only significantly associated with individual susceptibility to cancer in Caucasians, whereas the rs1799983 polymorphism was significantly associated with individual susceptibility to cancer in both Caucasians and Asians.

There are several points that need to be addressed about this meta-analysis. Firstly, previous experimental studies showed that mutant alleles of investigated polymorphisms were all correlated with reduced eNOS activity and decreased NO generation, which may partially explain our positive findings [60,61]. Secondly, the pathogenic mechanism of cancer is highly complex, and hence it is unlikely that a single gene polymorphism could significantly contribute to its development. As a result, to better illustrate potential correlations of certain gene polymorphisms with cancer, we strongly recommend further studies to perform haplotype analyses and explore potential gene-gene interactions. Thirdly, it is worth noting that Haque et al. also tried to analyze the effects of *eNOS* polymorphisms on cancer development through a meta-analysis in 2015, and significant associations with cancer were only detected for rs2070744 polymorphism in overall population [62]. Compared with this previous study, 10 more studies about rs869109213 polymorphism, 8 more studies about rs2070744 polymorphism, and 8 more studies about rs1799983 polymorphism were enrolled for analyses in our current meta-analysis. Therefore, our pooled findings should be considered as more conclusive. However, it is also notable that the sample sizes of several subgroup comparisons were still relatively small, and thus may be statistically inadequate to detect

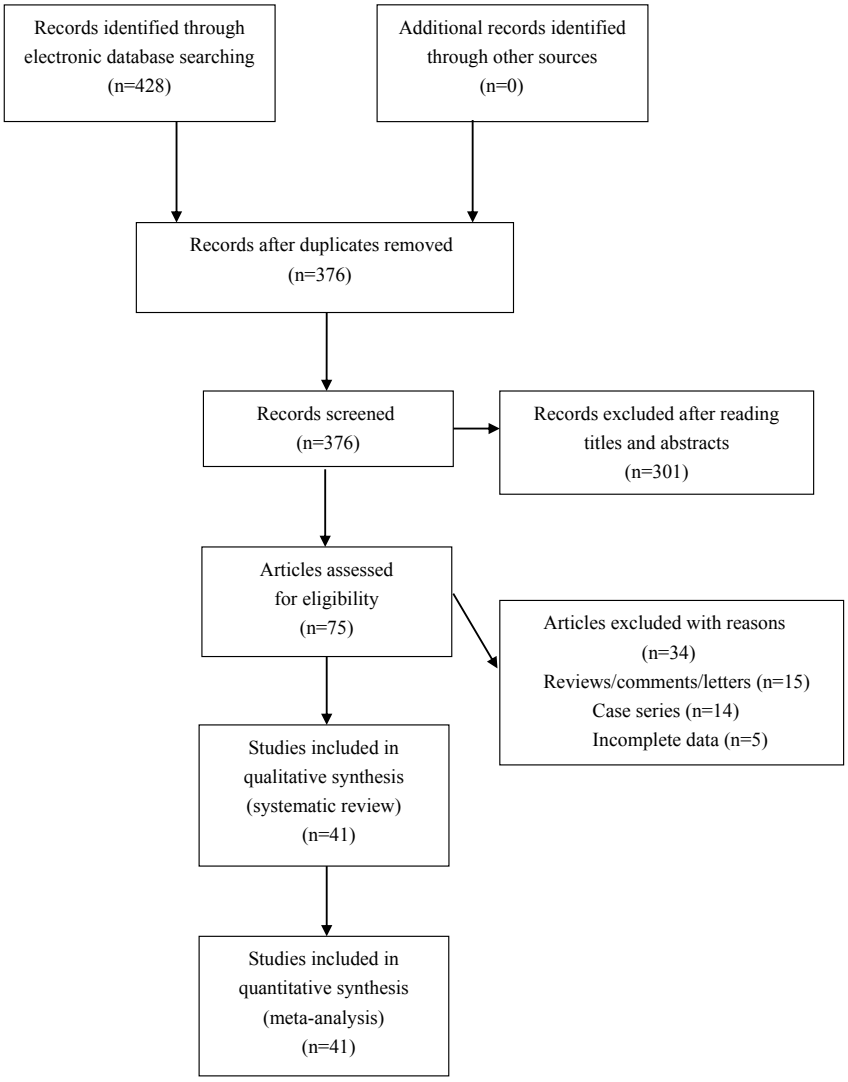

Fig. 1. Flowchart of study selection for the present study.

the actual relationship between *eNOS* polymorphisms and certain types of cancer. Thus, further studies with larger sample sizes are still needed to confirm our findings.

As with all meta-analysis, this study certainly has some limitations. First, our results were derived from unadjusted analyses due to lack of raw data, and lack of further adjusted analyses for age, gender and co-morbidity conditions may impact the reliability of our findings [63]. Second, obvious heterogeneities were found in several subgroups, which indicated that the controversial results of included studies could not be fully explained by differences in ethnic background and type of disease, and other baseline characteristics of participants may also contribute to between-study heterogeneities [64]. Third, associations between *eNOS* polymorphisms and cancer may also be modified by gene-gene and gene-environmental interactions. However, most eligible studies ignore these potential interactions, which impeded us to perform relevant analyses accordingly [65]. To sum up, our findings should be cautiously interpreted on account of above mentioned limitations.

5. Conclusions

In conclusion, our meta-analysis suggested that rs1799983, rs2070744 and rs869109213 polymorphisms may serve as genetic biomarkers of cancer in certain ethnicities. However, further well-designed studies are still warranted to confirm our findings.

Authors' contributions

Jun Nan and Dahe Ge conceived of the study, participated in its design. Jun Nan and Yaqing Liu conducted the systematic literature review. Yaqing Liu and Chunjin Xu performed data analyses. Jun Nan and Dahe Ge drafted the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding

None.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 1
The characteristics of included studies for *eNOS* gene polymorphisms and cancer.

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P*-value for HWE	NOS score
					Cases	Controls		
rs1799983 G/T					GG/GT/TT			
Arikan 2012	Turkey	Caucasian	Colorectal cancer	84/99	35/42/7	27/50/22	0.900	8
Basmaci 2016	Turkey	Caucasian	Multiple myeloma	77/77	37/25/15	51/25/1	0.281	8
Ben Chaaben 2015	Tunisia	Caucasian	Nasopharyngeal carcinoma	260/316	120/114/26	204/90/22	0.009	8
Brankovic 2013	Serbia	Caucasian	Prostate cancer	150/150	76/65/9	78/59/13	0.700	7
Ceylan 2016	Turkey	Caucasian	Prostate cancer	78/115	46/23/9	67/40/8	0.549	8
Chen 2018	Taiwan	Asian	Breast cancer	283/200	NA	NA	NA	7
Conde 2006	Spain	Caucasian	Colorectal cancer	355/538	135/160/60	216/235/87	0.090	7
Diler 2016	Turkey	Caucasian	Prostate cancer	84/116	6/55/23	65/41/10	0.343	8
Funke 2009	Germany	Caucasian	Colorectal cancer	632/604	289/285/58	271/272/61	0.547	7
Gao 2015	China	Asian	Breast cancer	873/1034	652/195/26	791/232/11	0.184	8
Ghilardi 2003	Italy	Caucasian	Breast cancer	71/91	26/36/9	39/47/5	0.056	7
Harman 2009	Turkey	Caucasian	Adrenal incidentaloma	50/30	30/11/9	16/6/8	0.002	8
Hefler 2002	Austria	Caucasian	Ovarian cancer	156/133	70/70/16	60/61/12	0.528	7
Hefler 2006	Austria	Caucasian	Breast cancer	269/244	118/117/34	118/109/17	0.135	7
Jang 2013	Korea	Asian	Colorectal cancer	528/509	417/102/9	431/76/2	0.484	8
Lee 2007	Korea	Asian	Breast cancer	1348/944	1134/203/11	792/151/1	0.023	7
Lee 2009	USA	Caucasian	Prostate cancer	1088/1293	517/468/103	607/557/129	0.941	7
Lee 2009	USA	African	Prostate cancer	97/373	77/20/0	280/88/5	0.514	7
Li 2009	USA	Mixed	Breast cancer	489/485	242/200/47	236/209/40	0.508	8
Lu 2006	USA	Caucasian	Breast cancer	421/423	189/193/39	199/186/38	0.559	8
Marangoni 2006	Brazil	African	Prostate cancer	84/65	30/50/4	30/29/6	0.789	7
Medeiros 2002	Portugal	Caucasian	Prostate cancer	125/153	49/61/15	70/65/18	0.626	8
Ozturk 2011	Turkey	Caucasian	Endometrial carcinoma	89/60	47/31/11	42/18/0	0.172	8
Polat 2015	Turkey	Caucasian	Bladder cancer	75/143	7/59/9	48/75/20	0.278	8
Polat 2016	Turkey	Caucasian	Prostate cancer	50/50	1/22/27	29/17/4	0.509	7
Riener 2004	Germany	Caucasian	Vulvar cancer	68/227	40/21/7	105/108/14	0.044	7
Royo 2006	Spain	Caucasian	Breast cancer	440/321	167/205/68	130/146/45	0.697	7
Ryk 2011	Sweden	Caucasian	Bladder cancer	262/150	128/106/28	75/62/13	0.971	8
Safarinejad 2013	Iran	Caucasian	Prostate cancer	170/340	120/48/2	248/89/3	0.101	8
Su 2018	Taiwan	Asian	Oral cancer	1200/1044	935/250/15	825/209/10	0.418	8
Tecder Ünal 2010	Turkey	Caucasian	Gastric cancer	46/46	18/26/2	19/25/2	0.079	7
Verim 2013	Turkey	Caucasian	Bladder cancer	66/88	7/49/10	31/44/13	0.682	7
Yanar 2016	Turkey	Caucasian	Larynx cancer	58/147	18/29/11	31/81/35	0.212	7
Yeh 2009	Taiwan	Asian	Colorectal cancer	702/728	568/124/10	575/143/10	0.744	8
Ziaei 2013	Iran	Caucasian	Prostate cancer	78/87	44/23/11	48/33/6	0.919	7
Zintzaras 2010	Greece	Caucasian	Breast cancer	306/131	119/141/46	50/65/16	0.464	8
rs2070744 T/C					TT/TC/CC			
Ben Chaaben 2015	Tunisia	Caucasian	Nasopharyngeal carcinoma	260/316	101/111/48	146/143/27	0.332	8
Brankovic 2013	Serbia	Caucasian	Prostate cancer	150/150	54/68/28	57/73/20	0.656	7
Chen 2018	Taiwan	Asian	Breast cancer	283/200	NA	NA	NA	7
Conde 2006	Spain	Caucasian	Colorectal cancer	368/547	107/184/77	152/273/122	0.978	7
Diler 2016	Turkey	Caucasian	Prostate cancer	84/116	30/30/24	47/56/13	0.545	8
Gao 2015	China	Asian	Breast cancer	873/1034	751/114/8	917/115/2	0.414	8
Ghilardi 2003	Italy	Caucasian	Breast cancer	71/91	22/35/14	37/42/12	0.988	7
Jang 2013	Korea	Asian	Colorectal cancer	509/528	418/87/4	395/128/5	0.124	8
Krishnaveni 2015	India	Caucasian	Gastric cancer	150/150	135/12/3	99/29/22	< 0.001	7
Lee 2007	Korea	Asian	Breast cancer	1364/956	1092/250/22	766/177/13	0.449	7
Lu 2006	USA	Caucasian	Breast cancer	421/423	167/200/54	203/185/35	0.428	8
Marangoni 2006	Brazil	African	Prostate cancer	71/72	30/32/9	29/35/8	0.595	7
Polat 2015	Turkey	Caucasian	Bladder cancer	75/143	24/40/11	56/72/15	0.245	8
Polat 2016	Turkey	Caucasian	Prostate cancer	50/50	32/11/7	21/24/5	0.623	7
Ryk 2011	Sweden	Caucasian	Bladder cancer	334/155	152/142/40	84/63/8	0.382	8
Safarinejad 2013	Iran	Caucasian	Prostate cancer	170/340	52/93/25	150/159/31	0.225	8
Su 2018	Taiwan	Asian	Oral cancer	1200/1044	942/239/19	824/208/12	0.781	8
Tecder Ünal 2010	Turkey	Caucasian	Gastric cancer	50/50	16/22/12	31/12/7	0.008	7
Yeh 2009	Taiwan	Asian	Colorectal cancer	683/726	566/110/7	604/116/6	0.869	8
rs869109213 VNTR					4b4b/4b4a/4a4a			
Amasyali 2012	Turkey	Caucasian	Bladder cancer	123/201	52/63/8	137/59/5	0.648	8
Basmaci 2016	Turkey	Caucasian	Multiple myeloma	77/77	40/28/9	57/18/2	0.690	8
Ben Chaaben 2015	Tunisia	Caucasian	Nasopharyngeal carcinoma	260/316	79/169/12	91/214/11	< 0.001	8
Chen 2018	Taiwan	Asian	Breast cancer	283/200	222/55/6	160/34/6	0.020	7
Diler 2016	Turkey	Caucasian	Prostate cancer	84/116	65/16/3	83/31/2	0.643	8
Gao 2015	China	Asian	Breast cancer	873/1034	722/140/11	858/164/12	0.194	8
Hefler 2002	Austria	Caucasian	Ovarian cancer	156/133	108/48/0	97/34/2	0.613	7
Hefler 2006	Austria	Caucasian	Breast cancer	269/270	196/68/5	193/75/2	0.066	7
Jang 2013	Korea	Asian	Colorectal cancer	528/509	434/87/7	409/98/2	0.126	8
Lu 2006	USA	Caucasian	Breast cancer	421/423	293/113/15	300/110/13	0.456	8
Medeiros 2002	Portugal	Caucasian	Prostate cancer	125/153	87/32/6	121/29/3	0.426	8
Ozturk 2011	Turkey	Caucasian	Endometrial carcinoma	89/60	48/31/10	43/16/1	0.723	8
Peddireddy 2018	India	Caucasian	Lung cancer	246/250	145/72/29	179/62/9	0.221	8
Polat 2015	Turkey	Caucasian	Bladder cancer	75/143	50/24/1	97/43/3	0.481	8

(*continued on next page*)

Table 1 (*continued*)

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P*-value for HWE	NOS score
					Cases	Controls		
Polat 2016	Turkey	Caucasian	Prostate cancer	50/50	41/7/2	36/12/2	0.449	7
Ramírez-Patiño 2013	Mexico	African	Breast cancer	425/279	331/94/0	244/34/1	0.873	8
Riener 2004	Germany	Caucasian	Vulvar cancer	65/227	48/17/0	171/53/3	0.625	7
Safarinejad 2013	Iran	Caucasian	Prostate cancer	170/340	101/54/15	249/88/3	0.111	8
Tecder Ünal 2010	Turkey	Caucasian	Gastric cancer	46/98	35/10/1	66/28/4	0.640	7
Yeh 2009	Taiwan	Asian	Colorectal cancer	713/723	591/115/7	605/112/6	0.746	8
Yuan 2013	China	Asian	Hepatocellular carcinoma	293/384	231/59/3	288/94/2	0.051	8
Zintzaras 2010	Greece	Caucasian	Breast cancer	306/131	214/83/9	78/48/5	0.472	8

AbbreviationsHWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; NA, Not available.

Table 2
Overall and subgroup analyses for *eNOS* gene polymorphisms and cancer.

Polymorphisms	Population	Sample size (Cases/controls)	Dominant comparison	Recessive comparison	Additive comparison	Allele comparison
			P value OR (95%CI)	*P* value OR (95%CI)	*P* value OR (95%CI)	*P* value OR (95%CI)
rs1799983	Overall	11212/11554	**0.01 0.85 (0.75–0.96)**	**0.007 1.31 (1.08–1.59)**	0.09 1.09 (0.99–1.20)	**0.005 0.86 (0.78–0.96)**
	Caucasian	5608/6172	**0.01 0.79 (0.66–0.95)**	**0.03 1.27 (1.02–1.58)**	0.08 1.13 (0.99–1.28)	**0.009 0.83 (0.73–0.96)**
	Asian	4934/4459	0.22 0.94 (0.85–1.04)	**0.0004 2.10 (1.39–3.17)**	0.86 1.01 (0.91–1.12)	0.05 0.91 (0.83–1.00)
	Prostate cancer	2004/2742	**0.05 0.67 (0.46–0.99)**	0.13 1.54 (0.88–2.69)	0.16 1.19 (0.93–1.52)	0.05 0.74 (0.54–1.01)
	Bladder cancer	403/381	0.09 0.37 (0.11–1.18)	0.80 1.06 (0.67–1.67)	0.11 2.04 (0.85–4.86)	**0.01 0.76 (0.61–0.94)**
	Colorectal cancer	2301/2478	0.99 1.00 (0.80–1.26)	0.73 0.92 (0.59–1.45)	0.63 1.03 (0.91–1.17)	0.84 1.02 (0.82–1.27)
	Breast cancer	4500/3873	0.22 0.94 (0.85–1.04)	**0.001 1.39 (1.14–1.70)**	0.60 0.97 (0.88–1.08)	**0.03 0.91 (0.84–0.99)**
	Sample size < 200	695/693	0.07 0.63 (0.39–1.03)	0.18 1.82 (0.76–4.32)	0.08 1.22 (0.98–1.51)	0.21 0.76 (0.50–1.17)
	Sample size ≥ 200	10517/10861	0.06 0.89 (0.79–1.00)	**0.007 1.17 (1.05–1.32)**	0.22 1.07 (0.96–1.19)	**0.02 0.89 (0.78–0.98)**
	p value of HWE ≥ 0.05	9486/10037	**0.009 0.85 (0.74–0.96)**	**0.01 1.29 (1.05–1.59)**	0.10 1.05 (0.99–1.12)	**0.002 0.85 (0.76–0.94)**
rs2070744	Overall	7166/7091	0.43 0.93 (0.79–1.11)	**0.004 1.47 (1.13–1.92)**	0.54 0.96 (0.84–1.09)	0.21 0.90 (0.77–1.06)
	Caucasian	2183/2531	0.37 0.88 (0.66–1.17)	**0.02 1.51 (1.08–2.13)**	0.64 0.95 (0.77–1.17)	0.21 0.86 (0.68–1.09)
	Asian	4912/4488	0.81 1.02 (0.87–1.20)	0.13 1.38 (0.91–2.07)	0.64 0.96 (0.81–1.14)	0.96 1.00 (0.83–1.19)
	Prostate cancer	525/728	0.79 0.94 (0.62–1.45)	**0.0007 1.77 (1.27–2.46)**	0.28 0.78 (0.50–1.22)	0.16 0.83 (0.64–1.08)
	Bladder cancer	409/298	**0.04 0.71 (0.52–0.98)**	**0.02 2.01 (1.14–3.52)**	0.58 1.09 (0.80–1.51)	**0.008 0.72 (0.57–0.92)**
	Colorectal cancer	1560/1801	0.27 1.17 (0.89–1.53)	0.67 0.94 (0.69–1.27)	0.35 0.87 (0.66–1.16)	0.28 1.13 (0.91–1.41)
	Breast cancer	3012/2704	**0.03 0.86 (0.75–0.98)**	**0.0005 1.61 (1.15–2.25)**	0.22 1.09 (0.95–1.26)	**0.002 0.83 (0.74–0.94)**
	Sample size < 200	326/379	0.56 0.84 (0.46–1.51)	**0.002 1.92 (1.27–2.90)**	0.58 0.85 (0.48–1.51)	0.18 0.77 (0.53–1.13)
	Sample size ≥ 200	6840/6712	0.59 0.95 (0.80–1.14)	0.05 1.37 (1.00–1.88)	0.86 0.99 (0.91–1.08)	0.52 0.94 (0.79–1.12)
	p value of HWE ≥ 0.05	6966/6891	0.14 0.91 (0.80–1.03)	< **0.0001 1.49 (1.27–1.75)**	0.73 0.99 (0.91–1.07)	**0.02 0.87 (0.77–0.97)**
rs869109213	Overall	5677/6117	0.05 0.85 (0.72–1.00)	< **0.0001 1.78 (1.38–2.30)**	0.23 1.09 (0.95–1.26)	**0.02 0.84 (0.72–0.98)**
	Caucasian	2562/2988	0.08 0.81 (0.65–1.02)	< **0.0001 2.07 (1.53–2.79)**	0.28 1.11 (0.92–1.33)	**0.04 0.80 (0.65–0.99)**
	Asian	2690/2320	0.72 1.03 (0.89–1.18)	0.41 1.24 (0.75–2.05)	0.55 0.96 (0.83–1.10)	0.90 1.01 (0.89–1.14)
	Prostate cancer	429/659	0.56 0.85 (0.50–1.46)	**0.0002 3.99 (1.93–8.23)**	0.47 1.11 (0.84–1.47)	0.36 0.79 (0.48–1.30)
	Bladder cancer	198/344	0.25 0.56 (0.21–1.52)	0.17 1.96 (0.74–5.20)	0.20 1.70 (0.75–3.86)	0.28 0.64 (0.29–1.42)
	Colorectal cancer	1241/1232	0.84 1.02 (0.83–1.26)	0.21 1.75 (0.73–4.19)	0.60 0.94 (0.76–1.17)	0.92 0.99 (0.82–1.20)
	Breast cancer	2577/2337	0.68 0.95 (0.74–1.22)	0.92 1.02 (0.66–1.58)	0.68 1.06 (0.81–1.37)	0.66 0.95 (0.78–1.17)
	Sample size < 200	262/285	0.56 0.80 (0.37–1.72)	**0.02 2.75 (1.19–6.33)**	0.52 1.14 (0.77–1.67)	0.47 0.76 (0.37–1.58)
	Sample size ≥ 200	5415/5832	0.08 0.86 (0.73–1.02)	< **0.0001 1.70 (1.30–2.22)**	0.26 1.09 (0.94–1.26)	**0.04 0.86 (0.73–1.00)**
	p value of HWE ≥ 0.05	5134/5601	0.05 0.83 (0.69–1.00)	< **0.0001 1.93 (1.47–2.55)**	0.22 1.10 (0.94–1.29)	**0.02 0.82 (0.69–0.97)**

Abbreviations: OR, Odds ratio; CI, Confidence interval; NA, Not available.
The values in bold represent there is statistically significant differences between cases and controls.

Informed consent

For this type of study formal consent is not required.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.niox.2018.12.006.

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