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Cumulative evidence of relationships between multiple variants in 8q24 region and cancer incidence

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Abstract

Genome-wide association studies (GWAS) have identified multiple independent cancer susceptibility loci at chromosome 8q24. We aimed to evaluate the associations between variants in the 8q24 region and cancer susceptibility. A comprehensive research synopsis and meta-analysis was performed to evaluate associations between 28 variants in 8q24 and risk of 7 cancers using data from 103 eligible articles totaling 146,932 cancer cases and 219,724 controls. Results: 20 variants were significantly associated with risk of prostate cancer, colorectal cancer, thyroid cancer, breast cancer, bladder cancer, stomach cancer, and glioma, including 1 variant associated with prostate cancer, colorectal cancer, and thyroid cancer. Cumulative epidemiological evidence of an association was graded as strong for DG8S737 -8 allele, rs10090154, rs7000448 in prostate cancer, rs10808556 in colorectal cancer, rs55705857 in gliomas, rs9642880 in bladder cancer, moderate for rs16901979, rs1447295, rs6983267, rs7017300, rs7837688, rs1016343, rs620861, rs10086908 associated in prostate cancer, rs10505477, rs6983267 in colorectal cancer, rs6983267 in thyroid cancer, rs13281615 in breast cancer, and rs1447295 in stomach cancer, weak for rs6983561, rs13254738, rs7008482, rs4242384 in prostate cancer. Data from ENCODE suggested that these variants with strong evidence and other correlated variants might fall within putative functional regions. Our study provides summary evidence that common variants in the 8q24 are associated with risk of multiple cancers in this large-scale research synopsis and meta-analysis. Further studies are needed to explore the mechanisms underlying variants in the 8q24 involved in various human cancers.

Abbreviations: ENCODE = Encyclopedia of DNA Elements, FPRP = false positive report probability, GWAS = genome-wide association studies, HWE = Hardy-Weinberg equilibrium, SNPs = single nucleotide polymorphisms.

Keywords: 8q24, cancer, genetic variant, meta-analysis, susceptibility

1. Introduction

The morbidity and mortality of cancers have been increasing worldwide. The genetic factors e.g., a single nucleotide polymorphism have been verified to be associated with the onset of cancers. Identification of genetic factors regulating the development and progression of cancers contributes to improvement of preventive measures and therapeutic outcomes.[1]

Genome-wide association studies (GWAS) have identified multiple independent cancer susceptibility loci at chromosome 8q24. These susceptibility loci do not affect coding regions of gene, however, they are in tight LD with many SNPs, often covering large haplotype blocks. The rs6983267, 1 of the variants in 8q24 region was initially identified as a susceptibility locus for colorectal cancer.[2,3] Then multiple loci, such as rs1447295, rs16901979, rs10090154 etc., were confirmed to be associated with prostate cancer.[4–6] In 2008, Eeles et al conducted a two-stage GWAS and identified several alleles associated with prostate cancer on chromosome 8q24.[7] More recently, several breast cancer,[8,9] gliomas,[10] bladder cancer,[11] and stomach cancer[12] risk regions in 8q24 have also been identified. Further study in a large-scale found that rs13281615 G-allele in 8q24 was associated with higher survival rates in breast cancer.[13] In addition, rs9642880 and rs1447295 located in 8q24 region were found to be associated with the risk of bladder[14] and stomach cancer,[15] respectively. In 2014, Skibola et al reported that rs13254990 was associated with follicular lymphoma risk by conducting a large-scale two-stage GWAS.[16]

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YuT and YT contributed equally to this work.

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A number of genetic studies have been done to evaluate the contribution of variants in the 8q24 region to risk of human cancer, however, results from these studies were generally inconsistent. In the present study, we performed a comprehensive meta-analysis, involving a total of 146,932 cancer cases and 219,724 controls, to evaluate all genetic studies that investigated associations between variants in the 8q24 region and risk of human cancers.

2. Methods

All methods were based on guidelines proposed by the Human Genome Epidemiology Network for systematic review of genetic association studies and followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

2.1. Search strategy and selection criteria

We systematically searched PubMed and Embase to identify genetic association studies published in print or online before November 30th, 2017 in English language using key terms "8q24" and "variant or polymorphism or genotype" and "cancer or carcinoma or tumor". The eligibility of each study was assessed independently by 2 investigators (Yu Tong and Ying Tang). The articles included in the meta-analysis must meet the following inclusion criteria:

1. evaluating the associations of genetic variants in the 8q24 with risk of human cancer;
2. providing age-adjusted or multivariate-adjusted risk estimates (e.g., relative risks (RRs), hazard ratios (HRs), odds ratios (ORs), 95% confidence intervals (CIs) or standard errors (SEs)) or sufficient data to calculate these estimates.

Studies were excluded when:

1. they lacked sufficient information;
2. they were not published as full reports, such as conference abstracts and letters to editors;
3. they were studies of cancer mortality (rather than incidence).

2.2. Data extraction

Data were extracted by 2 investigators (Yu Tong and Ying Tang), who used recommended guidelines for reporting on meta-analyses of observational studies. Data extracted from each eligible publication included first author, publishing year, study design, method of case selection, source population, ethnicity of participants, sample size, cancer type, variants, major and minor alleles, genotype counts for cases and controls, Hardy-Weinberg equilibrium (HWE) among controls. Ethnicity was classified as African (African descent), Asian (East Asian descent), Caucasian (European descent), or other (including Native Hawaiians, Latinos, Hispanic, etc.) based on the ethnicity of at least 80% of the study population. In total, 103 eligible publications had sufficient data available for extraction and inclusion in meta-analyses. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.3. Statistical analysis and assessment of cumulative evidence

The odds ratio was used as the metric of choice for each study. To detect overall genetic associations, allele frequencies were computed for studies reporting allele and genotype data. Pooled odds ratios were computed by the fixed effects model and the random effects model based on heterogeneity estimates. Once an overall gene effect was confirmed, the genetic effects and mode of inheritance were estimated using the genetic model-free approach suggested by Minelli et al. We performed Cochrans Q test and calculated I^2 statistic to evaluate heterogeneity between studies. I^2 values $<25\%$ represent no or little heterogeneity, values 25% to 50% represent moderate heterogeneity, and values $>50\%$ represent large heterogeneity. Sensitivity analyses were conducted to examine if the significant association would be lost when the first published report was excluded, or studies deviated from HWE in controls were excluded. Harbord test was performed to evaluate publication bias. All analyses were conducted using Stata, version 14.0 (StataCorp, 2017), with the *metan, metabias, metacum*, and *metareg* commands.

Venice criteria[17] was applied to evaluate the epidemiological credibility of significant associations identified by meta-analysis. Credibility was defined in 3 categories: amount of evidence (graded by the sum of test alleles or genotypes among cases and controls: A for >1000, B for 100–1000, and C for <100), replication of the association (graded by the heterogeneity statistic: A for $I^2<25\%$, B for I^2 between 25% and 50%, and C for $I^2>50\%$), and protection from bias (graded as A: there was no observable bias, and bias was unlikely to explain the presence of the association, B: bias could be present, C: bias was evident or was likely to explain the presence of the association. C was also assigned to an association with a summary OR less than 1.15, unless the association had been replicated by GWAS or GWAS meta-analysis from collaborative studies et al with no evidence of publication bias). Cumulative epidemiological evidence for significant associations was thought to be strong if all 3 grades were A, moderate if all 3 grades were A or B, and weak if any grade was C.

To determine whether a significant association could be excluded as a false positive finding, FPRP (false positive report probability) was calculated by the method described by Wacholder et al FPRP <0.05, $0.05 \leq$ FPRP ≤ 0.20, and FPRP >0.20 were considered strong, moderate, and weak evidence of true association, respectively.

2.4. Functional annotation

We conducted analyses to evaluate the potential functional effect of variants on 8q24 using data from the Encyclopedia of DNA Elements (ENCODE) Project and performed functional annotation for variants significantly associated with cancer risk through the UCSC Genome browser (http://genome.ucsc.edu/).

3. Results

3.1. Characteristics of the studies included in this meta-analysis

Our search yielded a total of 578 publications. Based on a review of titles and abstracts, 276 articles were retained. The full text of these 276 articles were reviewed in detail, and 103 studies were eligible for inclusion in the meta-analysis. The specific process for identifying eligible studies and inclusion and exclusion criteria are summarized in Figure 1. Characteristics of the included articles were presented in Table 1.

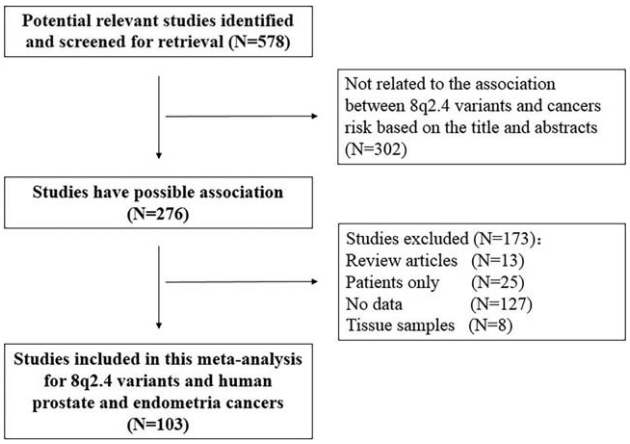

Figure 1. Flow diagram of included and excluded studies.

3.2. Associations between 8q24 variants and cancer risk

A summary of the meta-analysis findings regarding associations between 8q24 variants and cancer risk was shown in Table 2. Totally, 20 variants were nominally significantly associated with risk of prostate cancer, colorectal cancer, thyroid cancer, breast cancer, bladder cancer, stomach cancer, and gliomas ($P < .05$). Significant associations with prostate cancer risk were found for rs16901979 (OR = 1.456, 95% CI: 1.31–1.64; $P = 1.12 \times 10^{-11}$), rs1447295 (OR = 1.29, 95% CI: 1.21–1.38; $P = 2.74 \times 10^{-14}$), DG8S737 -8 allele (OR = 1.29, 95% CI: 1.12–1.48; $P = 2.83 \times 10^{-4}$), rs6983561 (OR = 1.29, 95% CI: 1.02–1.64; $P = .04$), rs10090154 (OR = 1.33, 95% CI: 1.17–1.52; $P = 1.87 \times 10^{-5}$), rs7000448 (OR = 1.11, 95% CI: 1.04–1.19; $P = .003$), rs13254738 (OR = 1.11, 95% CI: 1.01–1.22; $P = .026$), rs6983267 (OR = 1.14, 95% CI: 1.04–1.25; $P = .006$), rs7017300 (OR = 1.39, 95% CI: 1.15–1.68; $P = .001$), rs7837688 (OR = 1.48, 95% CI: 1.29–1.71; $P = 4.76 \times 10^{-8}$), rs1016343 (OR = 1.33, 95% CI: 1.20–1.48; $P = 5.64 \times 10^{-8}$), rs7008482 (OR = 0.77, 95% CI: 0.62–0.96; $P = .021$), rs4242384 (OR = 1.42, 95% CI: 1.05–1.92; $P = .022$), rs620861 (OR = 0.84, 95% CI: 0.77–0.92; $P = 7.49 \times 10^{-5}$), rs10086908 (OR = 0.73, 95% CI: 0.60–0.88; $P = .001$). Significant associations with colorectal cancer risk were found for rs10505477 (OR = 1.13, 95% CI:1.09–1.18; $P = 7.03 \times 10^{-11}$), rs6983267 (OR = 1.17, 95% CI:1.08–1.19; $P = 4.66 \times 10^{-7}$) and rs10808556 (OR = 1.18, 95% CI:1.12–1.25; $P = 2.10 \times 10^{-9}$).

Significant associations with thyroid cancer risk were found for rs6983267 (OR = 1.19, 95% CI: 1.08–1.31; $P = 3.57 \times 10^{-4}$). Significant associations with gliomas risk were found for rs55705857 (OR = 3.54, 95% CI: 2.90–4.33; $P = 2.31 \times 10^{-35}$). Significant associations with breast cancer risk were found for rs13281615 (OR = 1.13, 95% CI: 1.08–1.18; $P = 3.98 \times 10^{-7}$). Significant associations with bladder cancer risk were found for rs9642880 (OR = 1.25, 95% CI: 1.20–1.30; $P = 1.79 \times 10^{-27}$). Significant associations with stomach cancer risk were found for rs1447295 (OR = 0.80, 95% CI: 0.65–0.99; $P = .035$). No significant associations were found for rs4242382, rs4645959, rs7837328, rs16901966, rs10505476, rs13281615 with prostate cancer risk, rs1447295, rs7837328, rs10090154 with colorectal cancer risk, rs4295627 with gliomas risk, rs1562430, rs6983267 with breast cancer risk and rs6983267 with stomach cancer risk (data not shown).

3.3. Heterogeneity, sensitivity analysis and bias

As shown in Table 2, no or little heterogeneity was observed for associations of DG8S737 -8 allele ($I^2 = 2.32\%$, $P = .803$) and rs10090154 ($I^2 = 0.0\%$, $P = .873$) with prostate cancer, rs10808556 ($I^2 = 0.0\%$, $P = .394$) with colorectal cancer, rs55705857 ($I^2 = 10.9\%$, $P = .326$) for gliomas, rs9642880 ($I^2 = 4.10\%$, $P = .39$) with bladder cancer.

Moderate heterogeneity was observed for associations of rs7000448 ($I^2 = 36.2\%$, $P = .152$) with prostate cancer, rs10505477 ($I^2 = 29.2\%$, $P = .185$) with colorectal cancer and rs1447295 ($I^2 = 28.0\%$, $P = .249$) with stomach cancer.

Large heterogeneity was found for associations of rs16901979 ($I^2 = 84.3\%$, $P = .000$), rs1447295 ($I^2 = 77.6\%$, $P = .000$), rs6983561 ($I^2 = 92.2\%$, $P = .000$), rs6983267 ($I^2 = 90.5\%$, $P = .000$), rs13254738 ($I^2 = 59.8\%$, $P = .029$), rs7017300 ($I^2 = 83.3\%$, $P = .000$), rs7837688 ($I^2 = 80.1\%$, $P = .000$), rs1016343 ($I^2 = 70.2\%$, $P = .009$), rs7008482 ($I^2 = 69.2\%$, $P = .039$), rs4242384 ($I^2 = 81.3\%$, $P = .005$), rs620861 ($I^2 = 73.1\%$, $P = .005$), rs10086908 ($I^2 = 89.3\%$, $P = .000$) with prostate cancer, rs6983267 with colorectal cancer ($I^2 = 64.4\%$, $P = .000$) and rs6983267 with thyroid cancer ($I^2 = 78.6\%$, $P = .000$), rs13281615 ($I^2 = 58.9\%$, $P = .007$) with breast cancer.

We also performed sensitivity analysis to evaluate the stability of results of these associations and found that removal of a single study, the first published or studies deviated from HWE in controls did not change the summary ORs (Table 2).

3.4. Cumulative evidence of association

Epidemiological credibility was graded for the 23 identified significant associations (Table 2). Venice criteria was first applied to evaluate these associations. Strong for evidence of true association with cancer risk were assigned to DG8S737 -8 allele, rs10090154 in prostate cancer, rs10808556 in colorectal cancer, rs55705857 in gliomas, rs9642880 in bladder cancer, moderate were assigned to rs7000448 in prostate cancer, rs1447295 in stomach cancer, weak were assigned to other variants. We next evaluated the probability of true association with cancer risk for the nominally significant variants through calculating the FPRP value. Associations with cancer risk had a FPRP value < 0.05 for 18 variants (rs16901979, rs1447295, DG8S737 -8 allele, rs10090154, rs7000448, rs6983267, rs7017300, rs7837688, rs1016343, rs620861, rs10086908 in prostate cancer, rs10505477, rs6983267, rs10808556 in colorectal cancer, rs6983267 in thyroid cancer, rs55705857 in gliomas, rs13281615 in breast cancer, rs9642880 in bladder cancer), FPRP value 0.05 - 0.20 for 3 variants (rs13254738, rs4242384 in prostate cancer, rs1447295 in stomach cancer), and FPRP value >0.20 for rs6983561, rs7008482 in prostate cancer. Based on the FPRP value, we upgraded cumulative evidence from moderate to strong for rs7000448 in prostate cancer, weak to moderate for rs16901979, rs1447295, rs6983267, rs7017300, rs7837688, rs1016343, rs620861, rs10086908 associated with prostate cancer, rs10505477, rs6983267 with colorectal cancer, rs6983267 with thyroid cancer, and rs13281615 with breast cancer. Altogether, cumulative epidemiological evidence of an association was graded as strong for DG8S737 -8 allele (Fig. 2A), rs10090154 (Fig. 2B), rs7000448 (Fig. 2C) in prostate cancer, rs9642880 in bladder cancer (Fig. 2D), rs10808556 in colorectal cancer (Fig. 2E), rs55705857 in gliomas (Fig. 2F), moderate for rs16901979, rs1447295, rs6983267, rs7017300, rs7837688,

Table 1

Characteristics of the included articles.

Study, year	Study design	Country/region	Ethnicity	Variant	Cancer site	Cases/ controls
Geraldine Cancel-Tassin, 2015[20]	Population-based case–control study	France	African	rs16901979	prostate	489/534
Maurice P Zeegers, 2011[21]	Cohort Study	Netherlands	Caucasian	rs1447295	prostate	281/267
Marcelo Chen, 2010[22]	Case–control study	China	Asian	rs16901979	prostate	331/335
				rs6983561		324/336
Prodipto Pal, 2009[23]	Case–control study	USA	Caucasian	rs16901979	prostate	596/567
				rs1447295		
				rs6983267		
				rs1016343		
Marcelo Chen, 2009[24]	Hospital-based case–control study	China	Asian	rs1447295	prostate	340/337
Andreas Meyer, 2009[25]	Hospital-based case–control study	Germany	Caucasian	rs1447295	prostate	486/462
Iona Cheng, 2008[26]	Case–control study	USA	Caucasian	rs16901979	prostate	417/416
			African			89/87
			Caucasian	rs1447295		417/417
			African			89/89
			Caucasian	DG8S737		416/417
			African			89/89
			Caucasian	rs6983561		417/417
			African			88/89
			Caucasian	rs10090154		417/414
			African			89/88
			Caucasian	rs7000448		416/417
			African			89/89
			Caucasian	rs6983267		417/417
			African			89/89
			Caucasian	rs13254738		506/506
			African			89/88
Christiane Robbins, 2007[27]	Case–control study	USA	African	rs16901979	prostate	490/567
				rs1447295		
				DG8S737		
				rs6983267		
				rs7008482		
Miia Suuriniemi, 2007[28]	Population-based case–control study	USA	Caucasian	rs1447295	prostate	582/538
Fredrick R. Schumacher, 2007[29]	Nested case-control study	Multiple countries	Caucasian	rs1447295	prostate	5505/6270
			African			676/643
Julius Gudmundsson, 2007[30]	Case–control study	Iceland	Caucasian	rs16901979	prostate	2663/5509
			African			373/372
			Caucasian	rs1447295		
			African			
Gianluca Severi, 2007[31]	Case–control study	Australia	Caucasian	rs1447295	prostate	821/732
Dominika Wokołorczyk, 2008[32]	Case–control study	Poland	Caucasian	rs6983267	prostate	1910/1885
					colon	779/1910
					thyroid	485/1910
					breast	1006/1910
					stomach	488/1910
S. Lilly Zheng, 2007[33]	Case–control study	USA	Caucasian	rs16901979	prostate	1563/576
				rs1447295		
				rs6983267		
				rs7017300		
				rs7837688		
				rs10086908		
Jae Y. Joung, 2012[4]	Hospital-based case–control study	Korea	Asian	rs16901979	prostate	194/169
				rs1447295		
				rs6983267		
Naoki Terada, 2008[34]	Case–control study	Japanese	Asian	rs1447295	prostate	507/387
				rs6983267		
Michael N. Okobia, 2011[5]	Case–control study	Caribbean	African	rs16901979	prostate	338/426
				rs1447295		354/438
				rs6983267		343/426
Claudia A. Salinas, 2008[35]	Population-based case–control study	USA	Caucasian	rs1447295	prostate	1252/1233
				rs6983561		1264/1236
				rs10090154		1288/1250
				rs7000448		1262/1239

(*continued*)

Table 1

(continued).

Study, year	Study design	Country/region	Ethnicity	Variant	Cancer site	Cases/ controls
				rs6983267		1258/1238
				rs13254738		1256/1234
				rs7837688		1260/1241
				rs1016343		1253/1233
				rs7837328		1258/1239
Marnita L Benford,2010[36]	Case–control study	USA	Caucasian	rs16901979	prostate	192/512
				rs1447295		189/523
				rs6983561		186/908
				rs10090154		189/505
				rs4242382		193/1167
				rs4242384		193/524
Siqun Lilly Zheng, 2010[37]	Population-based case–control study	China	Asian	rs16901979	prostate	283/145
				rs1447295		284/151
				rs6983267		282/152
Rosalind A Eeles, 2007[7]	Population-based case–control study	United Kingdom	Caucasian	rs1447295	prostate	1906/1934
				rs6983267		
				rs7017300		
				rs7837688		
				rs1016343		
				rs4242384		
				rs620861		
				rs7837328		
Jielin Sun, 2008[38]	Population-based case–control study	USA	Caucasian	rs16901979	prostate	1625/560
				rs1447295		
				rs6983561		
				rs10090154		
				rs7000448		
				rs6983267		
				rs13254738		
				rs7017300		
				rs7837688		
				rs10086908		
Amalia Papanikolopoulou, 2012[39]	Case–control study	Greece	Caucasian	rs6983267	prostate	86/99
Kathryn L. Penney, 2009[40]	Case–control study	USA	Caucasian	rs6983267	prostate	1305/1402
				rs13254738		
Liang Wang, 2007[41]	Case–control study	USA	Caucasian	rs1447295	prostate	1121/545
				DG8S737		
S. Lilly Zheng, 2008[42]	Population-based case–control study	Sweden	Caucasian	rs16901979	prostate	2893/1781
				rs1447295		
				rs6983561		
				rs10090154		
				rs7000448		
				rs6983267		
				rs7017300		
				rs7837688		
Ying-Cai Tan, 2008[43]	Case–control study	India	Asian	rs16901979	prostate	153/227
				rs1447295		
				rs6983267		
Viorel Jinga, 2016[6]	Case–control study	Romania	Caucasian	rs16901979	prostate	955/1007
Cheryl D. Cropp, 2014[44]	Population-based case–control study	USA	Caucasian	rs7008482	prostate	522/510
Lin-Lin Zhang, 2014[45]	Case–control study	China	Asian	rs4242384	prostate	388/384
Ignacio F. San Francisco, 2014[46]	Case–control study	Chile	hispanic	rs1447295	prostate	83/21
				rs6983267		
				rs620861		
Adam B. Murphy, 2012[47]	Case–control study	Cameroon	African	rs16901979	prostate	308/469
				rs1447295		
				rs6983561		
				rs7000448		
				rs6983267		
				rs7008482		
Fang Liu, 2011[48]	Case–control study	China	Asian	rs16901979	prostate	1108/1525
				rs1447295		

(*continued*)

Table 1
(continued).

Study, year	Study design	Country/region	Ethnicity	Variant	Cancer site	Cases/ controls
				rs6983267		
				rs620861		
				rs10086908		
Ethan M. Lange, 2012[49]	Case–control study	USA	Caucasian	rs1447295	prostate	1176/1101
				rs6983267		
Bao-Li Chang, 2011[50]	Case–control study	USA	African	rs16901979	prostate	2642/2584
				rs1447295	prostate	3167/3325
				rs6983561	prostate	2764/3255
				rs10090154	prostate	1683/1403
				rs7000448	prostate	1698/2329
				rs6983267	prostate	3666/2992
				rs13254738	prostate	2557/2277
				rs7837688	prostate	636/330
				rs1016343	prostate	1975/1830
				rs7008482	prostate	2172/1760
				rs7837328	prostate	473/772
				rs10086908	prostate	861/876
Yunfei Wang, 2011[51]	Case–control study	USA	African	rs16901979	prostate	127/345
				rs1447295		
				rs6983561		
				rs10090154		
				rs7000448		
				rs6983267		
Tatsuya Hamano, 2010[52]	Case–control study	Japan	Asian	rs1447295	prostate	158/119
				DG8S737		
Dominika Wokołorczyk, 2010[53]	Hospital-based case–control study	Poland	Caucasian	rs1447295	prostate	690/602
				DG8S737		
Meredith Yeager, 2009[54]	Case–control study	USA	Caucasian	rs620861	prostate	10286/9135
Ali Amin Al Olama, 2009[55]	Case–control study	United Kingdom	Caucasian	rs6983561	prostate	1906/1934
				rs10090154		
				rs6983267		
				rs1016343		
				rs620861		
				rs10086908		
Miao Liu, 2009[56]	Case–control study	Japan	Asian	rs1447295	prostate	391/323
				rs6983267		
Jianfeng Xu, 2009[57]	Case–control study	USA	African	rs16901979	prostate	868/878
				rs1447295		
				rs6983267		
Joke Beuten, 2009[58]	Cohort Study	USA	Caucasian	rs7837328	prostate	601/840
			hispanic			196/472
Meredith Yeager, 2007[59]	Cohort Study	USA	Caucasian	rs1447295	prostate	4296/4299
				rs6983267		
				rs7837688		
Luis M. Real, 2014[60]	Case–control study	Spain	Caucasian	rs10505477	colon	500/801
				rs6983267		
A. Daraei, 2012[61]	Case–control study	Iran	Asian	rs6983267	colon	110/120
Mian Li, 2011[62]	Hospital-based case-control study	China	Asian	rs6983267	colon	430/786
R Cui, 2010[63]	Case-control study	Japan	Asian	rs6983267	colon	6161/4494
Anneke Middeldorp, 2009[64]	Case-control study	Netherlands	Caucasian	rs6983267	colon	995/1340
AM Pittman, 2008[65]	Case-control study	United Kingdom	Caucasian	rs6983267	colon	3583/2579
Li Li, 2008[66]	Population-based case–control study	USA	Caucasian	rs6983267	colon	561/721
Ian Tomlinson, 2007[2]	Case-control study	Netherlands	Caucasian	rs6983267	colon	4261/3752
Baiyu Yang, 2014[67]	Case-control study	USA	Caucasian	rs6983267	colon	90/132
Baiyu Yang, 2014[68]	Case-control study	USA	Caucasian	rs6983267	colon	401/518
Jenny N. Poynter, 2007[3]	Population-based case–control study	USA	Caucasian	rs10505477	colon	1341/2193
				rs6983267		1339/2191
Karen Curtin, 2009[69]	Cohort study	United Kingdom and USA	Caucasian	rs10505477	colon	1071/1040
				rs6983267		1071/1040
				rs10808556		925/934
Keitaro Matsuo, 2009[70]	Case-control study	Japan	Asian	rs6983267	colon	476/961
Clemens Schafmayer, 2009[71]	Case-control study	Germany	Caucasian	rs10505477	colon	2713/2718
				rs6983267		2712/2713

(*continued*)

Table 1

(continued).

Study, year	Study design	Country/region	Ethnicity	Variant	Cancer site	Cases/ controls
				rs10808556		2712/2713
SONIA S. KUPFER, 2010[72]	Case-control study	USA	African	rs6983267	colon	795/985
			Caucasian			399/367
Fang Xiong, 2010[73]	Case-control study	China	Asian	rs6983267	colon	2124/2124
S von Holst, 2010[74]	Case-control study	Sweden	Caucasian	rs6983267	colon	1737/1741
Shinya Ishimaru, 2012[75]	Case-control study	Japan	Asian	rs6983267	colon	1511/2098
				rs10808556		
Ioan Nicolae Mates, 2012[76]	Hospital-based case-control study	Romania	Caucasian	rs6983267	colon	151/182
Fen-xia Li, 2012[77]	Case-control study	China	Asian	rs6983267	colon	229/267
Sonia S.Kupfer, 2009[78]	Hospital-based case-control study	USA	Caucasian	rs10505477	colon	288/202
			African			281/237
			Caucasian	rs6983267		288/202
			African			281/237
Carolyn M Hutter, 2010[79]	Population-based case–control study	USA	Caucasian	rs10505477	colon	2089/2443
				rs6983267		2062/2418
Monir Sadat Haerian, 2014[80]	Case-control study	Iran	Caucasian	rs10505477	colon	165/151
				rs6983267		
Steven J.Lubbe, 2012[81]	Case-control study	United Kingdom	Caucasian	rs6983267	colon	3146/6051
Stephen B. Gruber, 2007[82]	Population-based case–control study	USA	Caucasian	rs10505477	colon	1860/1936
Ruta Sahasrabudhe, 2015[83]	Case–control study	Multiple countries	Caucasian	rs6983267	thyroid	2338/6256
			Caucasian			561/899
			Asian			448/1420
Abdelmounaim Akdi, 2011[84]	Case–control study	Spain	Caucasian	rs6983267	thyroid	398/479
Monica Cipollini, 2013[85]	Population-based case–control study	Italy	Caucasian	rs6983267	thyroid	1200/1196
Angela M Jones, 2011[86]	Case–control study	United Kingdom	Caucasian	rs6983267	thyroid	721/6115
Tatiana I. Rogounovitch, 2015[87]	Population-based case–control study	Japan	Asian	rs6983267	thyroid	486/2759
Yavuz Oktay, 2016[88]	Case–control study	Turkey	Caucasian	rs55705857	Gliomas	411/316
Robert B. Jenkins, 2012[10]	Case–control study	USA	Caucasian	rs55705857	Gliomas	852/789
			Caucasian	rs55705857	Gliomas	805/512
Yu Zhang, 2014[9]	Hospital-based case-control study	China	Asian	rs13281615	breast	482/527
Jingxuan Shan, 2012[89]	Case–control study	Tunisia	Caucasian	rs13281615	breast	629/365
Olivia Fletcher, 2008[8]	Case–control study	United Kingdom	Caucasian	rs13281615	breast	1470/1341
Isabel Elematore, 2014[90]	Case–control study	Chile	Caucasian	rs13281615	breast	347/801
Sharon N Teraoka, 2011[91]	Populationbased,nested case-control study	Denmark and USA	Caucasian	rs13281615	breast	705/1390
Daniele Campa, 2011[92]	Cohort study	Multiple countries	Caucasian	rs13281615	breast	8302/11615
Jirong Long, 2010[93]	Populationbased case-control study	China	Asian	rs13281615	breast	2945/2981
Montserrat Garcia-Closas, 2008[13]	Cohort study	Multiple countries	Asian	rs13281615	breast	14098/19314
Tatiana V. Gorodnova, 2010[94]	Case–control study	Russia	Caucasian	rs13281615	breast	140/174
Ayse Latif, 2014[95]	Case–control study	United Kingdom	Caucasian	rs13281615	breast	693/343
Rulla M. Tamimi, 2010[96]	Populationbased,nested case-control study	Sweden	Caucasian	rs13281615	breast	661/711
Morgan Rouprêt, 2011[97]	Case–control study	France	Caucasian	rs9642880	bladder	261/261
Ping Wang, 2014[98]	Case–control study	China	Asian	rs9642880	bladder	1210/1008
David R. Yates, 2013[99]	Case–control study	France	Caucasian	rs9642880	bladder	231/261
Meilin Wang, 2009[100]	Case–control study	China	Asian	rs9642880	bladder	230/255
Lambertus A. Kiemeney, 2008[11]	Case–control study	Iceland and Netherlands	Caucasian	rs9642880	bladder	3855/37985
Klaus Golka, 2009[14]	Case–control study	Germany	Caucasian	rs9642880	bladder	515/1592
Heather P. Tarleton, 2014[101]	Populationbased case-control study	China	Asian	rs1447295	stomach	184/384
Paul Lochhead, 2011[15]	Populationbased case-control study	Poland	Caucasian	rs1447295	stomach	286/365
Sungshim Lani Park, 2008[12]	Case–control study	USA	Caucasian	rs1447295	stomach	187/388

rs1016343, rs620861, rs10086908 associated in prostate cancer, rs10505477, rs6983267 in colorectal cancer, rs6983267 in thyroid cancer, rs13281615 in breast cancer, and rs1447295 in stomach cancer, weak for rs6983561, rs13254738, rs7008482, rs4242384 in prostate cancer.

3.5. Functional annotation

Data from the ENCODE Project suggested that variants located at 8q24 might be located in a region with strong enhancer activity and DNase I hypersensitivity site. The LD plots indicated that the genetic structure of and African ancestry (Fig. 3).

4. Discussion

To our knowledge, this study is the largest and most comprehensive assessment of literatures on associations between genetic variants in the 8q24 region and cancer risk. Preliminary meta-analyses were mostly limited to a single SNP in relation to 1 cancer. Here we performed a research synopsis and meta-analysis to systematically evaluate associations between variants in 8q24

Table 2

Details of protection from bias for genetic variants significantly associated with cancer risk in meta-analyses.

		Cancer risk						Initial study influence					
Variants	Cancer site	OR (95% CI)	*P* value	Venice criteria grade	Protection from bias	Reason for bias	Reason for bias exemption	OR (95% CI)	*P* value	Deviation from HWE	OR <1.15	*P* value for publication bias	*P* value for small study bias
rs16901979	prostate	1.46 (1.31–1.64)	1.12×10^{-11}	ACA	A	NA	Identified by GWAS	1.39 (1.30–1.48)	2.99×10^{-24}	No	No	.828	.817
rs1447295	prostate	1.29 (1.21–1.38)	2.74×10^{-14}	ACA	A	NA	Identified by GWAS	1.29 (1.20–1.39)	3.65×10^{-12}	No	No	.234	.157
DG8S737-8 allele	prostate	1.29 (1.12–1.48)	2.83×10^{-4}	AAA	A	NA	Identified by GWAS	1.30 (1.09–1.55)	.004	No	No	.592	.648
rs6983561	prostate	1.29 (1.02–1.64)	.04	ACA	A	NA	Replicated across studies with no evidence of publication bias	1.29 (1.00–1.67)	.049	No	No	.977	.887
rs10090154	prostate	1.33 (1.17–1.52)	1.87×10^{-5}	AAA	A	NA	Identified by GWAS	1.29 (1.05–1.58)	.014	No	No	.641	.668
rs7000448	prostate	1.11 (1.04–1.19)	.003	ABA	A	Low OR	Replicated across studies with no evidence of publication bias	1.11 (1.03–1.21)	.01	No	Yes	.868	.889
rs13254738	prostate	1.11 (1.01–1.22)	.026	ACA	A	Low OR	Replicated across studies with no evidence of publication bias	1.13 (1.04–1.23)	.005	No	Yes	.599	.601
rs6983267	prostate	1.14 (1.04–1.25)	.006	ACA	A	Low OR	Replicated across studies with no evidence of publication bias	1.14 (1.03–1.25)	.011	No	Yes	.577	.582
rs7017300	prostate	1.39 (1.15–1.68)	.001	ACA	A	NA	Identified by GWAS	1.37 (1.08–1.75)	.009	No	No	.564	.531
rs7837688	prostate	1.48 (1.29–1.71)	4.76×10^{-8}	ACA	A	NA	Identified by GWAS	1.45 (1.24–1.68)	2.14×10^{-6}	No	No	0.950	0.792
rs1016343	prostate	1.33 (1.20–1.48)	5.64×10^{-8}	ACA	A	NA	Identified by GWAS	1.31 (1.15–1.49)	3.05×10^{-5}	No	No	0.882	0.865
rs7008482	prostate	0.77 (0.62–0.96)	.021	ACA	A	Low OR	Replicated across studies with no evidence of publication bias	0.86 (0.77–0.96)	.008	No	Yes	.549	.533
rs4242384	prostate	1.42 (1.05–1.92)	.022	ACA	A	NA	Identified by GWAS	1.22 (1.01–1.48)	.044	No	No	.376	.340
rs620861	prostate	0.84 (0.77–0.92)	7.49×10^{-5}	ACA	A	Low OR	Identified by GWAS	0.86 (0.78–0.95)	.003	No	Yes	.943	.939
rs10086908	prostate	0.73 (0.60–0.88)	.001	ACA	A	Low OR	Replicated across studies with no evidence of publication bias	0.81 (0.76–0.86)	1.66×10^{-10}	No	Yes	.339	.428
rs10505477	colon	1.13 (1.09–1.18)	7.03×10^{-11}	ABA	A	Low OR	Identified by GWAS	1.15 (1.11–1.20)	1.20×10^{-11}	No	Yes	.963	.958
rs6983267	colon	1.17 (1.08–1.19)	4.66×10^{-7}	ACA	A	NA	Identified by GWAS	1.18 (1.13–1.23)	9.75×10^{-16}	No	No	.366	.340
rs10808556	colon	1.18 (1.12–1.25)	2.10×10^{-9}	AAA	A	NA	Replicated across studies with no evidence of publication bias	1.19 (1.12–1.27)	8.41×10^{-9}	No	No	.298	.306
rs6983267	thyroid	1.19 (1.08–1.31)	3.57×10^{-4}	ACA	A	NA	Replicated across studies with no evidence of publication bias	1.19 (1.07–1.33)	.001	No	No	.911	.887
rs55705857	gliomas	3.54 (2.90–4.33)	2.31×10^{-35}	AAA	A	NA	Replicated across studies with no evidence of publication bias	3.30 (2.59–4.20)	2.73×10^{-22}	No	No	.298	.346
rs13281615	breast	1.13 (1.08–1.18)	3.98×10^{-7}	ACA	A	Low OR	Identified by GWAS	1.11 (1.06–1.17)	5.36×10^{-6}	No	Yes	.503	.499
rs9642880	bladder	1.25 (1.20–1.30)	1.79×10^{-27}	AAA	A	NA	Identified by GWAS	1.19 (1.10–1.29)	1.42×10^{-5}	No	No	.610	.623
rs1447295	stomach	0.80 (0.65–0.99)	.035	ABA	A	Low OR	Replicated across studies with no evidence of publication bias	0.75 (0.58–0.96)	.025	No	Yes	.234	.157

region and risk of 7 human cancers using data from 103 articles total 146,932 cancer cases and 219,724 controls. Our study not only provides an update of the variants analyzed previously, but also evaluates more variants that have not been analyzed in previous meta-analyses.

Of the 28 variants located in 8q24, 20 were significantly associated with risk of prostate cancer, colorectal cancer, thyroid cancer, breast cancer, bladder cancer, stomach cancer and glioma, including 1 variant associated with prostate cancer, colorectal cancer and thyroid cancer. Using the Venice criteria and false-positive report probability tests, we graded 6 variants (DG8S737 -8 allele, rs10090154, rs7000448 in prostate cancer, rs10808556 in colorectal cancer, rs55705857 in gliomas, rs9642880 in bladder cancer) strong for cumulative evidence of significant associations with cancer risk. In addition, we performed functional annotation for variants significantly associated with cancer risk using data from the ENCODE Project and the UCSC Genome browser and found that these variants might be located in a region with strong enhancer activity and DNase I hypersensitivity site.

Multiple genetic variants on chromosome 8q24 have been reported to be significantly associated with an increased susceptibility to prostate, colorectal, breast cancer, et al. These risk loci are located in a cancer-associated regions "gene desert", a few hundred kilobases telomeric to the Myc gene. It was predicted that these risk-associated variants could affect the regulation or transcription of the gene, such as MYC, TCF7L2, FAM84B, et al outside the 8q24 region. Another speculation is

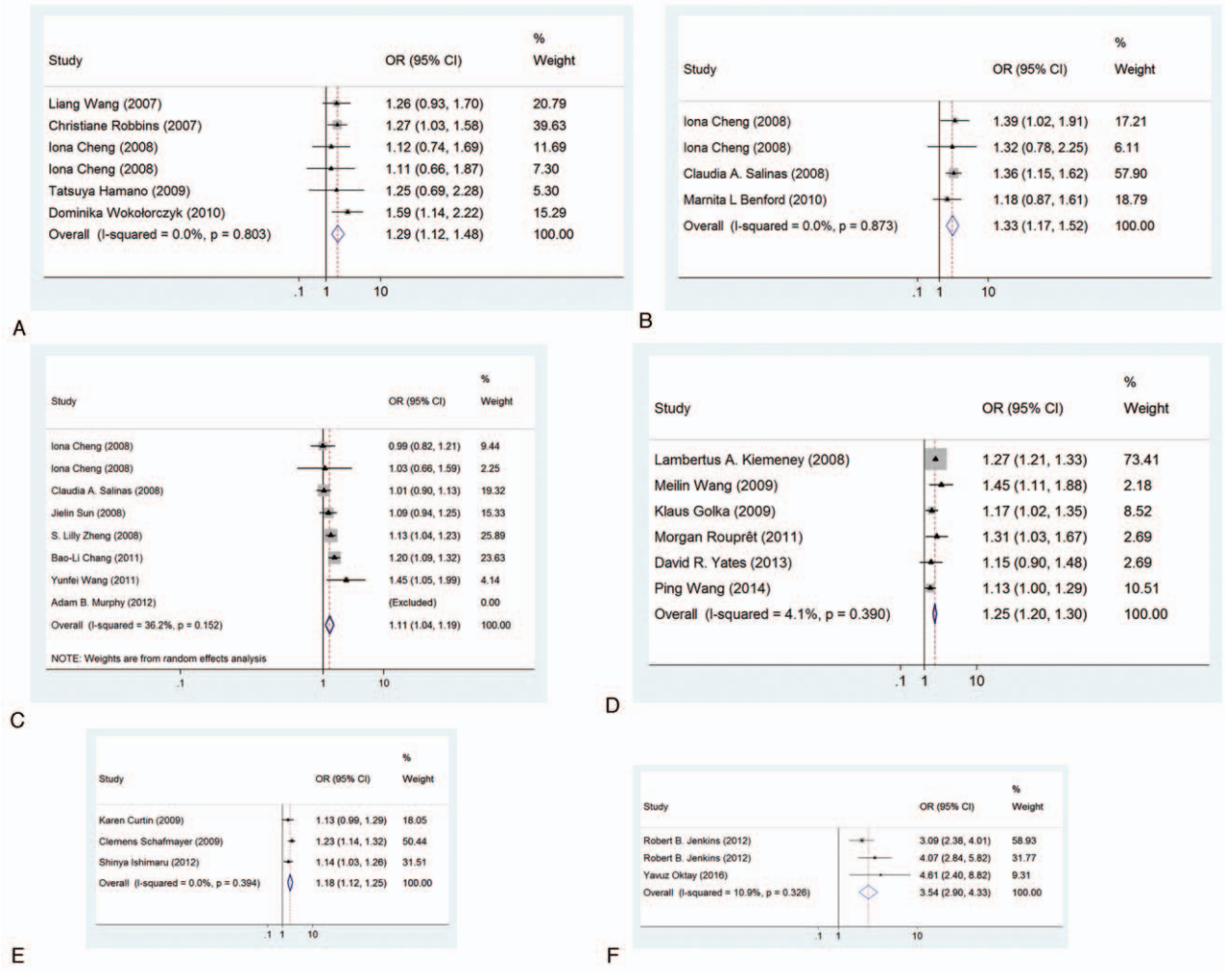

Figure 2. Forest plots for associations between selected variants in the 8q24 region and cancer risk. A: Associations of DG8S737-8 allele with prostate cancer risk. B: Associations of rs10090154 with prostate cancer risk. C: Associations of rs7000448 with prostate cancer risk. D: Associations of rs9642880 with bladder cancer risk. E: Associations of rs10808556 with colorectal cancer risk. F: Associations of rs55705857 with gliomas. The OR of each study is represented by a square, and the size of the square represents the weight of each study with respect to the overall estimate. 95% CIs are represented by the horizontal lines, and the diamond represents the overall estimate and its 95% CI.

that some risk-associated variants are linked to these risk-associated SNPs. In 2010, Sotelo et al found that there are enhancer elements located within the cancer-associated regions can regulate Myc promoter activity, and the previously identified cancer risk locus, rs6983267, located within this enhancer, acts as a functional variant in the regulation of Myc transcription.[18] Soon after, Hazelett and his colleagues reported that the G allele at rs183373024 may result in the downregulation of a tumor-suppressor-like gene target of the FoxA1 enhancer.[19] Therefore, 8q24 can be viewed as an enhancers region affecting cancer risk via the regulation of distant gene expression. Our study revealed strong evidence of an association with cancer risk for 6 variants, indicating that there might be different causal variants and functional mechanisms involved in associations of variants in the 8q24 with risk of human cancers.

There are several limitations of the study. First, a unified analysis standard across studies such as the control, could not be defined for lack of raw data from the original publications. Second, it is likely that some publications were overlooked, some relevant published studies with null results may not be identified. Third, due to insufficient data, we were unable to evaluate publication bias for associations between several variants in 8q24 region and cancer. Finally, we conducted meta-analysis based on minor allele of a variant, future studies with much larger sample size are warranted to confirm these associations.

5. Conclusions

Our study provides summary evidence that common variants in the 8q24 are associated with risk of prostate cancer, colorectal cancer, thyroid cancer, breast cancer, bladder cancer, stomach cancer, and glioma in this large-scale research synopsis and meta-analysis, suggesting that variants in the 8q24 region are related mechanistically to the development of cancer. Interactions of SNP-SNP, gene–gene, and gene–environment should be addressed in future large multicentric studies to explore the mechanisms underlying variants in the 8q24 involved in various human cancers.

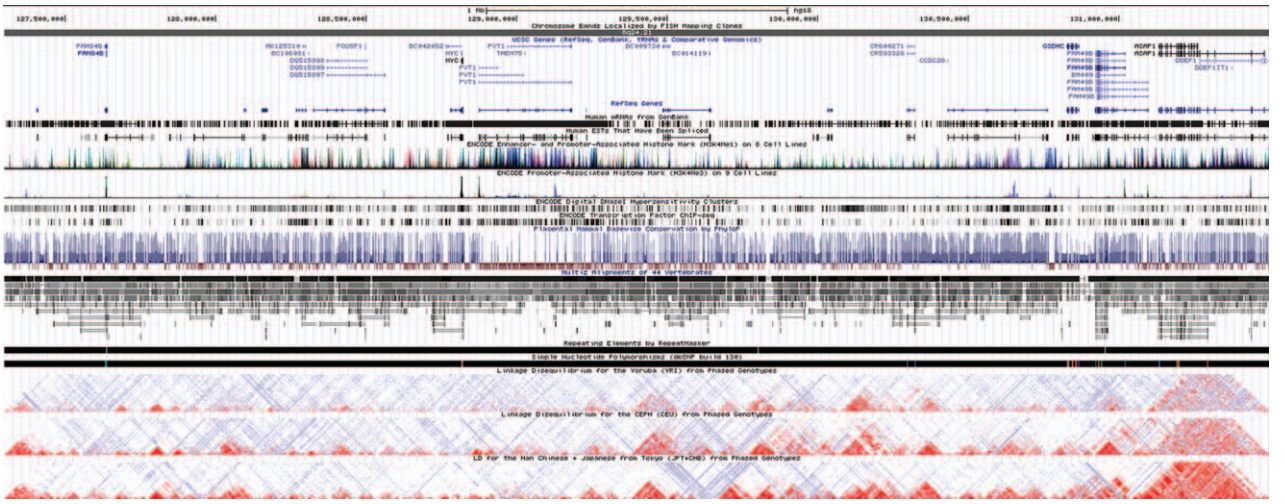

Figure 3. Evidence from ENCODE data for regulatory function of SNPs in 8q24 using the UCSC Genome Browser. The plot represent 8q24.21 region (NCBI Human Genome GRCh37). Tracks (from top to bottom) in each of the plots are Genome Base Position, Chromosome Bands, UCSC Genes, Human mRNAs from GenBank, Human ESTs That Have Been Spliced, ENCODE Enhancer- and Promoter-Associated Histone Mark (H3K4Me1) on 8 Cell Lines, ENCODE Promoter-Associated Histone Mark (H3K4Me3) on 9 Cell Lines, ENCODE Digital DNaseI Hypersensitivity Clusters, ENCODE Transcription Factor ChIP-seq, ENCODE Chromatin State Segmentation by HMM from Broad Institute, Simple Nucleotide Polymorphisms (dbSNP build 130), Linkage Disequilibrium (LD) for the Yoruba (YRI) from Phased Genotypes, LD for the CEPH (CEU) from Phased Genotypes, and LD for the Han Chinese+Japanese from Tokyo (CHB+JPT) from Phased genotypes.

Author contributions

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