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, thyroid cancer, and kidney 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, rs9683267, 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.

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, rs1090154 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, respectively. In 2014, Skibola et al reported that rs13254990 was associated with follicular lymphoma risk by conducting a large-scale two-stage GWAS.[16]
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 Cochran’s Q test and calculated I² statistic to evaluate heterogeneity between studies. I² 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 meta, 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 I² < 25%, B for I² between 25% and 50%, and C for I² > 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 ≤ 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.
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 < 0.5). Significant associations with prostate cancer risk were found for rs16901979 (OR = 1.456, 95% CI: 1.31–1.64; P = 1.12 × 10^{-11}), rs1447295 (OR = 1.29, 95% CI: 1.21–1.38; P = 2.74 × 10^{-14}), DG85737-8 allele (OR = 1.29, 95% CI: 1.12–1.48; P = 2.83 × 10^{-4}), rs6983561 (OR = 1.29, 95% CI: 1.02–1.64; P = 0.04), rs10090154 (OR = 1.33, 95% CI: 1.17–1.52; P = 1.87 × 10^{-3}), rs7000448 (OR = 1.11, 95% CI: 1.04–1.19; P = 0.03), rs13254738 (OR = 1.11, 95% CI: 1.01–1.22; P = 0.026), rs6983267 (OR = 1.14, 95% CI: 1.04–1.25; P = 0.006), rs7017300 (OR = 1.39, 95% CI: 1.15–1.68; P = 0.001), rs7837688 (OR = 1.48, 95% CI: 1.29–1.71; P = 4.76 × 10^{-10}), rs1016343 (OR = 1.33, 95% CI: 1.20–1.48; P = 5.64 × 10^{-9}), rs7008482 (OR = 0.77, 95% CI: 0.62–0.96; P = 0.021), rs4242384 (OR = 1.42, 95% CI: 1.05–1.92; P = 0.022), rs620861 (OR = 0.84, 95% CI: 0.77–0.92; P = 7.49 × 10^{-5}), rs10086908 (OR = 0.73, 95% CI: 0.60–0.88; P = 0.001). Significant associations with colorectal cancer risk were found for rs10505477 (OR = 1.13, 95% CI: 1.09–1.18; P = 7.03 × 10^{-13}), rs6983267 (OR = 1.17, 95% CI: 1.08–1.19; P = 4.66 × 10^{-7}) and rs10808556 (OR = 1.18, 95% CI: 1.12–1.25; P = 2.10 × 10^{-8}).

Significant associations with thyroid cancer risk were found for rs6983267 (OR = 1.19, 95% CI: 1.08–1.31; P = 3.57 × 10^{-4}), rs5705857 (OR = 3.54, 95% CI: 2.90–4.33; P = 2.31 × 10^{-35}), rs13281615 (OR = 1.13, 95% CI: 1.08–1.18; P = 3.98 × 10^{-7}), rs9642880 (OR = 1.25, 95% CI: 1.20–1.30; P = 1.79 × 10^{-27}).

Significant associations with stomach cancer risk were found for rs1447295 (OR = 0.80, 95% CI: 0.65–0.99; P = 0.035). No significant associations 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 DG85737-8 allele (I^2 = 2.32%, P = 0.803) and rs10090154 (I^2 = 0.0%, P = 0.873) with prostate cancer, rs10808556 (I^2 = 0.0%, P = 0.394) with colorectal cancer, rs5705857 (I^2 = 10.9%, P = 0.326) for gliomas, rs9642880 (I^2 = 4.10%, P = 0.39) with bladder cancer.

Moderate heterogeneity was observed for associations of rs7000448 (I^2 = 36.2%, P = 0.152) with prostate cancer, rs10505477 (I^2 = 29.2%, P = 0.185) with colorectal cancer and rs1447295 (I^2 = 28.0%, P = 0.249) with stomach cancer.

Large heterogeneity was found for associations of rs16901979 (I^2 = 84.3%, P = 0.000), rs1447295 (I^2 = 77.6%, P = 0.000), rs6983561 (I^2 = 92.2%, P = 0.000), rs6983267 (I^2 = 90.5%, P = 0.000), rs13254738 (I^2 = 59.8%, P = 0.029), rs7017300 (I^2 = 83.3%, P = 0.000), rs7837688 (I^2 = 80.1%, P = 0.000), rs1016343 (I^2 = 70.2%, P = 0.009), rs7008482 (I^2 = 84.2%, P = 0.039), rs4242384 (I^2 = 81.3%, P = 0.005), rs620861 (I^2 = 73.1%, P = 0.005), rs10086908 (I^2 = 89.3%, P = 0.000) with prostate cancer, rs6983267 with colorectal cancer (I^2 = 64.4%, P = 0.000) and rs6983267 with thyroid cancer (I^2 = 78.6%, P = 0.000), rs13281615 (I^2 = 58.9%, P = 0.007) 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 evidence 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 DG85737-8 allele, rs10090154 in prostate cancer, rs10808556 in colorectal cancer, rs5705857 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, DG85737-8 allele, rs10090154, rs7000448, rs9683267, rs7017300, rs7837688, rs1016343, rs620861, rs10086908 in prostate cancer, rs10505477, rs6983267, rs10808556 in colorectal cancer, rs6983267 in thyroid cancer, rs5705857 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 rs9683561, 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, rs9683267, 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 DG85737-8 allele (Fig. 2A), rs10090154 (Fig. 2B), rs7000448 (Fig. 2C) in prostate cancer, rs9642880 in bladder cancer (Fig. 2D), rs10808556 in colorectal cancer (Fig. 2E), rs5705857 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 Zegers, 2011[21] | Cohort Study                                | Netherlands       | Caucasian | rs16901979 | prostate     | 281/267        |
| Marcelo Chen, 2010[22] | Case–control study                          | China             | Asian     | rs6983561  | prostate     | 331/335        |
| Prodipto Pal, 2009[23] | Case–control study                          | USA               | Caucasian | rs16901979 | prostate     | 596/567        |
|                      |                                               |                   |           | rs1447295 | prostate     |                |
|                      |                                               |                   |           | rs1447295 | prostate     |                |
|                      |                                               |                   |           | rs6983267 | prostate     |                |
|                      |                                               |                   |           | rs1016343 | prostate     |                |
| 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               | African   | rs16901979 | prostate     | 417/416        |
|                      |                                               |                   |           | rs1447295 | prostate     | 89/87          |
|                      |                                               |                   |           | rs1447295 | prostate     | 89/89          |
|                      |                                               |                   |           | rs6983561 | prostate     | 417/417        |
|                      |                                               |                   |           | rs6983267 | prostate     | 89/89          |
|                      |                                               |                   |           | rs10090154 | prostate     | 417/414        |
|                      |                                               |                   |           | rs10090154 | prostate     | 89/88          |
|                      |                                               |                   |           | rs7000448 | prostate     | 416/417        |
|                      |                                               |                   |           | rs7000448 | prostate     | 89/89          |
|                      |                                               |                   |           | rs6983267 | prostate     | 417/417        |
|                      |                                               |                   |           | rs6983267 | prostate     | 89/89          |
|                      |                                               |                   |           | rs13254738 | prostate     | 506/506        |
|                      |                                               |                   |           | rs13254738 | prostate     | 89/88          |
| Christiane Robbins, 2007[27] | Case–control study                          | USA               | African   | rs16901979 | prostate     | 490/567        |
|                      |                                               |                   |           | rs1447295 | prostate     |                |
|                      |                                               |                   |           | 1447296   | prostate     |                |
|                      |                                               |                   |           | DG8S737   | prostate     |                |
|                      |                                               |                   |           | rs6983267 | prostate     |                |
|                      |                                               |                   |           | rs6983267 | prostate     |                |
|                      |                                               |                   |           | rs6983267 | prostate     |                |
| 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     | 550/5270       |
| Julius Gudmundsson, 2007[30] | Case–control study                          | Iceland           | Caucasian | rs16901979 | prostate     | 676/643        |
|                      |                                               |                   |           | rs1447295 | prostate     | 2663/5500      |
|                      |                                               |                   |           | rs1447295 | prostate     | 373/372        |
| Gianluca Severi, 2007[31] | Case–control study                          | Australia         | Caucasian | rs1447295 | prostate     | 821/732        |
| Dominika Wokolenczyk, 2008[32] | Case–control study                          | Poland            | Caucasian | rs6983267 | prostate     | 1910/1885      |
|                      |                                               |                   |           | rs6983267 | prostate     | 779/1910       |
|                      |                                               |                   |           | rs6983267 | prostate     | 485/1910       |
|                      |                                               |                   |           | rs6983267 | prostate     | 1006/1910      |
|                      |                                               |                   |           | rs6983267 | prostate     | 488/1910       |
| S. Lilly Zheng, 2007[33]  | Case–control study                          | USA               | Caucasian | rs16901979 | prostate     | 1563/576       |
|                      |                                               |                   |           | rs1447295 | prostate     |                |
|                      |                                               |                   |           | rs1447295 | prostate     |                |
|                      |                                               |                   |           | rs6983267 | prostate     |                |
|                      |                                               |                   |           | rs6983267 | prostate     |                |
|                      |                                               |                   |           | rs6983267 | prostate     |                |
|                      |                                               |                   |           | rs7017300 | prostate     |                |
|                      |                                               |                   |           | rs7837688 | prostate     |                |
|                      |                                               |                   |           | rs11069089| prostate     |                |
|                      |                                               |                   |           | rs11069089| prostate     |                |
|                      |                                               |                   |           | rs11069089| prostate     |                |
|                      |                                               |                   |           | rs11069089| prostate     |                |
|                      |                                               |                   |           | rs11069089| prostate     |                |
| Jae Y. Young, 2012[4]   | Hospital-based case–control study           | Korea             | Asian     | rs16901979 | prostate     | 194/169        |
| Naoki Terada, 2006[34]  | Case–control study                          | Japanese          | Asian     | rs1447295 | prostate     | 507/387        |
| Michael N. Okobia, 2011[35] | Case–control study                          | Caribbean         | African   | rs16901979 | prostate     | 338/426        |
|                      |                                               |                   |           | rs1447295 | prostate     | 354/438        |
|                      |                                               |                   |           | rs1447295 | prostate     | 343/426        |
| Claudia A. Salinas, 2008[36] | Population-based case–control study         | USA               | Caucasian | rs1447295 | prostate     | 1252/1233      |
|                      |                                               |                   |           | rs6983561 | prostate     | 1264/1236      |
|                      |                                               |                   |           | rs6983561 | prostate     | 1288/1250      |
|                      |                                               |                   |           | rs6983561 | prostate     | 1262/1239      |

(continued)
| Study, year                  | Study design         | Country/region | Ethnicity | Variant       | Cancer site | Cases/ controls |
|-----------------------------|----------------------|----------------|-----------|---------------|-------------|-----------------|
| Marnita L Benford, 2010[36] | Case–control study  | USA            | Caucasian | rs6983267     | prostate    | 1258/1238       |
|                             |                      |                |           | rs13254738    |             | 1256/1234       |
|                             |                      |                |           | rs7837688     |             | 1260/1241       |
|                             |                      |                |           | rs1016343     |             | 1253/1233       |
|                             |                      |                |           | rs7837328     |             | 1258/1239       |
| Siqun Lilly Zheng, 2010[37] | Population-based case–control study | China     | Asian     | rs16901979    | prostate    | 192/512         |
|                             |                      |                |           | rs1447295     |             | 189/523         |
|                             |                      |                |           | rs6983561     |             | 186/908         |
|                             |                      |                |           | rs10090154    |             | 189/505         |
|                             |                      |                |           | rs4242382     |             | 193/1167        |
|                             |                      |                |           | rs4242384     |             | 193/524         |
| Rosalind A Eeles, 2007[7]   | Population-based case–control study | United Kingdom | Caucasian | rs1447295     | prostate    | 283/145         |
|                             |                      |                |           | rs6983267     |             | 284/151         |
|                             |                      |                |           | rs7837328     |             | 282/152         |
| Jielin Sun, 2008[38]        | Population-based case–control study | USA        | Caucasian | rs16901979    | prostate    | 1906/1934       |
|                             |                      |                |           | rs1447295     |             | 1125/560        |
| 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       |
| Liang Wang, 2007[41]        | Case–control study  | USA            | Caucasian | rs1447295     | prostate    | 1121/545        |
| S. Lilly Zheng, 2008[42]    | Population-based case–control study | Sweden     | Caucasian | rs16901979    | prostate    | 2893/1781       |
| Ying-Cai Tan, 2008[43]     | Case–control study  | India          | Asian     | rs16901979    | prostate    | 153/227         |
| Vorel Jinga, 2016[44]      | Case–control study  | Romania        | Caucasian | rs16901979    | prostate    | 955/1007        |
| Cheryl D. Cropp, 2014[45]  | Population-based case–control study | USA        | Caucasian | rs7000448     | prostate    | 522/510         |
| Lin-Lin Zhang, 2014[46]    | Case–control study  | China          | Asian     | rs4242384     | prostate    | 388/384         |
| Ignacio F. San Francisco, 2014[47] | Case–control study | Chile      | Hispanic  | rs1447295     | prostate    | 83/21           |
| Adam B. Murphy, 2012[48]   | Case–control study  | Cameroon       | African   | rs16901979    | prostate    | 308/469         |
| Fang Liu, 2011[49]         | Case–control study  | China          | Asian     | rs16901979    | prostate    | 1108/1525       |

(continued)
| Study, year                     | Study design                        | Country/region | Ethnicity | Variant | Cancer site  | Cases/controls |
|--------------------------------|-------------------------------------|----------------|-----------|---------|--------------|----------------|
| Ethan M. Lange, 2012[49]       | Case–control study                  | USA            | Caucasian | rs6983267| prostate     | 1176/1101      |
|                                |                                     |                |           | rs620861 | prostate     | 2642/2584      |
|                                |                                     |                |           | rs10086908| prostate     | 3167/3325      |
|                                |                                     |                |           | rs1447295| prostate     | 2764/3255      |
|                                |                                     |                |           | rs6983561| prostate     | 1683/1403      |
|                                |                                     |                |           | rs10090154| prostate     | 1698/2329      |
|                                |                                     |                |           | rs7000448| prostate     | 3666/2992      |
|                                |                                     |                |           | rs6983567| prostate     | 2557/2277      |
|                                |                                     |                |           | rs13264798| prostate     | 636/330        |
|                                |                                     |                |           | rs7837695| prostate     | 1975/1830      |
|                                |                                     |                |           | rs1016343| prostate     | 2172/1760      |
|                                |                                     |                |           | rs7837382| prostate     | 473/772        |
|                                |                                     |                |           | rs16091979| prostate     | 861/876        |
|                                |                                     |                |           | rs1447295| prostate     | 127/345        |
| Bao-Li Chang, 2011[50]         | Case–control study                  | USA            | African   | rs1447295| prostate     | 158/119        |
|                                |                                     |                |           | rs6983561| prostate     | 690/602        |
|                                |                                     |                |           | rs6983267| prostate     | 10286/9135     |
|                                |                                     |                |           | rs6983267| prostate     | 1906/1934      |
| Yunfei Wang, 2011[51]          | Case–control study                  | USA            | African   | rs1447295| prostate     | 391/323        |
|                                |                                     |                |           | rs6983561| prostate     | 868/878        |
|                                |                                     |                |           | rs6983267| prostate     | 601/840        |
|                                |                                     |                |           | rs1447295| prostate     | 196/472        |
|                                |                                     |                |           | rs6983267| prostate     | 4296/4299      |
| Tatsuya Hamano, 2010[52]       | Case–control study                  | Japan          | Asian     | rs1447295| prostate     | 158/119        |
| Dominika Wokolorczyk, 2010[53]| Hospital-based case–control study   | Poland         | Caucasian | rs1447295| prostate     | 690/602        |
| Meredith Yeager, 2009[54]      | Case–control study                  | USA            | Caucasian | rs1447295| prostate     | 10286/9135     |
| Ali Amin Al Olama, 2009[55]    | Case–control study                  | USA            | Caucasian | rs1447295| prostate     | 1906/1934      |
|                                |                                     |                |           | rs6983561| prostate     | 391/323        |
|                                |                                     |                |           | rs6983267| prostate     | 868/878        |
|                                |                                     |                |           | rs1447295| prostate     | 601/840        |
|                                |                                     |                |           | rs6983267| prostate     | 196/472        |
|                                |                                     |                |           | rs6983267| prostate     | 4296/4299      |
| Miao Liu, 2009[56]             | Case–control study                  | Japan          | Asian     | rs1447295| prostate     | 158/119        |
| Jianfeng Xu, 2009[57]          | Case–control study                  | USA            | African   | rs1447295| prostate     | 690/602        |
|                                |                                     |                |           | rs6983267| prostate     | 10286/9135     |
|                                |                                     |                |           | rs6983267| prostate     | 1906/1934      |
|                                |                                     |                |           | rs1447295| prostate     | 391/323        |
|                                |                                     |                |           | rs6983267| prostate     | 868/878        |
|                                |                                     |                |           | rs1447295| prostate     | 601/840        |
|                                |                                     |                |           | rs6983267| prostate     | 196/472        |
|                                |                                     |                |           | rs6983267| prostate     | 4296/4299      |
| Luis M. Real, 2014[58]         | Case–control study                  | Spain          | Asian     | rs1447295| prostate     | 158/119        |
|                                |                                     |                |           | rs6983267| prostate     | 690/602        |
|                                |                                     |                |           | rs1447295| prostate     | 10286/9135     |
|                                |                                     |                |           | rs6983267| prostate     | 1906/1934      |
|                                |                                     |                |           | rs1447295| prostate     | 391/323        |
|                                |                                     |                |           | rs6983267| prostate     | 868/878        |
|                                |                                     |                |           | rs1447295| prostate     | 601/840        |
|                                |                                     |                |           | rs6983267| prostate     | 196/472        |
|                                |                                     |                |           | rs6983267| prostate     | 4296/4299      |
| A. Daraei, 2012[59]            | Case–control study                  | Iran           | Asian     | rs1447295| prostate     | 110/120        |
| Mian Li, 2011[60]              | Hospital-based case–control study   | China          | Asian     | rs1447295| prostate     | 430/786        |
|                                | Case–control study                  | Japan          | Asian     | rs1447295| prostate     | 616/1494       |
|                                | Case–control study                  | Netherlands    | Caucasian | rs1447295| prostate     | 861/2329       |
|                                | Population-based case–control study| USA            | Caucasian | rs1447295| prostate     | 3583/2579      |
|                                | Case–control study                  | Netherlands    | Caucasian | rs1447295| prostate     | 561/721        |
|                                | Case–control study                  | USA            | Caucasian | rs1447295| prostate     | 4261/3752      |
|                                | Case–control study                  | USA            | Caucasian | rs1447295| prostate     | 90/132         |
|                                | Case–control study                  | USA            | Caucasian | rs1447295| prostate     | 401/518        |
|                                | Case–control study                  | USA            | Caucasian | rs1447295| prostate     | 1341/2193      |
|                                | Case–control study                  | USA            | Caucasian | rs1447295| prostate     | 1339/2191      |
|                                | Case–control study                  | United Kingdom | Caucasian | rs1447295| prostate     | 1071/1040      |
|                                | Case–control study                  | United Kingdom | Caucasian | rs1447295| prostate     | 1071/1040      |
|                                | Case–control study                  | China          | Asian     | rs1447295| prostate     | 476/961        |
| Benpeng Zhang, 2014[61]        | Case–control study                  | Germany        | Caucasian | rs1447295| prostate     | 2712/2718      |
|                                | Case–control study                  | Germany        | Caucasian | rs1447295| prostate     | 2712/2713      |

(continued)
Table 1 (continued).

| Study, year | Study design | Country/region | Ethnicity | Variant | Cancer site | Cases/controls |
|-------------|--------------|----------------|-----------|----------|-------------|----------------|
| MONIRA S. KUPER, 2010[79] | Case-control study | USA | African | rs1088556 | colon | 2712/2713 |
| Fang Xiong, 2010[78] | Case-control study | China | Asian | rs6983267 | colon | 2124/2124 |
| S von Hövel, 2010[77] | Case-control study | Sweden | Caucasian | rs6983267 | colon | 1757/1741 |
| Shiying Ishimaru, 2012[76] | Case-control study | Japan | Asian | rs6983267 | colon | 1511/2008 |
| Ioan Nicolaie Matei, 2012[75] | Hospital-based case-control study | Romania | Caucasian | rs1088556 | colon | 151/182 |
| Fen-xia Li, 2012[74] | Case-control study | China | Asian | rs6983267 | colon | 229/267 |
| Sonia S.Kuper, 2009[73] | Hospital-based case-control study | USA | Caucasian | rs10505477 | colon | 286/202 |
| Carolyn M Hutter, 2010[72] | Population-based case-control study | USA | Caucasian | rs10505477 | colon | 2069/2443 |
| Morir Sadat Haerian, 2014[71] | Case-control study | Iran | Caucasian | rs10505477 | colon | 165/151 |
| Steven J.Lube, 2012[70] | Case-control study | United Kingdom | Caucasian | rs6983267 | colon | 1514/6051 |
| Stephen B. Gruber, 2007[69] | Population-based case-control study | USA | Caucasian | rs10505477 | colon | 1860/13936 |
| Ruta Sahasrabudhe, 2013[68] | Case-control study | Multiple countries | Caucasian | rs6983267 | thyroid | 561/899 |
| Abdelmounaim Akl, 2011[67] | Case-control study | Spain | Caucasian | rs6983267 | thyroid | 4008/3479 |
| Monira Cipollini, 2013[66] | Population-based case-control study | Italy | Caucasian | rs6983267 | thyroid | 1200/1196 |
| Angela M Jones, 2011[65] | Case-control study | United Kingdom | Caucasian | rs6983267 | thyroid | 82/6151 |
| Tatiana I. Rogoznitzh, 2013[64] | Population-based case-control study | Slovenia | Caucasian | rs6983267 | thyroid | 1200/1196 |
| Yuan Xu, 2012[63] | Case-control study | Multiple countries | Caucasian | rs6983267 | thyroid | 347/6150 |
| Robert B. Jenkins, 2012[62] | Case-control study | USA | Caucasian | rs6983267 | thyroid | 852/789 |
| Yu Zhang, 2011[61] | Hospital-based case-control study | China | Asian | rs13298156 | breast | 285/257 |
| Jingshan Shu, 2012[60] | Case-control study | China | Asian | rs13298156 | breast | 629/365 |
| Olivia Fletcher, 2008[59] | Case-control study | United Kingdom | Caucasian | rs13298156 | breast | 1470/1341 |
| Isabel Blematone, 2011[58] | Case-control study | Chile | Caucasian | rs13298156 | breast | 347/601 |
| Sharon N Temeka, 2011[57] | Population-based case-control study | United Kingdom | Caucasian | rs13298156 | breast | 1200/1196 |
| Daniele Campa, 2011[56] | Cohort study | Multiple countries | Caucasian | rs13298156 | breast | 830/11651 |
| Jie Long, 2010[55] | Cohort study | China | Asian | rs13298156 | breast | 2945/2981 |
| Montserrat Garcia-Closas, 2008[54] | Cohort study | Multiple countries | Caucasian | rs13298156 | breast | 14098/13014 |
| Tatiana V. Gorodnova, 2010[53] | Case-control study | Russia | Caucasian | rs13298156 | breast | 140/174 |
| Ayse Latif, 2011[52] | Case-control study | United Kingdom | Caucasian | rs13298156 | breast | 693/343 |
| Rulla M. Tanimii, 2010[51] | Population-based case-control study | Sweden | Caucasian | rs13298156 | breast | 661/711 |
| Morgan Rupprecht, 2011[50] | Case-control study | France | Caucasian | rs642880 | bladder | 1261/261 |
| Ping Wang, 2011[49] | Case-control study | China | Asian | rs642880 | bladder | 1210/1000 |
| David R. Yates, 2011[48] | Case-control study | China | Asian | rs642880 | bladder | 230/255 |
| Melvin Wang, 2009[47] | Case-control study | Iceland and Netherlands | Caucasian | rs642880 | bladder | 3853/37985 |
| Lambertas A. Klemeny, 2008[46] | Case-control study | Germany | Caucasian | rs642880 | bladder | 515/1592 |
| Klaus Gokka, 2009[45] | Case-control study | China | Asian | rs642880 | bladder | 184/384 |
| Heather P. Tarleton, 2014[44] | Population-based case-control study | Poland | Caucasian | rs1447295 | stomach | 286/365 |
| Paul Lockhead, 2011[43] | Population-based case-control study | USA | Caucasian | rs1447295 | stomach | 197/388 |

rs1016343, rs620861, rs10885908 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, rs424384 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.
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, thyroid cancer and breast cancer. Using the Venice criteria and false-positive report probability tests, we graded 6 variants (DGS8737 -8 allele, rs10090154, rs7000448 in prostate cancer, rs10808556 in colorectal cancer, rs5705857 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
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 represents 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 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.

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References
[1] Bhat M, Robichaud N, Hulea L, et al. Targeting the translation machinery in cancer. Nat Rev Drug Discov 2015;14:261–78.
[2] Tomlinson I, Webb E, Carvajal-Carmona L, et al. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24. Nat Genet 2007;39:984–8.
[3] Poynter JN, Figueiredo JC, Conti DV, et al. Variants on 9p24 and 8q24 are associated with risk of colorectal cancer: results from the Colon Cancer Family Registry. Cancer Res 2007;67:11128–32.
[4] Jeong JY, Park S, Yoon H, et al. Association of common variations of 8q24 with the risk of prostate cancer in Koreans and a review of the Asian population. BJU Int 2012;110(6 Pt B):E318–325.
[5] Okobia MN, Zmuda JM, Ferrell RE, et al. Chromosome 8q24 variants are associated with prostate cancer risk in a high risk population of African ancestry. Prostate 2011;71:1054–63.
[6] Jinga V, Coki BE, Manolescu A, et al. Replication study of 34 common SNPs associated with prostate cancer in the Romanian population. J Cell Molec Med 2016;20:594–600.
[7] Eeles RA, Kote-Jarai Z, Giles GG, et al. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 2008;40:316–21.
[8] Fletcher O, Johnson N, Gibson L, et al. Association of genetic variants at 8q24 with breast cancer risk. Cancer Epidemiol Biomarkers Prev 2008;17:702–5.
[9] Zhang Y, Yi P, Chen W, et al. Association between polymorphisms within the susceptibility region 8q24 and breast cancer in a Chinese population. Tumour Biol 2014;35:2649–54.
[10] Jenkins RB, Xiao Y, Scotte H, et al. A low-frequency variant at 8q24.21 is strongly associated with risk of oligodendrogliomas and astrocytomas with IDH1 or IDH2 mutation. Nat Genet 2012;44:1122–5.
[11] Kiemeney LA, Thorlacius S, Sulem P, et al. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. Nat Genet 2008;40:1307–12.
[12] Park SL, Chang SG, Cai L, et al. Associations between variants of the 8q24 chromosome and nine smoking-related cancer sites. Cancer Epidemiol Biomarkers Prev 2008;17:3193–202.
[13] Garcia-Closas M, Hall P, Nevanlinna H, et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. PLoS Genet 2008;4:e1000054.
[14] Golka K, Hermes M, Selinski S, et al. Susceptibility to urinary bladder cancer: relevance of rs9642880[T], GSTM10/0 and occupational exposure. Pharmacogenet Genom 2009;19:903–6.
[15] Lojchek P, Ng MT, Hold GL, et al. Possible association between a genetic polymorphism at 8q24 and risk of upper gastrointestinal cancer. Eur J Cancer Prev 2011;20:54–7.
[16] Sibolola CF, Berndt SI, Vijai J, et al. Genome-wide association study identifies five susceptibility loci for follicular lymphoma outside the HLA region. Am J Hum Genet 2014;95:462–71.
[17] Ioannidis JP, Boffetta P, Little J, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. Int J Epidemiol 2008;37:120–32.
[18] Sotelo J, Esposito D, Duhacon MA, et al. Long-range enhancers on 8q24 regulate c-Myc. Proc Natl Acad Sci USA 2010;107:3001–5.
[19] Hazlelet DJ, Coeteeza SG, Coeteeza GA. A rare variant, which destroys a FoxA1 site, is associated with prostate cancer risk. Cell Cycle 2013;12:379–80.
[20] Cancel-Tassin G, Romana M, Gaffory C, et al. Region 2 of 8q24 is associated with the risk of aggressive prostate cancer in Caribbean men of African descent from Guadeloupe (French West Indies). Asia J Androl 2015;17:1179–9.
[21] Zeegers MP, Khan HS, Schouten LJ, et al. Genetic marker polymorphisms on chromosome 8q24 and prostate cancer in the Dutch population: DG8S737 may not be the causative variant. Eur J Hum Genet 2011;19:118–20.
[22] Chen M, Huang YC, Yang S, et al. Common variants at 8q24 are associated with prostate cancer risk in Taiwanese men. Prostate 2010;70:502–7.
[23] Pal P, Xi H, Guha S, et al. Common variants in 8q24 are associated with risk for prostate cancer and tumor aggressiveness in men of European ancestry. Prostate 2009;69:1548–56.
[24] Chen M, Huang YC, Ko IL, et al. The rs1447295 at 8q24 is a risk variant for prostate cancer in Taiwanese men. Urol Oncol 2009;27:373–6.
[26] Cheng I, Plummer SJ, Jorgenson E, et al. 8q24 and prostate cancer: association with advanced disease and meta-analysis. Eur J Hum Genet 2008;16:496–502.

[27] Robbins C, Torres JB, Hooker S, et al. Confirmation study of prostate cancer risk variants at 8q24 in African Americans identifies a novel risk locus. Genome Res 2007;17:1717–22.

[28] Sournimni M, Agalliu I, Schaaf DJ, et al. Confirmation of a positive association between prostate cancer risk and a locus at chromosome 8q24. Cancer Epidemiol Biomarkers Prev 2007;16:809–14.

[29] Schumacher FR, Fiegelson HS, Cox DG, et al. A common 8q24 variant in prostate and breast cancer from a large nested case-control study. Cancer Res 2007;67:2951–6.

[30] Gudmundsson J, Sulem P, Manolescu A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet 2007;39:631–7.

[31] Severi G, Hayes VM, Padilla EJ, et al. The common variant rs1447295 on chromosome 8q24 and prostate cancer risk: results from an Australian population-based case-control study. Cancer Epidemiol Biomarkers Prev 2007;16:10–2.

[32] Wokolborszczyk D, Grimsbick W, Sikorski A, et al. A range of cancers is associated with the rs6983267 marker on chromosome 8. Cancer Res 2008;68:9982–6.

[33] Zheng SL, Sun J, Cheng Y, et al. Association between two unlinked loci at 8q24 and prostate cancer risk among European Americans. J Natl Cancer Inst 2007;99:1525–33.

[34] Terada N, Tsuchiya N, Ma Z, et al. Association of genetic polymorphisms at 8q24 with the risk of prostate cancer in a Japanese population. Prostate 2008;68:1689–95.

[35] Salman CA, Kwon E, Carlson CS, et al. Multiple independent genetic variants in the 8q24 region are associated with prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2008;17:1203–13.

[36] Benford ML, VanCleave TT, Lavender NA, et al. 8q24 sequence variants in relation to prostate cancer risk among men of African descent: a case-control study. BMC Cancer 2010;10:34.

[37] Zheng SL, Hsing AW, Sun J, et al. Association of 17 prostate cancer susceptibility loci with prostate cancer risk in Chinese men. Prostate 2010;70:425–32.

[38] Sun J, Lange EM, Isaacs SD, et al. Chromosome 8q24 risk variants in hereditary and non-hereditary prostate cancer patients. Prostate 2008;68:489–97.

[39] Papankolokpoulo A, Landt O, Ntoumas K, et al. The multi-cancer marker, rs6983267, located at region 3 of chromosome 8q24, is associated with prostate cancer in Greek patients but does not contribute to the aggressiveness of the disease. Clin Chem Lab Med 2011;50:379–85.

[40] Penney KL, Salinas CA, Pomerantz M, et al. Evaluation of 8q24 and 17q risk loci and prostate cancer mortality. Clin Cancer Res 2010;15:3223–30.

[41] Wang L, McDonnell SK, Slusser JP, et al. Two common chromosome 8q24 variants are associated with increased risk for prostate cancer. Cancer Res 2007;67:2944–50.

[42] Zheng SL, Sun J, Wirkwhan F, et al. Cumulative association of five genetic variants with prostate cancer. N Engl J Med 2008;358:910–5.

[43] Tan YC, Zeigler-Johnson C, Mittal RD, et al. The rs1447295 and DG8S737 markers with familial prostate cancer and high grade disease. J Urol 2010;184:738–42.

[44] Wokolborszczyk D, Grimsbick W, Stojecki M, et al. The rs1447295 and DG8S737 markers on chromosome 8q24 and cancer risk in the Polish population. Eur J Cancer Prev 2010;19:167–71.

[45] Kote-Jarai Z, Amin Al Olama A, Leongamornlert D, et al. Identification of a novel prostate cancer susceptibility variant in the KLK3 gene transcript. Hum Genet 2011;129:687–94.

[46] Al Olama AA, Kote-Jarai Z, Giles GG, et al. Multiple loci on 8q24 associated with prostate cancer susceptibility. Nat Genet 2009;41:1058–60.

[47] Liu M, Kuroksaki T, Suzuki M, et al. Significance of common variants on human chromosome 8q24 in relation to the risk of prostate cancer in native Japanese men. BMC Genet 2009;10:37.

[48] Xu J, Kibel AS, Hu JJ, et al. Prostate cancer risk associated loci in African Americans. Cancer Epidemiol Biomarkers Prev 2009;18:2145–9.

[49] Beuten J, Gelfond JA, Martinez-Fierro ML, et al. Association of chromosome 8q variants with prostate cancer risk in Caucasian and African American men. Carcinogenesis 2009;30:681–5.

[50] Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 2007;39:645–9.

[51] Real LM, Ruiz A, Gayan J, et al. A colorectal cancer susceptibility variant in 8q26 in the Spanish population identified by genome-wide association analysis. PLoS One 2014;9:e101178.

[52] Daraei A, Salehi R, Salehi M, et al. Effect of the rs6983267 polymorphism in the 8q24 region and rs4449903 polymorphism in EGFR gene on the risk of sporadic colorectal cancer in Iranian population. Med Oncol 2012;29:1044–5.

[53] Li M, Zhou Y, Chen P, et al. Genetic variants on chromosome 8q24 and colorectal neoplasia risk: a case-control study in China and a meta-analysis of the published literature. PLoS One 2011;6:e18251.

[54] Cui B, Okada Y, Jiang SG, et al. Common variant in 8q26-q27 is associated with distal colon cancer in an Asian population. Gut 2011;60:799–805.

[55] Middeldorp A, Jagmohan-Changur S, van Eijk R, et al. Enrichment of low penetration susceptibility loci in a Dutch familial colorectal cancer cohort. Cancer Epidemiol Biomarkers Prev 2009;18:3062–7.

[56] Pittman AM, Broederick P, Sullivan K, et al. CASP8 variants D302H and -652 6N ins/del do not influence the risk of colorectal cancer in the United Kingdom population. Br J Cancer 2008;98:1434–6.

[57] Li L, Plummer SJ, Thompson CL, et al. A common 8q24 variant and the risk of colon cancer: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2008;17:339–42.

[58] Yang B, Thayagarajan B, Gross MD, et al. Genetic variants at chromosome 8q24, colorectal epithelial cell proliferation, and risk for incident, sporadic colorectal adenomas. Mol Carcinog 2014;53(Suppl 1):E187–192.

[59] Yang B, Thayagarajan B, Gross MD, et al. No evidence that associations of incident, sporadic colorectal adenoma with its major modifiable risk factors differ by chromosome 8q24 region rs6983267 genotype. Mol Carcinog 2014;53(Suppl 1):E193–200.

[60] Curtin K, Lin WY, George R, et al. Meta association of colorectal cancer confirms risk alleles at 8q24 and 18q21. Cancer Epidemiol Biomarkers Prev 2009;18:616–21.

[61] Matsuo K, Suzuki T, Ito H, et al. Association between an 8q24 locus and the risk of colorectal cancer in Japanese. BMC Cancer 2009;9:379.

[62] Schafmayer C, Buch S, Volzke H, et al. Investigation of the colorectal cancer susceptibility region on chromosome 8q24 in a large German case-control sample. Int J Cancer 2009;124:75–80.

[63] Kupfer SS, Anderson JR, Hooker S, et al. Genetic heterogeneity in colorectal cancer associations between African and European Americans. Gastroenterology 2010;139:1677–85, 1685 e1671.1678.

[64] Xiong F, Wu C, Bi X, et al. Risk of genome-wide association study–identified genetic variants for colorectal cancer in a Chinese population. Cancer Epidemiol Biomarkers Prev 2010;19:1855–61.

[65] von Holst S, Picelli S, Edler D, et al. Association studies on I1 published colorectal cancer risk loci. Br J Cancer 2010;103:575–80.
[75] Ishimaru S, Mimori K, Yamamoto K, et al. Increased risk for CRC in diabetic patients with the nonrisk allele of SNPs at 8q24. Ann Surg Oncol 2012;19:2853-8.

[76] Mates IN, Jinga V, Csiki IE, et al. Single nucleotide polymorphisms in colorectal cancer: associations with tumor site and TNM stage. J Gastrointestin Liver Dis 2012;21:45–52.

[77] Li FX, Yang XX, Hu NY, et al. Single-nucleotide polymorphism associations for colorectal cancer in southern chinese population. Chin J Cancer Res 2012;24:29–35.

[78] Kupfer SS, Torres JB, Hooker S, et al. Novel single nucleotide polymorphism associations with colorectal cancer on chromosome 8q24 in African and European Americans. Carcinogenesis 2009;30:1353–7.

[79] Hutter CM, Slattery ML, Duggan DJ, et al. Characterization of the association between 8q24 and colon cancer: gene-environment exploration and meta-analysis. BMC Cancer 2010;10:670.

[80] Haerian MS, Haerian BS, Rooki H, et al. Association of 8q24.21 rs10505477-rs6983267 haplotype and age at diagnosis of colorectal cancer. Asian Pac J Cancer Prev 2012;13:369–74.

[81] Lubbe SJ, Whiffin N, Chandler I, et al. Relationship between 16 susceptibility loci and colorectal cancer phenotype in 3146 patients. Carcinogenesis 2012;33:108–12.

[82] Gruber SB, Moreno V, Rozej LS, et al. Genetic variation in 8q24 associated with risk of colorectal cancer. Cancer Biol Ther 2007;6:1143–7.

[83] Sahasrabudhe R, Estrada A, Lott P, et al. The 8q24 rs6983267G variant is associated with increased thyroid cancer risk. Endocr Relat Cancer 2015;22:841–9.

[84] Akdi A, Perez G, Pastor S, et al. Common variants of the thyroglobulin gene are associated with differentiated thyroid cancer risk. Thyroid 2011;21:519–25.

[85] Cipollini M, Figloldi G, Garritano S, et al. Risk of differentiated thyroid carcinoma and polymorphisms within the susceptibility cancer region 8q24. Cancer Epidemiol Biomarkers Prev 2013;22:2121–5.

[86] Jones AM, Howarth KM, Martin L, et al. Thyroid cancer susceptibility polymorphisms: confirmation of loci on chromosomes 9q22 and 14q13, validation of a recessive 8q24 locus and failure to replicate a locus on 5q24. J Med Genet 2012;49:158–63.

[87] Rogoumovitch TI, Bychkov A, Takahashi M, et al. The common genetic variant rs944289 on chromosome 14q13.3 associates with risk of both malignant and benign thyroid tumors in the Japanese population. Thyroid 2015;25:333–40.

[88] Öktay Y, Ulgen E, Can O, et al. IDH-mutant glioma specific association of rs5703587 located at 8q24.21 involves MYC deregulation. Sci Rep 2016;6:27569.

[89] Shan J, Mahfoudh W, Dsouza SP, et al. Genome-Wide Association Studies (GWAS) breast cancer susceptibility loci in Arabs: susceptibility and prognostic implications in Tunisians. Breast Cancer Res Treat 2012;135:715–24.

[90] Elematore I, Gonzalez-Hormazabal P, Reyes JM, et al. Association of genetic variants at TOX3, 2q35 and 8q24 with the risk of familial and early-onset breast cancer in a South-American population. Mol Biol Rep 2014;41:3715–22.

[91] Teraoka SN, Bernstein JI, Heiner AS, et al. Single nucleotide polymorphisms associated with risk for contralateral breast cancer in the Women’s Environment, Cancer, and Radiation Epidemiology (WECARE) Study. Breast Cancer Res 2011;13:R114.

[92] Campa D, Kaaks R, Le Marchand L, et al. Interactions between genetic variants and breast cancer risk factors in the breast and prostate cancer cohort consortium. J Natl Cancer Inst 2011;103:1252–63.

[93] Long J, Shu XO, Cai Q, et al. Evaluation of breast cancer susceptibility loci in Chinese women. Cancer Epidemiol Biomarkers Prev 2010;19:2357–65.

[94] Gorodnova TV, Kulagina E, Yanus GA, et al. Distribution of FGFR2, TNRC9, MAP3K1, LSP1, and 8q24 alleles in genetically enriched breast cancer patients versus elderly tumor-free women. Cancer Genet Cytogenet 2010;199:69–72.

[95] Latif A, Hadfield KD, Roberts SA, et al. Breast cancer susceptibility variants alter risks in familial disease. J Med Genet 2010;47:126–31.

[96] Tamini RM, Lagiou P, Cuzick J, et al. Birth weight, breast cancer susceptibility loci, and breast cancer risk. Cancer Causes Control 2010;21:689–96.

[97] Roupret M, Drouin SJ, Cancel-Tassin G, et al. Genetic variability in 8q24 confers susceptibility to urothelial carcinoma of the upper urinary tract and is linked with patterns of disease aggressiveness at diagnosis. J Urol 2012;187:424–8.

[98] Wang P, Ye D, Guo J, et al. Genetic score of multiple risk-associated single nucleotide polymorphisms is a marker for genetic susceptibility to bladder cancer. Genes Chromosomes Cancer 2014;53:31–40.

[99] Yates DR, Roupret M, Drouin SJ, et al. Genetic polymorphisms on 8q24.1 and 4p16.3 are not linked with urothelial carcinoma of the bladder in contrast to their association with aggressive upper urinary tract tumours. World J Urol 2013;31:53–9.

[100] Wang M, Wang M, Zhang W, et al. Common genetic variants on 8q24 contribute to susceptibility to bladder cancer in a Chinese population. Carcinogenesis 2009;30:991–6.

[101] Tarleton HP, Chang SC, Park SL, et al. Genetic variation at 8q24, family history of cancer, and upper gastrointestinal cancers in a Chinese population. Fam Cancer 2014;13:45–56.