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Pleiotropic effects of genetic risk variants for other cancers on colorectal cancer risk: PAGE, GECCO, and CCFR Consortia

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Abstract

Objective—Genome-wide association studies (GWAS) have identified a large number of single nucleotide polymorphisms (SNPs) associated with a wide array of cancer sites. Several of these variants demonstrate associations with multiple cancers, suggesting pleiotropic effects and shared biological mechanisms across some cancers. We hypothesized that SNPs previously associated with other cancers may additionally be associated with colorectal cancer. In a large-scale study, we examined 171 SNPs previously associated with 18 different cancers for their associations with colorectal cancer.

Design—We examined 13,338 colorectal cancer cases and 40,967 controls from three consortia: Population Architecture using Genetics and Epidemiology (PAGE), Genetic Epidemiology of Colorectal Cancer (GECCO), and the Colon Cancer Family Registry (CCFR). Study-specific logistic regression results, adjusted for age, sex, principal components of genetic ancestry, and/or study specific factors (as relevant) were combined using fixed-effect meta-analyses to evaluate the association between each SNP and colorectal cancer risk. A Bonferroni-corrected p-value of 2.92×10^{-4} was used to determine statistical significance of the associations.

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CONTRIBUTIONS

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COMPETING INTERESTS

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Results—Two correlated SNPs—rs10090154 and rs4242382—in Region 1 of chromosome 8q24, a prostate cancer susceptibility region, demonstrated statistically significant associations with colorectal cancer risk. The most significant association was observed with rs4242382 (meta-analysis OR=1.12; 95% CI: 1.07–1.18; $P=1.74\times 10^{-5}$), which also demonstrated similar associations across racial/ethnic populations and anatomical sub-sites.

Conclusion—This is the first study to clearly demonstrate Region 1 of chromosome 8q24 as a susceptibility locus for colorectal cancer, thus adding colorectal cancer to the list of cancer sites linked to this particular multi-cancer risk region at 8q24.

Keywords

colorectal cancer; pleiotropy; genome-wide association study; single nucleotide polymorphism

INTRODUCTION

Since the first series of genome-wide association studies (GWAS) for cancer were published in 2007, several hundred common genetic variants have been associated with a wide array of cancer sites [1]. As GWAS continue to identify variants associated with cancer, patterns of pleiotropic associations have emerged that highlight key loci and shared pathways that affect multiple cancer sites. For instance, genetic variants at chromosome 8q24 have been associated with cancers of the prostate, colorectum, breast, bladder, and other sites [2, 3, 4, 5, 6, 7]. Similarly, genetic variants in and near the telomerase reverse transcriptase (*TERT*) gene, which encodes for telomerase activity, have been associated with glioma, lung, prostate, colorectal, and other cancers [5, 8, 9, 10, 11], emphasizing the importance of cellular aging in cancer development.

Pleiotropy occurs when a genetic locus is associated with multiple phenotypic traits. Accordingly, any genetic difference at a pleiotropic locus may have wide-ranging effects across different cell types. Evidence of pleiotropic associations can improve our understanding of disease etiology by identifying shared molecular components underlying disease risk and by validating the pathogenicity of variants at a locus [12]. To illustrate, a recent study of the genetic overlap between systematic lupus erythematosus and other autoimmune diseases found novel pleiotropic associations that support a role for T cell and innate immune response pathways, providing valuable evidence for dissecting the biological mechanisms that underlie their shared etiologies [13].

Previous analyses of shared genetic variants across cancers have focused primarily on hereditary disorders such as the Lynch and Li-Fraumeni syndromes. Although multiple cancer types are known to cluster within families [14], studies of shared genetic factors across various non-familial cancers have been limited. Given the numerous associations reported by GWAS of cancer, we now have an opportunity to assess pleiotropy across different cancers. These pleiotropic associations may have been missed in prior GWAS of colorectal cancer (CRC) due to smaller sample sizes and the stringent threshold of significance of testing hundreds of thousands to millions of SNPs in GWAS. For this study, we tested GWAS-identified risk variants of 18 other cancers for pleiotropic associations with CRC risk in a large-scale collaboration, including multiple racial/ethnic groups. Specifically, we conducted a meta-analysis study of 13,338 CRC cases and 40,967 controls from 16 studies of three consortia: Population Architecture using Genetics and Epidemiology (PAGE); Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO); and the Colon Cancer Family Registry (CCFR).

METHODS

Study participants

Three consortia contributed data to this meta-analysis study: PAGE [15]; GECCO [11, 16]; and CCFR [17]. This collaboration comprised 13,338 CRC cases and 40,967 controls from 16 studies (Supplemental Table 1). Briefly, PAGE studies included: Atherosclerosis Risk in Communities (ARIC) [18], which is part of Causal Variants Across the Life Course (CALiCo); Epidemiologic Architecture for Genes Linked to Environment (EAGLE), which accesses the Vanderbilt University biorepository (BioVU) [19]; Multiethnic Cohort (MEC) [20]; and the Women's Health Initiative (WHI). GECCO studies included: the french Association STudy Evaluating RISK for sporadic colorectal cancer (ASTERISK) [21]; Hawaii Colorectal Cancer Studies 2 & 3 (Colo2&3) [22]; Darmkrebs: Chancen der Verhütung durch Screening (DACHS) [22]; Diet, Activity, and Lifestyle Study (DALIS) [23]; Health Professionals Follow-up Study (HPFS) [24]; Nurses' Health Study (NHS); Ontario Familial Colorectal Cancer Registry (OFCCR) [25] [26]; Physicians' Health Study (PHS) [27]; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [28, 29]; Post-Menopausal Hormones Supplemental Study to the Colon Cancer Family Registry (PMH-CCFR) [30]; VITamins And Lifestyle (VITAL) study [31]; and the Women's Health Initiative (WHI) [32, 33]. While WHI participates in both PAGE and GECCO, only WHI data as a part of GECCO was used. CCFR [17] included a population-based case-control subset.

Demographic, genetic and epidemiologic information was obtained by each study according to its enrollment, genotyping, and assessment protocols. Case and control definitions, as well as factors used in matching, differed by study (Supplemental Material, Supplemental Table 2). The majority of studies utilized incident CRC cases; controls had no diagnosis of CRC. Six GECCO studies (DACHS, DALIS, HPFS, NHS, PLCO, and WHI) contained study-specific subsets that were genotyped and analyzed individually due to differences in sample collection, year of ascertainment, or controls used for each subset (Supplemental Material; Supplemental Table 2). This led to a total of 22 analytic subsets from the 16 studies. Supplemental Figure 1 shows the participating studies and overall study design. Institutional review board approval was obtained for all studies.

SNP selection and genotyping

A total of 171 SNPs previously associated with 18 cancers other than CRC were selected by PAGE researchers (Supplemental Table 3). These SNPs were identified to be associated with cancer, as of January 2010, from the NHGRI GWAS catalog (<http://www.genome.gov/26525384>) [1] as well as review of the cancer GWAS and fine-mapping literature [15]. References for each selected SNP are provided in Supplemental Table 3. The risk allele for each SNP was defined as the allele associated with an increased risk of cancer in prior publications. For SNPs associated with multiple cancer sites, the first reported GWAS was used in assigning the risk allele. These SNPs were genotyped using a custom panel in each PAGE study with the exception of ARIC. In ARIC, GECCO, and CCFR, genotype data were abstracted from previously generated GWAS data.

To control for potential bias due to population stratification (i.e. confounding due to racial/ethnic differences in allele frequencies and disease risk), 128 ancestry informative markers that capture the major continental genetic diversity [34] were genotyped in all PAGE studies with the exception of ARIC. Principal components were estimated from these markers by EIGENSTRAT [35] and included in regression models, providing objective quantitative estimates of genetic ancestry in comparison to self-reported race/ethnicity. In ARIC, CCFR,

and GECCO, principal components of ancestry were derived from the GWAS dataset of each study using EIGENSTRAT [35].

In addition to directly genotyping, imputation for some of the 171 cancer risk variants was conducted in studies having GWAS data (ARIC study in PAGE and each study in GECCO) to estimate genotypes for untyped SNPs based on shared haplotypes and correlation with genotyped SNPs. Standard quality-assurance and quality-control measures were utilized to ensure genotyping quality. Further details are provided in the Supplementary Material. The majority of the 171 SNPs of interest were available across studies (97% SNPs were genotyped or imputed in all 22 analytic study sets; Supplemental Table 3).

Statistical analyses

For each study the association between each SNP and CRC was estimated using unconditional logistic regression. SNPs were coded additively with 0, 1, 2 referring to the number of risk alleles (or the allele dosage for imputed SNPs). Primary models were adjusted for age, sex, and the most relevant principal components of genetic ancestry to account for relevant population substructure for each study. A few studies were additionally adjusted for study center (CCFR, DAL5, PLCO, and DACHS), study component (WHI), smoking (PHS), or batch effects (ASTERISK). To examine patterns of associations across race/ethnicity, each study with at least 80 CRC cases per race/ethnicity conducted analyses stratified by racial/ethnic population. Polytomous unconditional logistic regression was also performed in each study to examine associations across anatomical sub-site (colon versus rectum). This method allowed us to simultaneously examine the associations for colon and rectal cancer in a single regression model, providing an efficient approach and the ability to test for heterogeneity in effects by anatomical sub-site.

To examine whether the top associations found for the prostate cancer risk variants at Region 1 of chromosome 8q24 were independent from Region 3, an established colorectal risk region at 8q24, rs6983267 (a Region 3 CRC risk variant; meta-analysis OR=1.14; $P=5\times 10^{-14}$) was included in the regression model with each Region 1 prostate cancer risk variant.

Log odds regression estimates were combined across studies using inverse-variance weighted, fixed-effect meta-analysis in METAL [36] for overall and stratified analyses. Heterogeneity P-values were estimated based on Cochran's Q statistic. SNP associations demonstrating heterogeneity in associations across studies at $P<0.05$ were additionally examined using random-effects meta-analysis (Supplemental Table 4). A Bonferroni-corrected $P=2.92\times 10^{-4}$ (nominal alpha/number of SNPs tested=0.05 /171) was used to determine the statistical significance of the overall association for each SNP with CRC.

RESULTS

The main characteristics of the 54,305 subjects (13,338 cases; 40,967 controls) are presented in Supplemental Table 1. The PAGE studies consisted of six different racial/ethnic populations, whereas the GECCO and CCFR consisted of European ancestry populations. In sum, the majority of the subjects were of European ancestry (80.6%) with the remainder comprising 7.0% African American, 4.5% Hispanic, 6.4% Asian, and 1.4% Pacific Islander or Native American ancestry. Most studies ascertained men and women (51.1% women overall), with the exception of WHI and NHS (women only) and HPFS and PHS (men only). Age varied across studies: ARIC ascertained younger adults (mean age of cases=55.8, controls=54.0) whereas the MEC ascertained older adults (mean age of cases=70.0, controls=68.4). Disease stage and anatomical sub-site also varied across studies: EAGLE-

BioVU, a clinic-based collection of patients, had the largest proportions of advanced stage disease (59.2%) and rectal tumors (42%).

A total of 171 risk variants for 18 cancers other than CRC, representing 100 unique chromosomal regions, were tested in 13,338 cases and 40,967 controls from 16 studies across three consortia. Of the 171 risk variants, 16 variants were nominally associated with CRC at $P < 0.05$ (Supplemental Table 3, Figure 1), which was more than the ~ 9 associations expected by chance ($171 \text{ SNPs} \times 0.05 = 8.55$). These 16 risk variants consisted of 1 basal cell carcinoma SNP, 1 breast cancer SNP, 1 glioma SNP, 1 leukemia SNP, 2 lung cancer SNPs, 1 Non-Hodgkin's Lymphoma SNP, 8 prostate cancer SNPs, and 1 testicular cancer SNP (Figure 1, Supplemental Table 3). Four of these 16 variants are correlated (8q24 Region 1 variants; $r^2 > 0.88$ in HapMap CEU[37]) and may not represent independent results.

Two correlated prostate cancer risk variants (rs10090154 and rs4242382; $r^2 = 0.79$ in CEU) in Region 1 of chromosome 8q24 (125.6–129.4 Mb [38]) demonstrated statistically significant associations with CRC, reaching a conservative Bonferroni-corrected criterion of significance ($P < 2.92 \times 10^{-4}$). For the most statistically significant association, rs4242382, we observed a 12% increased risk of CRC among CRC cases in comparison to controls (overall meta-analysis odds ratio (OR)=1.12, 95% Confidence Interval (CI)=1.07–1.18; $P = 1.74 \times 10^{-5}$; Figure 2) and no evidence of heterogeneity across studies ($P_{\text{het}} = 0.07$). Notably, the associations with rs10090154 and rs4242382 remained statistically significant when adjusting for rs6983267, a CRC risk variant in Region 3 of 8q24 (Region 3 adjusted meta-analysis $\text{OR}_{\text{rs10090154}} = 1.11$; $P = 5.0 \times 10^{-5}$ and $\text{OR}_{\text{rs4242382}} = 1.11$; $P = 5.7 \times 10^{-5}$). Two additional prostate cancer risk variants in Region 1 of 8q24 (rs7837688, rs1447295) and one in Region 3 (rs7000448) were also associated with CRC ($P = 3.32 \times 10^{-4}$ – 4.85×10^{-3}) though they did not reach our conservative threshold of statistical significance. These five prostate cancer SNPs demonstrated similar positive associations with CRC for the corresponding prostate cancer risk alleles. These SNPs are located upstream of *MYC* at chromosome 8q24, spanning ~ 98 kb, and are in various amounts of linkage disequilibrium among HapMap Europeans. The Region 1 variants appear correlated with each other ($r^2 > 0.88$) but not with the Region 3 variant ($r^2 = 0.02$; HapMap release 22 CEU).

Outside of chromosome 8q24, we observed a marginally significant association with rs2736100, a glioma risk variant at the *TERT* locus at 5p15, and CRC (meta-analysis for the G allele OR=0.94; 95% CI: 0.91–0.97; $P = 6.57 \times 10^{-4}$; $P_{\text{het}} \text{ studies} = 0.31$; Supplemental Table 3). This inverse association with CRC was in the opposite direction to that observed with the glioma G risk allele of this SNP (Figure 3). Another potentially interesting inverse association was observed with the A risk allele of rs981782, a breast cancer variant at the *HCN1* locus at 5p12 (meta-analysis OR=0.96; 95% CI: 0.93–0.99; $P = 0.009$; $P_{\text{het}} \text{ studies} = 0.79$; Supplemental Table 3).

Next, we evaluated the 16 associations at $P < 0.05$ for patterns of associations across race/ethnicity and anatomical sub-site (Supplemental Tables 5 and 6). We observed no evidence of heterogeneity in associations by race/ethnicity, with the exception of a potentially nominal association with rs7837688 ($P_{\text{het}} = 0.049$). For the most statistically significant overall association, rs4242382, we observed consistent positive associations at $P < 0.05$ for African American (OR=1.22; 95% CI: 1.03–1.45; $P = 0.024$), Asian (OR=1.28; 95% CI: 1.09–1.51; $P = 3.06 \times 10^{-3}$), and European ancestry populations (OR=1.10; 95% CI: 1.04–1.17; $P = 1.91 \times 10^{-3}$). In addition, we observed generally similar directions of association in colon and rectal tumors (Supplemental Table 6). Nominal evidence of heterogeneity in associations by anatomical sub-site was observed for rs11155133 at chromosome 6q24 ($P_{\text{het}} = 0.03$), where a stronger inverse association was observed for rectal cancer (meta-analysis OR=0.60; $P = 0.001$) than colon cancer (meta-analysis OR=0.87; $P = 0.059$).

DISCUSSION

In this large meta-analysis of 54,305 CRC cases and controls, we examined GWAS-identified risk variants of other cancers for their effects on CRC risk. To our knowledge, this is the first systematic analysis of pleiotropic associations of risk variants for other cancers with CRC. We identified two correlated SNPs—rs10090154 and rs4242382—at Region 1 of chromosome 8q24, a well-established prostate cancer susceptibility locus that demonstrated robust associations with CRC and reached a conservative criterion of statistical significance. We also observed a notable association at *TERT*, a key susceptibility locus for several cancers.

Chromosome 8q24 has been identified as an important risk locus for multiple cancers [2, 3, 4, 5, 6, 39, 40, 41, 42, 43], including CRC [44, 45, 46, 47, 48]. Distinct regions within this locus defined by their linkage disequilibrium structure have been associated with various cancers. SNPs within Region 3, initially identified as a 60kb region from 128.48 to 128.54 Mb at 8q24 [38], have been consistently associated with CRC in GWAS [44, 45, 46, 47, 48] and subsequent follow-up studies [11] [49, 50, 51, 52, 53]. Although associations between Region 3 of chromosome 8q24 and CRC risk are well-established, our findings appear to be the first demonstration of highly significant associations with Region 1. Prior candidate gene studies [49, 52, 54, 55, 56], all of smaller size, have not shown a statistically significant association between Region 1 and CRC, perhaps due to their limited statistical power as well as for prior GWAS of CRC [45, 46, 47, 48, 57, 58, 59, 60] and their stringent thresholds for genome-wide significance. Substantially large sample sizes are needed to have sufficient power to identify these small genetic associations, as seen here with the Region 1 variant rs4242382. While our study observed a modest increase in CRC risk (OR = 1.12) in 54,305 CRC cases and controls, the original finding for this SNP and prostate cancer observed a larger increase in risk (OR = 1.66) in 10,234 prostate cancer cases and controls [6]. By comparison, the largest pooled GWAS of CRC published to date included 27,809 CRC cases and controls [61]. Importantly, we were able to demonstrate that our most statistically significant associations at Region 1 of chromosome 8q24 were independent of the established Region 3 CRC risk variant, while maintaining a conservative threshold of statistical significance ($P < 5.7 \times 10^{-5}$). Although not residing within a known gene, recent functional work indicates that these 8q24 regions contain long range tissue-specific enhancers that physically interact with the *MYC* oncogene [62], potentially influencing tumorigenesis. Furthermore, a recent study found that mice deficient in *Myc-355*, a putative regulatory element that contains the Region 3 rs6983267 variant, were resistant to induced intestinal tumors [63].

TERT, which encodes for telomerase reverse transcriptase, has been identified by GWAS as a susceptibility gene for several cancers [4, 5, 8, 10, 64, 65, 66, 67]. For example, the G allele of rs2736100, located in intron 2 of *TERT*, has been associated with an increased risk of lung adenocarcinoma and glioma and a decreased risk of testicular cancer in prior GWAS [5, 8, 9, 66]. These different directions of association across cancer sites may be due to context specific differences in regulation of nearby genes, just as transcription factors can serve as both oncogenes and tumor suppressors [68]. Our findings of an association between rs2736100 and CRC corroborates a recent study by Kinnersley et al. that reported a 7% increased risk of CRC with the T allele ($P = 2.49 \times 10^{-5}$), using genotype data from six CRC cancer GWAS and an additional replication series [69]. As genotype data from the CCFR were used in both our study and this report [69], we further examined the association between rs2736100 and CRC without the CCFR: a similar nominally significant positive association was observed (meta-analysis OR for the T allele = 1.05; 95% CI: 1.01–1.09; $P = 0.007$). This provides further data for the involvement of *TERT* in CRC susceptibility. Additionally, an overall meta-analysis between our findings and those of Kinnersley et al.

resulted in a more significant association between rs2736100 and CRC (meta-analysis OR for the T allele=1.06; 95% CI: 1.04–1.09; $P=7.99\times 10^{-7}$).

The numerous risk loci identified by GWAS of cancer provide a valuable opportunity to assess similarities in the genetic susceptibility of different malignancies. Pleiotropic associations can underscore established etiologic links as well as uncover novel connections that provide new clues to shared molecular pathways [12]. Although cancer is a complex and heterogeneous disease with more than 200 different types, our findings identify shared genetic susceptibility variants between CRC and other cancers of the prostate, lung, breast, testis, and glioma. While the magnitudes of these associations are small, the cumulative effect of many such CRC risk variants may help explain the heritability of CRC [70]. Furthermore, these pleiotropic associations may indicate the biological importance of such shared genetic regions and suggest they should be prioritized for future functional and fine-mapping efforts. Specifically, our findings provide additional evidence for Region 1 of chromosome 8q24 and *TERT* as two such priority regions.

Our study is strengthened by the large number of subjects from well-designed CRC studies and the inclusion of multiple racial/ethnic populations. Limitations of this study include reduced study power for 6 SNPs that were not available across all studies. In addition, the smaller number of non-European ancestry participants limits our ability to fully explore generalizability across race/ethnicity. Finally, as more recent GWAS have identified several hundred new cancer risk loci, these variants remain to be evaluated for their pleiotropic effects with CRC.

In summary, our study indicates that several risk variants identified for other cancers also contribute to CRC risk. For the first time, these findings clearly demonstrate the importance of Region 1 at chromosome 8q24 in CRC susceptibility, and further bolster the evidence of this region as a multi-cancer risk locus. Further replication and future research into the biological mechanisms by which inherited differences in shared cancer risk loci influence CRC will expand our understanding of the key contributors to CRC development.

Supplementary Material

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Abbreviations

GWAS	genome-wide association study
PAGE	Population Architecture using Genetics and Epidemiology
GECCO	Genetic Epidemiology of Colorectal Cancer
CCFR	Colon Cancer Family Registry
SNP	single nucleotide polymorphism
TERT	telomerase reverse transcriptase
CRC	colorectal cancer
ARIC	Atherosclerosis Risk in Communities
CALiCo	Causal Variants Across the Life Course

EAGLE	Epidemiologic Architecture for Genes Linked to Environment
BioVu	Vanderbilt University biorepository
MEC	Multiethnic Cohort
WHI	Women's Health Initiative
ASTERISK	Association Study Evaluating RISK for sporadic colorectal cancer
Colo 2&3	Hawaii Colorectal Cancer Studies 2 & 3
DACHS	Darmkrebs: Chancen der Verhütung durch Screening (DACHS)
DALS	Diet, Activity, and Lifestyle Study (DALS)
HPFS	Health Professionals Follow-up Study
NHS	Nurses' Health Study
OFCCR	Ontario Familial Colorectal Cancer Registry
PHS	Physicians' Health Study (PHS)
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PMH-CCFR	Post-Menopausal Hormones Supplemental Study to the Colon Cancer Family Registry
VITAL	VITamins And Lifestyle part of GECCO

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SUMMARY BOX

What is known on this topic?

- Several hundred common genetic variants have been associated with a wide array of cancer types.
- Only a small proportion of the heritability of colorectal cancer can be explained by the currently identified risk loci from genome-wide association studies of colorectal cancer.
- Identifying shared genetic associations between diseases (i.e. pleiotropy) is a useful approach to identify new risk loci and may elucidate common etiologies and help in risk prediction.

What this study adds?

- This study clearly shows that two genetic variants in Region 1 of the 8q24 locus, a prostate cancer risk region, are also associated with colorectal cancer risk.
- Furthermore, this study provides additional evidence that the *TERT* locus is associated with colorectal cancer.

How might it impact on clinical practice in the foreseeable future?

- Colorectal risk variants may be used as part of a risk prediction model to define high-risk populations for targeted screening regimens and, possibly, inform clinical decision making.

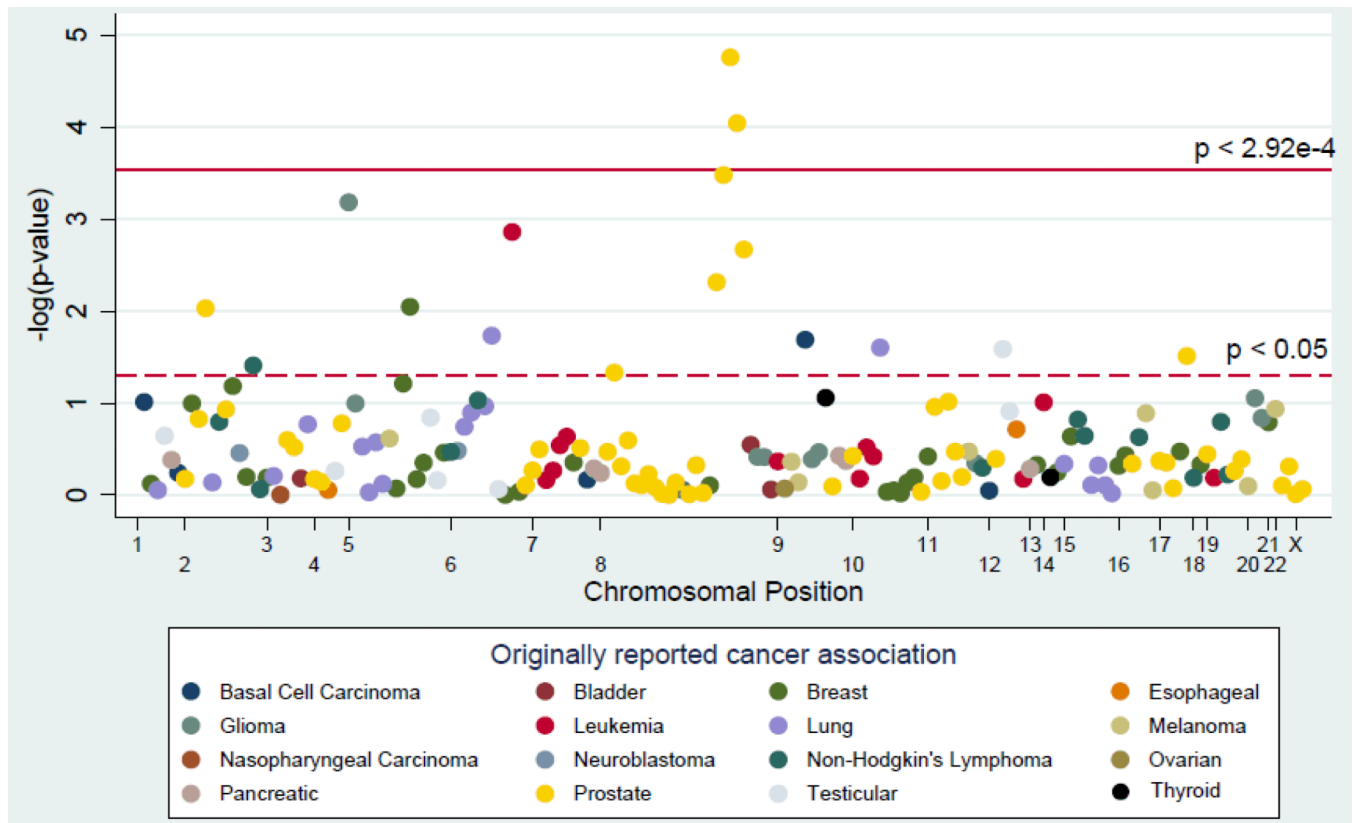


Figure 1. Manhattan plot of the meta-analysis association between risk variants of 18 other cancers and colorectal cancer
 The solid line is the Bonferroni-corrected significance threshold. Each association is colored according to the cancer for which the SNP was originally reported, and positioned on the x-axis according to its genomic position.

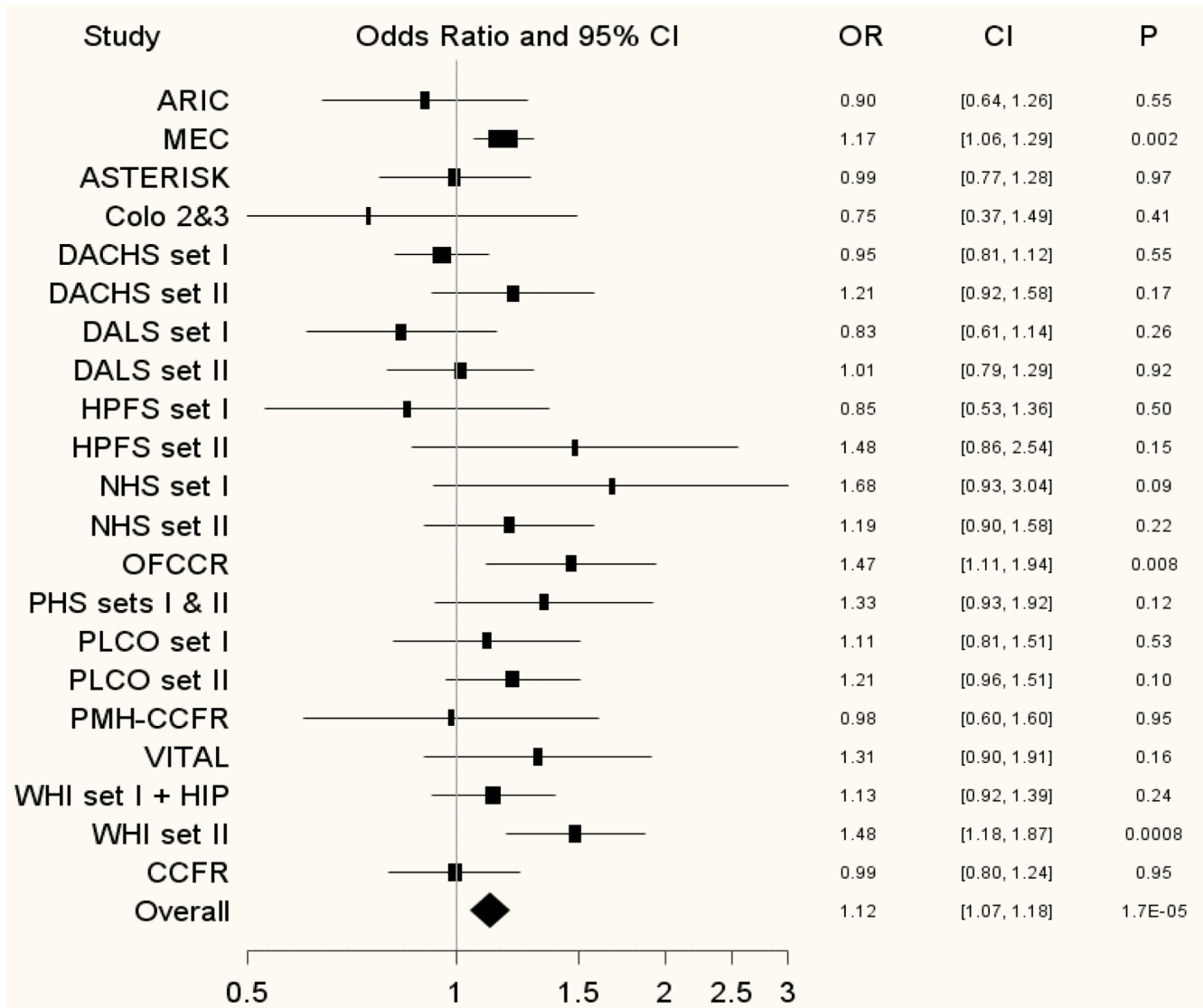


Figure 2. Forest plot of the association between rs4242382 at Region 1 of chromosome 8q24 and colorectal cancer risk

Study specific and meta-analysis associations are plotted, modeling the A risk allele for prostate cancer.

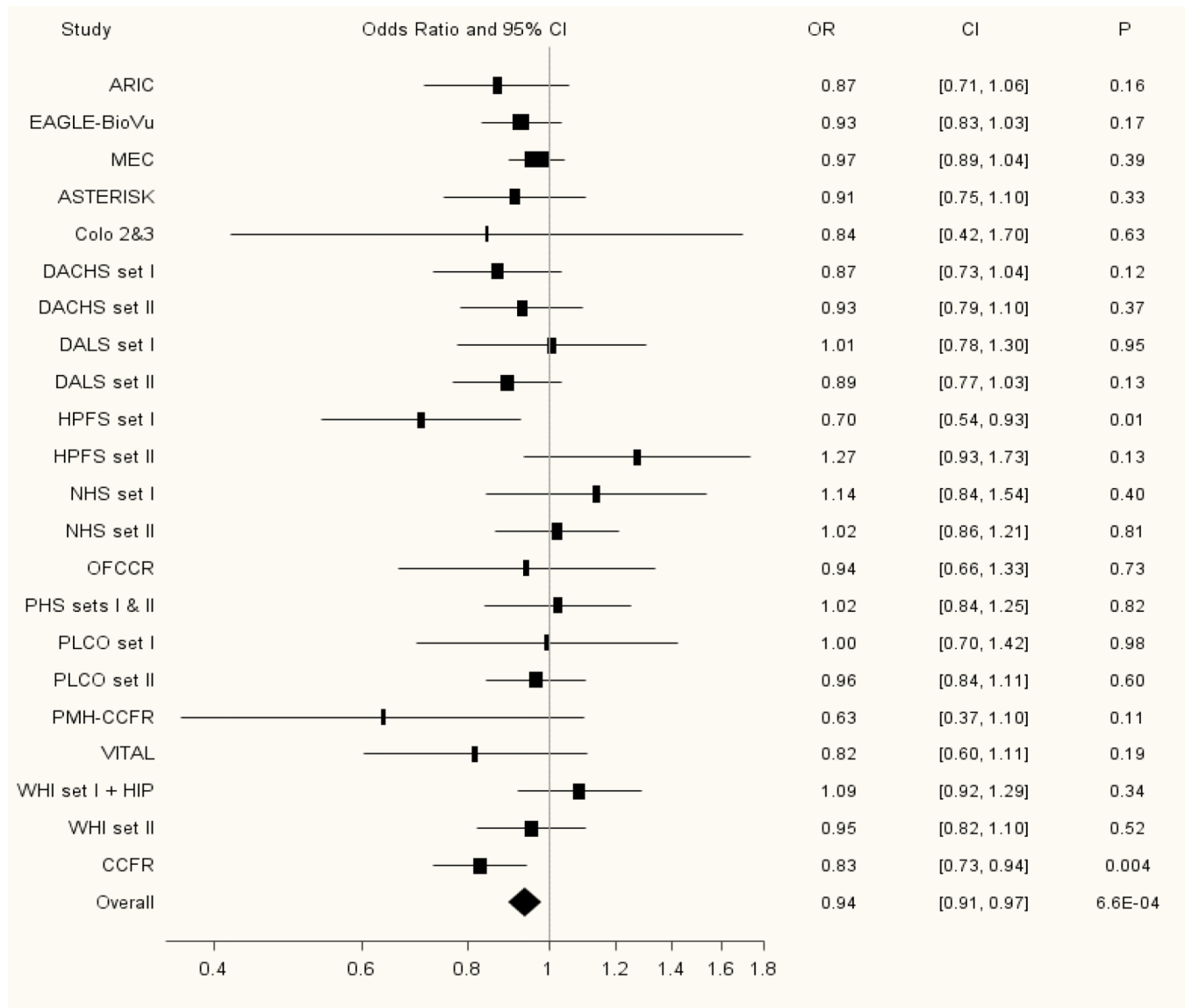


Figure 3. Forest plot of the association between rs2736100 at the *TERT* locus at 5p15 and colorectal cancer risk
Study specific and meta-analysis associations are plotted, modeling the G risk allele for glioma.