



Digital Commons@

Loyola Marymount University
LMU Loyola Law School

Health and Human Sciences Faculty Works

Health and Human Sciences

2014

Genetic Variation At 8Q24, Family History Of Cancer, And Upper Gastrointestinal Cancers In A Chinese Population

Heather P. Tarleton

Loyola Marymount University, heather.tarleton@lmu.edu

Shen-Chih Chang

University of California, Los Angeles

Sungshim Lani Park

University of Hawaii, Manoa

Lin Cai

Fujian Medical University

Baoguo Ding

Taixing City Center for Disease Control and Prevention

See next page for additional authors

Follow this and additional works at: https://digitalcommons.lmu.edu/hhsc_fac



Part of the [Cancer Biology Commons](#)

Digital Commons @ LMU & LLS Citation

Tarleton, Heather P.; Chang, Shen-Chih; Park, Sungshim Lani; Cai, Lin; Ding, Baoguo; He, Na; Hussain, Shehnaz K.; Jiang, Qingwu; Mu, Li-Na; Rao, Jianyu; Wang, Hua; You, Nai-Chieh Y.; Yu, Shun-Zhang; Zhao, Jin-Kou; and Zhang, Zuo-Feng, "Genetic Variation At 8Q24, Family History Of Cancer, And Upper Gastrointestinal Cancers In A Chinese Population" (2014). *Health and Human Sciences Faculty Works*. 2. https://digitalcommons.lmu.edu/hhsc_fac/2

This Article - post-print is brought to you for free and open access by the Health and Human Sciences at Digital Commons @ Loyola Marymount University and Loyola Law School. It has been accepted for inclusion in Health and Human Sciences Faculty Works by an authorized administrator of Digital Commons@Loyola Marymount University and Loyola Law School. For more information, please contact digitalcommons@lmu.edu.

Authors

Heather P. Tarleton, Shen-Chih Chang, Sungshim Lani Park, Lin Cai, Baoguo Ding, Na He, Shehnaz K. Hussain, Qingwu Jiang, Li-Na Mu, Jianyu Rao, Hua Wang, Nai-Chieh Y. You, Shun-Zhang Yu, Jin-Kou Zhao, and Zuo-Feng Zhang



Published in final edited form as:

Fam Cancer. 2014 March ; 13(1): 45–56. doi:10.1007/s10689-013-9673-4.

Genetic variation at 8q24, family history of cancer, and upper gastrointestinal cancers in a Chinese population

Heather P. Tarleton¹, Shen-Chih Chang², Sungshim Lani Park³, Lin Cai⁴, Baoguo Ding⁵, Na He⁶, Shehnaz K. Hussain⁷, Qingwu Jiang⁸, Li-Na Mu⁹, Jianyu Rao¹⁰, Hua Wang¹¹, Nai-Chieh Y. You¹², Shun-Zhang Yu¹³, Jin-Kou Zhao¹⁴, and Zuo-Feng Zhang¹⁵

Heather P. Tarleton: heather.tarleton@lmu.edu; Shen-Chih Chang: shenchih@ucla.edu; Sungshim Lani Park: slanipark@gmail.com; Lin Cai: cailin.ucla@gmail.com; Baoguo Ding: dbgtx@163.com; Na He: nhe@shmu.edu.cn; Shehnaz K. Hussain: SKHussain@ucla.edu; Qingwu Jiang: jiangqw@fudan.edu.cn; Li-Na Mu: linamu@buffalo.edu; Jianyu Rao: jrao@mednet.ucla.edu; Hua Wang: Hua@jscdc.cn; Nai-Chieh Y. You: yuko@ucla.edu; Shun-Zhang Yu: szyu@shmu.edu.cn; Jin-Kou Zhao: button.zhao@gmail.com; Zuo-Feng Zhang: zfzhang@ucla.edu

¹Department of Health and Human Sciences, Loyola Marymount University, Los Angeles, CA, USA ²Department of Epidemiology, School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, CA, USA ³Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA ⁴Department of Epidemiology, School of Public Health, Fujian Medical University, Fuzhou, China ⁵Taixing City Center for Disease Control and Prevention (CDC), Taixing City, Jiangsu, China ⁶Fudan University School of Public Health, Shanghai, China ⁷Department of Epidemiology and Jonsson Comprehensive Cancer Center's Cancer Prevention and Control Program, School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, CA, USA ⁸Fudan University School of Public Health, Shanghai, China ⁹Department of Social and Preventive Medicine, State University of New York (SUNY) at Buffalo, NY, USA ¹⁰Department of Epidemiology, School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, CA, USA ¹¹Monitoring and Evaluation Unit, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland ¹²Department of Epidemiology, School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, CA, USA ¹³Fudan University School of Public Health, Shanghai, China ¹⁴Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu, China ¹⁵Department of Epidemiology and Jonsson Comprehensive Cancer Center's Cancer Prevention and Control Program, School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, CA, USA

Abstract

Genetic variation at 8q24 is associated with prostate, bladder, breast, colorectal, thyroid, lung, ovarian, UADT, liver and stomach cancers. However, a role for variation at 8q24 in familial clustering of upper gastrointestinal cancers has not been studied. In order to explore potential inherited susceptibility, we analyzed epidemiologic data from a population-based case-control study of upper gastrointestinal cancers from Taixing, China. The study population includes 204 liver, 206 stomach, and 218 esophageal cancer cases and 415 controls. Associations between 8q24

Correspondence and request for reprints to: Zuo-Feng Zhang, M.D., Ph.D., Department of Epidemiology, School of Public Health, University of California, Los Angeles, 71-225 CHS, Box 951772, 650 Charles E Young Drive, South, Los Angeles, CA 90095-1772, U.S.A. Phone: 310-825-8418, Fax: 310-206-6039, zfzhang@ucla.edu.

Authors' Contributions

HPT designed and carried out the statistical analyses and drafted the manuscript. SCC conducted the genotyping and contributed to the interpretation of laboratory and epidemiological data. SLP and SKH participated in manuscript writing and editing. LC, BD, NH, QJ, LNM, JR, HW, NCYY, SZY, JKZ, and ZFZ conceived and conducted the Taixing study, interpreted epidemiological data, and participated in manuscript editing.

Conflict of Interest

The authors' have no financial or non-financial conflict of interests to declare.

rs1447295, rs16901979, rs6983267 and these cancers were stratified by family history of cancer. Odds ratios and 95% confidence intervals were adjusted for potential confounders: age, sex, education, tobacco smoking, alcohol consumption, and BMI at interview. We also adjusted for hepatitis B and aflatoxin (liver cancer) and *Helicobacter pylori* (stomach cancer). In a dominant model, among those with a family history of cancer, rs1447295 was positively associated with liver cancer (OR_{adj} 2.80; 95% CI 1.15–6.80). Heterogeneity was observed ($P_{\text{heterogeneity}}=0.029$) with rs6983267 and liver cancer, with positive association in the dominant model among those with a family history of cancer and positive association in the recessive model among those without a family history of cancer. When considered in a genetic risk score model, each additional 8q24 risk genotype increased the odds of liver cancer by two-fold among those with a family history of cancer (OR_{adj} 2.00; 95% CI 1.15–3.47). These findings suggest that inherited susceptibility to liver cancer may exist in the Taixing population and that variation at 8q24 might be a genetic component of that inherited susceptibility.

Keywords

Liver cancer; stomach cancer; esophageal cancer; hepatitis B; 8q24 SNPs; family history of cancer

Introduction

Family history of cancer has been associated with several cancers, including cancers of the liver, stomach, and esophagus [1–7]. Shared environmental risk factors, such as hepatitis B and C, and *Helicobacter pylori* (*H. pylori*) infection, have been associated with liver and stomach cancers, respectively, and might have a role in familial clustering of these cancers. Familial clustering of upper gastrointestinal (GI) cancers might also be attributable to inherited genetic factors. Prospective cohort studies of twins have suggested that one-third of most cancers are attributable to inherited genetic factors [8,9]. Genetic studies of familial cancers often focus on highly penetrant genetic mutations; however, low penetrance genetic factors have been associated with susceptibility to liver, stomach, and esophageal cancers [10–13]. A few of the low penetrance genetic factors that are of great interest to cancer epidemiology are at 8q24.

Genome-wide association studies (GWAS) and case-control studies have associated variation at 8q24 with prostate, bladder, breast, colorectal, thyroid, lung, ovarian, UADT, liver and stomach cancers [9,14–20,12,21–24]. Colorectal cancer cases with a family history of cancer have been observed as having a greater number of 8q24 risk alleles, in comparison to those colorectal cancer cases without a family history of colorectal cancer [25]. Additionally, in a family history-stratified analysis of cancer in a Polish population, 8q24 single nucleotide polymorphism (SNPs) were associated with prostate, laryngeal, lung, and kidney cancers among those with a family history of cancer, with noteworthy heterogeneity in family history-stratified associations for laryngeal and lung cancers [26]. In this study, we stratified the association of three 8q24 SNPs (rs1447295, rs16901979, rs6983267) and liver, stomach, and esophageal cancers in a Chinese population by family history of cancer. To our knowledge, this is the first study of 8q24 SNPs, family history of cancer, and these three upper GI cancers in a Chinese population.

Methods

Study Design and Participants

Epidemiologic data and biological specimens were collected in a population-based case-control study in Taixing City, Jiangsu Province, China. Study protocols were approved by the Institutional Review Board at the University of California, Los Angeles and all

participants provided written informed consent. The study design and population have been described in detail elsewhere [27,28,13]. Briefly, eligible cases and controls were residents of Taixing City for at least 10 years and were at least 20 years of age at the time of recruitment. Newly diagnosed cases of stomach, liver, and esophageal cancers were identified between June 1, 2000 and December 30, 2000 using the Taixing Population-based Tumor Registry from the Taixing Center for Disease Prevention and Control. Population-based controls were randomly selected from a list of Taixing City residents and frequency-matched to all upper GI cases on sex, age (5-year categories), and residential village or block. The participation rates were 65% for stomach (n=206), 57% for liver (n=204), 67% (n=218) for esophageal cancer cases, and 89% (n=415) for controls.

Epidemiologic Data and Biological Specimen Collection

Epidemiologic data were collected by a standard questionnaire during 40–60 minute interviews with a trained interviewer. Questionnaires were standardized with questions on common exposures, in addition to specific questions for each cancer site. The collected data include demographics, personal habits, cigarette smoking, passive smoke exposure, alcohol consumption, tea consumption, occupational history, family history of cancer in consanguineal relatives and non-consanguineal spouses, frequency of diet and food intake, and medical history. DNA was isolated from peripheral blood samples collected from 395 interviewed controls and from 196 stomach, 194 liver, and 205 esophageal cancer cases interviewed. Measurement of exposure to hepatitis B and *H. pylori* has been described previously [28,13]. Plasma aflatoxin B1 (AFB1)-albumin adduct levels were determined using a competitive enzyme-linked immunosorbent assay, as described previously [29]. Biological specimens have been stored at -70°C in the Molecular Epidemiology Laboratories of Fudan University School of Public Health and the University of California, Los Angeles School of Public Health.

SNP Selection and Genotyping

Taixing study biospecimens were previously genotyped for three 8q24 SNPs (rs1447295, rs16901979, rs6983267) and main associations reported [30]. Genotypic data for all three 8q24 SNPs are included in this study given the location of the SNPs in unique regions of 8q24, published associations in GWAS and case-control studies of colorectal and prostate cancers, and linkage disequilibrium below the threshold of $r^2=0.80$ [31,32,14,33,34,15,18]. SNP genotyping was performed on a TaqMan platform with an ABI 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). SNP-specific primers and probes were custom-designed for the ABI TaqMan system. Approximately 5% of samples were randomly selected and duplicated for quality control. The concordance rate between duplicates was >99%. The automatic call rates were >96% for all three SNPs. Laboratory technicians were blinded to the case/control status of all samples and to the inclusion of duplicate samples for quality control.

Statistical Analysis

All data analyses were performed using SASv9.2 software (SAS Institute Inc., Cary, NC, USA). Linkage disequilibrium between 8q24 SNPs was examined using the Proc Allele command in SAS for pairwise comparison of all three 8q24 SNP alleles in controls. Family history of any cancer (yes or no) and family history of index cancer (yes or no) were determined by self-reported history of cancer in at least one consanguineal relative (mother, father, sister, brother, daughter, son, grandfather, grandmother, maternal/paternal uncle, maternal/paternal aunt). Unconditional logistic regression was used to estimate crude and adjusted odds ratios (OR_{adj}) and their 95% confidence intervals (CI). Covariates adjusted for include age (continuous), sex (male=0 or female=1), education (illiterate=0, primary

school=1, middle school=2, senior high school/bachelor/higher degree=3), smoking status (never=0 or ever=1), number of smoking pack-years (continuous), alcohol drinking frequency (never=0, occasionally=1, often=2, everyday=3), body-mass-index (BMI [kg/m²], continuous), AFB1-albumin adduct levels (liver only, quintiles), hepatitis B serum antigen (liver only, positive=1 or negative=0), and *H. pylori* infection (stomach only, positive=1 or negative=0). The Taixing study population is 100% Han Chinese, therefore, ethnicity was not included as a covariate.

Tests for Hardy-Weinberg Equilibrium and differences in minor allele frequencies were previously evaluated for all three SNPs using the χ^2 test [30]. We used the TT genotype as the referent for rs6983267 and the CC genotype as the referent for rs1447295 and rs16901979, so that odds ratios were modeled for the genotype homozygous for the cancer risk alleles [35–37]. Odds ratios for the stratified analysis were estimated using unconditional logistic regression, with adjustment for previously described covariates.

Cancer risk estimation can be improved by examining multiple loci simultaneously [38–40]. Therefore, in this study, we use a simple count approach to genetic risk scoring to examine the three 8q24 SNPs collectively for potential improvement in the risk estimated with each individual SNP. Under the simple count approach, we calculated a SNP-set score by assigning a value of “0” to the major homozygous genotype of each SNP and “1” to the heterozygous and minor homozygous genotype of each SNP (dominant model). In order to reduce the bias caused by missing data, we did not include any participants who had one or more missing genotypes for the 8q24 SNPs. Values were summed across all three SNPs in order to determine a SNP-set score for each participant. The dominant model was chosen based on our previously published analysis of the main association of each SNP with each cancer site [30].

To test for departures from multiplicativity, we compared the full unconditional logistic regression model with the product term (family history x SNP [dichotomized under the dominant model]) to the full model without the product term. The antilog of the coefficient estimated for the product term was interpreted as the ratio of odds ratios (ROR), with a ROR = 1 indicating a departure from multiplicativity and from the null hypothesis. The RORs and their 95% CIs were estimated using unconditional logistic regression, with adjustment for previously described covariates.

Results

Select characteristics of the Taixing study population were previously reported and are presented in Table 1 [27,28,13]. Briefly, liver, esophageal, and stomach cancer cases are 78%, 65%, and 67% male, and 69% of controls are male. Tobacco smoking (ever smoking) was reported by 53%, 54%, and 53% of liver, esophageal, and stomach cancer cases, and by 48% of controls. Approximately 65% of liver cancer cases were positive for hepatitis B exposure and 9% were positive for hepatitis C exposure, compared to 25% (hepatitis B) and 3% (hepatitis C) of controls. Thirty-five percent (35%) of stomach cancer cases were exposed to *H. pylori* as defined by the presence of anti-(CagA-HP) IgG, compared to 28% of controls. Among 202 esophageal cases, cancer was located in the upper (n=125, 61.8%), middle (n=58, 28.7%), and lower (n=19, 9.4%) third of the esophagus. Cancer was located in the cardia (n=93, 71%), body (n=18, 13.7%), antrum (n=17, 13%), and pylorus (n=3, 2.3%) of 131 stomach cancer cases. Liver cancer was distributed between the left (n=78, 55.3%) and right (n=63, 44.7%) lobes in 141 liver cancer cases.

Family history of any cancer was positively associated with liver (OR_{adj} 2.52; 95% CI, 1.63–3.88) and stomach (OR_{adj} 1.41; 95% CI 0.91–2.18) cancers (Table 2). The positive

associations persisted in the analysis of family history of liver cancer (OR_{adj} 3.76; 95% CI 2.13–6.63) and family history of stomach cancer (OR_{adj} 4.56; 95% CI 2.17–9.58); however, no clear association was found between family history of cancer and esophageal cancer (Table 2). The 8q24 SNPs included in this study (rs6983267, rs1447295, rs16901979) are not in linkage disequilibrium ($r^2 < 0.20$) with one another. Genotype frequencies for their association with liver, stomach, and esophageal cancers have been reported elsewhere [30] and are presented in Table 3. In our previously published study, we did not observe a relationship between the A risk allele of rs1447295 and esophageal, stomach, or liver cancers [30]. In this study, after stratification on family history of cancer (Table 4), we observed a positive association between rs1447295 and liver cancer among those with a family history of cancer (OR_{adj} 2.80; 95% CI 1.15–6.80), in the dominant model, consistent with a departure from multiplicativity (ROR_{adj} 2.54; 95% CI 0.94–6.87). The observed association persisted in the hepatitis B negative subgroup analysis (OR_{adj} 3.52; 95% CI 1.10–11.1) presented in Table 5 and is consistent with the analysis of family history of cancer in first-degree relatives only (Supplemental Table).

In this study, we observed family history of cancer as a modifier of the association of rs6983267 and liver cancer ($P_{heterogeneity}=0.029$). Among those with family history of cancer, the GT heterozygous genotype (OR_{adj} 2.67; 95% CI 1.00–6.82) and rs6983267 in the dominant model (OR_{adj} 2.17; 95% CI 0.89–5.28) are positively associated with liver cancer; however, among those without a family history of cancer, the positive association is observed for the GG rare homozygous genotype (OR_{adj} 2.05; 95% CI 0.96–4.38) and rs6983267 in the recessive model (OR_{adj} 2.15; 95% CI 1.11–4.16). A similar pattern of association was also suggested among those with a family history of cancer in first-degree relatives only (Supplemental Table). The observed heterogeneity is consistent with a departure from multiplicativity (ROR_{adj} 1.81; 95% CI 0.67–4.85) and persisted in the hepatitis B negative subgroup analysis ($P_{heterogeneity}=0.040$) presented in Table 5. No clear association was observed between 8q24 SNPs and stomach and esophageal cancers in family history-stratified analyses.

The departures from multiplicativity observed with the 8q24 SNPs are consistent with the genetic risk score for the 8q24 SNP-set and family history of cancer (Table 6). There is a two-fold greater risk of liver cancer (OR_{adj} 2.00; 95% CI 1.15–3.47), per additional 8q24 SNP risk genotype, among those with a family history of cancer ($P_{heterogeneity}=0.086$).

Discussion

In this study, family history of cancer is associated with cancers of the liver and stomach. We observed that rs1447295 was positively associated with liver cancer among those who reported having a family history of cancer. The relationship between the A risk allele of rs1447295 and liver cancer in those with a family history of cancer, but not in those without a family history of cancer, is consistent with previously published studies that reported positive associations for rs1447295 and familial prostate cancer [41–44]. A functional role for the A risk allele of rs1447295 has yet to be established. There is evidence of linkage disequilibrium (LD) between rs1447295 and DG8S737, a microsatellite that is positively associated with prostate cancers, and also the suggestion that both mark a functional causal variant [45,18,42,43,19,46]. DG8S737 was not assayed in this study and we could not assess a potential association with liver cancer or potential LD with rs1447295 within this population.

In addition to our findings with rs1447295, we also observed heterogeneity in the family history-stratified association of rs6983267 and liver cancer that might potentially indicate inherited susceptibility to the risk associated with the recessive G allele in familial cancer

clusters. Our findings in this candidate gene study of rs6983267 and liver cancer are similar to another recent candidate gene study, where the G allele was associated with thyroid cancer in a recessive inheritance model [23]. The Jones et al. (2012) study also observed heterogeneity in the association of thyroid cancer and recessive GG homozygotes, in comparison to GT heterozygotes. We did not detect an additive relationship for rs6983267 and liver cancer, among those with a family history of cancer, which might be due to sample size or to a non-additive mechanism. Inherited allelic instability at rs6983267 might also explain our findings of GT heterozygotes with a family history of cancer experiencing the same risk as recessive GG homozygotes without a family history of cancer.

Functional studies have demonstrated that the G risk allele of rs6983267 enhances transcription of the *Myc* oncogene, which in turn affects Wnt pathway signaling [47–55]. Beebe-Dimmer and colleagues have published their observations of preferential germline transmission of the G risk allele of rs6983267 in familial prostate cancer cases [41]. Tuupanen and colleagues have suggested a role for allelic imbalance at rs6983267 and amplification of the G risk allele by comparing germline rs6983267 genotypes of colorectal cancer patients and their relatives, with somatic rs6983267 genotypes of patients' tumors [36,51]. In light of these studies, our findings are consistent with rs6983267 operating in families as what Tuupanen et al. describe as a “germline predisposition SNP to somatic tumor evolution” [36].

The heterogeneity in the 8q24 genetic risk score by family history of cancer is consistent with previously reported observations in familial colorectal cancer cases [25] and could potentially be explained by allelic transmission disequilibrium in families or by co-inheritance of 8q24 loci with an unknown disease marker. Our findings demonstrate the importance of including family history of cancer in studies of low penetrance genetic variation to generate hypotheses that can be tested in subsequent family-based studies.

This study had some limitations. Although genotypic and infection-related data are not affected by recall bias, recall bias may be present in self-reported family history of cancer and may be differential. However, we expect this bias to be minimal given that previously published studies have reported allelic transmission disequilibrium and have observed a difference in the number of risk alleles transmitted to familial cancer cases [34,43,41,56]. A strength of this study is the ability to stratify on family history of any cancer and family history of index cancer in a racially homogenous population. Studies of familial clustering of liver cancer in Asian populations have partially attributed observed positive associations to hepatitis B infection. We cannot rule out shared environmental factors; however, we were able to adjust our ORs for those infectious risk factors associated with liver and stomach cancers, and shared within families. Our adjusted estimates are consistent with published studies of hepatitis B-negative European and American populations, which reported ORs ranging from 1.4–2.4 for the association of family history of cancer and liver cancer [2,5]. Furthermore, the magnitude and direction of associations that we observed in the overall population persisted in our hepatitis B-negative subgroup analysis.

In conclusion, this study finds that the association of rs6983267 and rs1447295 with liver cancer varies by family history of cancer. The hypothesis generated in this study, namely that there is an inherited predisposition towards allelic imbalance or loss of heterozygosity at rs6983267, warrants further investigation in larger population-based and family-based studies. Further investigation is also needed into the genetic epidemiology of rs6983267 and rs1447295, in order to understand the potential for linkage with causal markers or possible transmission disequilibrium of risk alleles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are indebted to our study participants, whose contributions made this research possible. We thank all of the clinicians, interviewers and staff and acknowledge the groundwork that they laid for this and future studies. This work was supported in part by National Institute of Environmental Health Sciences, National Cancer Institute, Department of Health and Human Services grants ES06718, ES01167, DA11386, CA90833, CA77954, CA09142, CA96134, and by the Alper Research Center for Environmental Genomics of the UCLA Jonsson Comprehensive Cancer Center. HPT was supported by National Cancer Institute grant CA09142.

List of abbreviations

SNP	Single nucleotide polymorphism
GI	gastrointestinal
<i>H. pylori</i>	<i>Helicobacter pylori</i>
OR	odds ratio
CI	confidence interval
ROR	ratio of odds ratios
GWAS	genome wide association study
BMI	body-mass-index
LD	linkage disequilibrium

References

1. Dhillon PK, Farrow DC, Vaughan TL, Chow WH, Risch HA, Gammon MD, Mayne ST, Stanford JL, Schoenberg JB, Ahsan H, Dubrow R, West AB, Rotterdam H, Blot WJ, Fraumeni JF Jr. Family history of cancer and risk of esophageal and gastric cancers in the United States. *Int J Cancer*. 2001; 93(1):148–152. [pii]. 10.1002/ijc.1294 [PubMed: 11391635]
2. Donato F, Gelatti U, Chiesa R, Albertini A, Bucella E, Boffetta P, Tagger A, Ribero ML, Portera G, Fasola M, Nardi G. A case-control study on family history of liver cancer as a risk factor for hepatocellular carcinoma in North Italy. Brescia HCC Study. *Cancer Causes Control*. 1999; 10 (5): 417–421. [PubMed: 10530612]
3. Fernandez E, La Vecchia C, D'Avanzo B, Negri E, Franceschi S. Family history and the risk of liver, gallbladder, and pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 1994; 3 (3):209–212. [PubMed: 8019368]
4. Gao Y, Hu N, Han X, Giffen C, Ding T, Goldstein A, Taylor P. Family history of cancer and risk for esophageal and gastric cancer in Shanxi, China. *BMC Cancer*. 2009; 9:269. 1471-2407-9-269 [pii]. 10.1186/1471-2407-9-269 [PubMed: 19656375]
5. Hassan MM, Spitz MR, Thomas MB, Curley SA, Patt YZ, Vauthey JN, Glover KY, Kaseb A, Lozano RD, El-Deeb AS, Nguyen NT, Wei SH, Chan W, Abbruzzese JL, Li D. The association of family history of liver cancer with hepatocellular carcinoma: a case-control study in the United States. *J Hepatol*. 2009; 50 (2):334–341. S0168-8278(08)00633-8 [pii]. 10.1016/j.jhep.2008.08.016 [PubMed: 19070394]
6. Shin CM, Kim N, Yang HJ, Cho SI, Lee HS, Kim JS, Jung HC, Song IS. Stomach cancer risk in gastric cancer relatives: interaction between *Helicobacter pylori* infection and family history of gastric cancer for the risk of stomach cancer. *J Clin Gastroenterol*. 2009; 44 (2):e34–39.10.1097/MCG.0b013e3181a159c4 [PubMed: 19561529]
7. Yatsuya H, Toyoshima H, Tamakoshi A, Kikuchi S, Tamakoshi K, Kondo T, Mizoue T, Tokui N, Hoshiyama Y, Sakata K, Hayakawa N, Yoshimura T. Individual and joint impact of family history

- and *Helicobacter pylori* infection on the risk of stomach cancer: a nested case-control study. *Br J Cancer*. 2004; 91(5):929–934. 6602067 [pii]. 10.1038/sj.bjc.6602067 [PubMed: 15280918]
8. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000; 343 (2):78–85. [PubMed: 10891514]
 9. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, Rafnar T, Bergthorsson JT, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Xu J, Blondal T, Kostic J, Sun J, Ghosh S, Stacey SN, Mouy M, Saemundsdottir J, Backman VM, Kristjansson K, Tres A, Partin AW, Albers-Akkers MT, Godino-Ivan Marcos J, Walsh PC, Swinkels DW, Navarrete S, Isaacs SD, Aben KK, Graif T, Cashy J, Ruiz-Echarri M, Wiley KE, Suarez BK, Witjes JA, Frigge M, Ober C, Jonsson E, Einarsson GV, Mayordomo JI, Kiemeny LA, Isaacs WB, Catalona WJ, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet*. 2007; 39 (5):631–637. ng1999 [pii]. 10.1038/ng1999 [PubMed: 17401366]
 10. Hu N, Goldstein AM, Albert PS, Giffen C, Tang ZZ, Ding T, Taylor PR, Emmert-Buck MR. Evidence for a familial esophageal cancer susceptibility gene on chromosome 13. *Cancer Epidemiol Biomarkers Prev*. 2003; 12 (10):1112–1115. [PubMed: 14578153]
 11. Shih WL, Yu MW, Chen PJ, Yeh SH, Lo MT, Chang HC, Liaw YF, Lin SM, Liu CJ, Lee SD, Lin CL, Hsiao CK, Yang SY, Chen CJ. Localization of a susceptibility locus for hepatocellular carcinoma to chromosome 4q in a hepatitis B hyperendemic area. *Oncogene*. 2006; 25 (22):3219–3224. 1209345 [pii]. 10.1038/sj.onc.1209345 [PubMed: 16407824]
 12. Guo Y, Fang J, Liu Y, Sheng HH, Zhang XY, Chai HN, Jin W, Zhang KH, Yang CQ, Gao HJ. Association between polymorphism rs6983267 and gastric cancer risk in Chinese population. *World J Gastroenterol*. 2011; 17 (13):1759–1765. 10.3748/wjg.v17.i13.1759 [PubMed: 21483638]
 13. Mu LN, Lu QY, Yu SZ, Jiang QW, Cao W, You NC, Setiawan VW, Zhou XF, Ding BG, Wang RH, Zhao J, Cai L, Rao JY, Heber D, Zhang ZF. Green tea drinking and multigenetic index on the risk of stomach cancer in a Chinese population. *Int J Cancer*. 2005; 116 (6):972–983. 10.1002/ijc.21137 [PubMed: 15856451]
 14. Tomlinson I, Webb E, Carvajal-Carmona L, Broderick P, Kemp Z, Spain S, Penegar S, Chandler I, Gorman M, Wood W, Barclay E, Lubbe S, Martin L, Sellick G, Jaeger E, Hubner R, Wild R, Rowan A, Fielding S, Howarth K, Silver A, Atkin W, Muir K, Logan R, Kerr D, Johnstone E, Sieber O, Gray R, Thomas H, Peto J, Cazier JB, Houlston R. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. *Nat Genet*. 2007; 39 (8):984–988. ng2085 [pii]. 10.1038/ng2085 [PubMed: 17618284]
 15. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, Staats BJ, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Gelmann EP, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover R, Hunter DJ, Chanock SJ, Thomas G. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet*. 2007; 39 (5):645–649. ng2022 [pii]. 10.1038/ng2022 [PubMed: 17401363]
 16. Zhang X, Chen Q, He C, Mao W, Zhang L, Xu X, Zhu J, Chen B. Polymorphisms on 8q24 are associated with lung cancer risk and survival in Han Chinese. *PLoS One*. 2012; 7 (7):e41930. 10.1371/journal.pone.0041930 [PubMed: 22848662]
 17. Ghousaini M, Song H, Koessler T, Al Olama AA, Kote-Jarai Z, Driver KE, Pooley KA, Ramus SJ, Kjaer SK, Hogdall E, DiCioccio RA, Whittemore AS, Gayther SA, Giles GG, Guy M, Edwards SM, Morrison J, Donovan JL, Hamdy FC, Dearnaley DP, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Brown PM, Hopper JL, Neal DE, Pharoah PD, Ponder BA, Eeles RA, Easton DF, Dunning AM. Multiple loci with different cancer specificities within the 8q24 gene desert. *J Natl Cancer Inst*. 2008; 100 (13):962–966. 10.1093/jnci/djn190 [PubMed: 18577746]
 18. Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Cazier JB, Sainz J, Jakobsdottir M, Kostic J, Magnusdottir DN, Ghosh S, Agnarsson K, Birgisdottir B, Le Roux L, Olafsdottir A, Blondal T, Andresdottir M, Gretarsdottir

- OS, Bergthorsson JT, Gudbjartsson D, Gylfason A, Thorleifsson G, Manolescu A, Kristjansson K, Geirsson G, Isaksson H, Douglas J, Johansson JE, Balter K, Wiklund F, Montie JE, Yu X, Suarez BK, Ober C, Cooney KA, Gronberg H, Catalona WJ, Einarsson GV, Barkardottir RB, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. A common variant associated with prostate cancer in European and African populations. *Nat Genet.* 2006; 38 (6):652–658. ng1808 [pii]. 10.1038/ng1808 [PubMed: 16682969]
19. Suuriniemi M, Agalliu I, Schaid DJ, Johanneson B, McDonnell SK, Iwasaki L, Stanford JL, Ostrander EA. Confirmation of a positive association between prostate cancer risk and a locus at chromosome 8q24. *Cancer Epidemiol Biomarkers Prev.* 2007; 16 (4):809–814. 16/4/809 [pii]. 10.1158/1055-9965.EPI-06-1049 [PubMed: 17416775]
 20. Cortesiss VK, Yuan JM, Van Den Berg D, Jiang X, Gago-Dominguez M, Stern MC, Castela JE, Xiang YB, Gao YT, Pike MC, Conti DV. Risk of urinary bladder cancer is associated with 8q24 variant rs9642880[T] in multiple racial/ethnic groups: results from the Los Angeles-Shanghai case-control study. *Cancer Epidemiol Biomarkers Prev.* 2010; 19 (12):3150–3156. 1055-9965.EPI-10-0763 [pii]. 10.1158/1055-9965.EPI-10-0763 [PubMed: 21051319]
 21. Kiemene LA, Thorlacius S, Sulem P, Geller F, Aben KK, Stacey SN, Gudmundsson J, Jakobsdottir M, Bergthorsson JT, Sigurdsson A, Blondal T, Witjes JA, Vermeulen SH, Hulsbergen-van de Kaa CA, Swinkels DW, Ploeg M, Cornel EB, Vergunst H, Thorgeirsson TE, Gudbjartsson D, Gudjonsson SA, Thorleifsson G, Kristinsson KT, Mouy M, Snorraddottir S, Placidi D, Campagna M, Arici C, Koppova K, Gurzau E, Rudnai P, Kellen E, Polidoro S, Guarrera S, Sacerdote C, Sanchez M, Saez B, Valdivia G, Ryk C, de Verdier P, Lindblom A, Golka K, Bishop DT, Knowles MA, Nikulasson S, Petursdottir V, Jonsson E, Geirsson G, Kristjansson B, Mayordomo JI, Steineck G, Porru S, Buntinx F, Zeegers MP, Fletcher T, Kumar R, Matullo G, Vineis P, Kiltie AE, Gulcher JR, Thorsteinsdottir U, Kong A, Rafnar T, Stefansson K. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. *Nat Genet.* 2008; 40 (11):1307–1312. ng.229 [pii]. 10.1038/ng.229 [PubMed: 18794855]
 22. Goode EL, Chenevix-Trench G, Song H, Ramus SJ, Notaridou M, Lawrenson K, Widschwendter M, Vierkant RA, Larson MC, Kjaer SK, Birrer MJ, Berchuck A, Schildkraut J, Tomlinson I, Kiemene LA, Cook LS, Gronwald J, Garcia-Closas M, Gore ME, Campbell I, Whittemore AS, Sutphen R, Phelan C, Anton-Culver H, Pearce CL, Lambrechts D, Rossing MA, Chang-Claude J, Moysich KB, Goodman MT, Dork T, Nevanlinna H, Ness RB, Rafnar T, Hogdall C, Hogdall E, Fridley BL, Cunningham JM, Sieh W, McGuire V, Godwin AK, Cramer DW, Hernandez D, Levine D, Lu K, Iversen ES, Palmieri RT, Houlston R, van Altna AM, Aben KK, Massuger LF, Brooks-Wilson A, Kelemen LE, Le ND, Jakubowska A, Lubinski J, Medrek K, Stafford A, Easton DF, Tyrer J, Bolton KL, Harrington P, Eccles D, Chen A, Molina AN, Davila BN, Arango H, Tsai YY, Chen Z, Risch HA, McLaughlin J, Narod SA, Ziogas A, Brewster W, Gentry-Maharaj A, Menon U, Wu AH, Stram DO, Pike MC, Beesley J, Webb PM, Chen X, Ekici AB, Thiel FC, Beckmann MW, Yang H, Wentzensen N, Lissowska J, Fasching PA, Despierre E, Amant F, Vergote I, Doherty J, Hein R, Wang-Gohrke S, Lurie G, Carney ME, Thompson PJ, Runnebaum I, Hillemanns P, Durst M, Antonenkova N, Bogdanova N, Leminen A, Butzow R, Heikkinen T, Stefansson K, Sulem P, Besenbacher S, Sellers TA, Gayther SA, Pharoah PD. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. *Nat Genet.* 2010; 42 (10):874–879.10.1038/ng.668 [PubMed: 20852632]
 23. Jones AM, Howarth KM, Martin L, Gorman M, Mihai R, Moss L, Auton A, Lemon C, Mehanna H, Mohan H, Clarke SE, Wadsley J, Macias E, Coatesworth A, Beasley M, Roques T, Martin C, Ryan P, Gerrard G, Power D, Bremner C, Tomlinson I, Carvajal-Carmona LG. 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 (3):158–163.10.1136/jmedgenet-2011-100586 [PubMed: 22282540]
 24. Lochhead P, Ng MT, Hold GL, Rabkin CS, Vaughan TL, Gammon MD, Risch HA, Lissowska J, Mukhopadhyay I, Chow WH, El-Omar EM. Possible association between a genetic polymorphism at 8q24 and risk of upper gastrointestinal cancer. *Eur J Cancer Prev.* 2011; 20 (1):54–57.10.1097/CEJ.0b013e328341e320 [PubMed: 21102338]
 25. Middeldorp A, Jagmohan-Changur S, van Eijk R, Tops C, Devilee P, Vasen HF, Hes FJ, Houlston R, Tomlinson I, Houwing-Duistermaat JJ, Wijnen JT, Morreau H, van Wezel T. Enrichment of low penetrance susceptibility loci in a Dutch familial colorectal cancer cohort. *Cancer Epidemiol*

- Biomarkers Prev. 2009; 18 (11):3062–3067. 1055-9965.EPI-09-0601 [pii]. 10.1158/1055-9965.EPI-09-0601 [PubMed: 19843678]
26. Wokolorczyk D, Gliniewicz B, Sikorski A, Zlowocka E, Masojc B, Debniak T, Matyjasik J, Mierzejewski M, Medrek K, Oszutowska D, Suchy J, Gronwald J, Teodorczyk U, Huzarski T, Byrski T, Jakubowska A, Gorski B, van de Wetering T, Walczak S, Narod SA, Lubinski J, Cybulski C. A range of cancers is associated with the rs6983267 marker on chromosome 8. *Cancer Res.* 2008; 68 (23):9982–9986. 68/23/9982 [pii]. 10.1158/0008-5472.CAN-08-1838 [PubMed: 19047180]
 27. Lu H, Cai L, Mu LN, Lu QY, Zhao J, Cui Y, Sul JH, Zhou XF, Ding BG, Elashoff RM, Marshall J, Yu SZ, Jiang QW, Zhang ZF. Dietary mineral and trace element intake and squamous cell carcinoma of the esophagus in a Chinese population. *Nutr Cancer.* 2006; 55 (1):63–70.10.1207/s15327914nc5501_8 [PubMed: 16965242]
 28. Mu LN, Cao W, Zhang ZF, Cai L, Jiang QW, You NC, Goldstein BY, Wei GR, Chen CW, Lu QY, Zhou XF, Ding BG, Chang J, Yu SZ. Methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C polymorphisms and the risk of primary hepatocellular carcinoma (HCC) in a Chinese population. *Cancer Causes Control.* 2007; 18 (6):665–675.10.1007/s10552-007-9012-x [PubMed: 17503006]
 29. Chen SY, Chen CJ, Tsai WY, Ahsan H, Liu TY, Lin JT, Santella RM. Associations of plasma aflatoxin B1-albumin adduct level with plasma selenium level and genetic polymorphisms of glutathione S-transferase M1 and T1. *Nutr Cancer.* 2000; 38 (2):179–185.10.1207/S15327914NC382_6 [PubMed: 11525595]
 30. Park SL, Chang SC, Cai L, Cordon-Cardo C, Ding BG, Greenland S, Hussain SK, Jiang Q, Liu S, Lu ML, Mao JT, Morgenstern H, Mu LN, Ng LJ, Pantuck A, Rao J, Reuter VE, Tashkin DP, You NC, Yu CQ, Yu SZ, Zhao JK, Belldegrun A, Zhang ZF. Associations between variants of the 8q24 chromosome and nine smoking-related cancer sites. *Cancer Epidemiol Biomarkers Prev.* 2008; 17 (11):3193–3202. 17/11/3193 [pii]. 10.1158/1055-9965.EPI-08-0523 [PubMed: 18990762]
 31. Haiman CA, Le Marchand L, Yamamoto J, Stram DO, Sheng X, Kolonel LN, Wu AH, Reich D, Henderson BE. A common genetic risk factor for colorectal and prostate cancer. *Nat Genet.* 2007; 39 (8):954–956. ng2098 [pii]. 10.1038/ng2098 [PubMed: 17618282]
 32. Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC, Waliszewska A, Neubauer J, Tandon A, Schirmer C, McDonald GJ, Greenway SC, Stram DO, Le Marchand L, Kolonel LN, Frasco M, Wong D, Pooler LC, Ardlie K, Oakley-Girvan I, Whittemore AS, Cooney KA, John EM, Ingles SA, Altshuler D, Henderson BE, Reich D. Multiple regions within 8q24 independently affect risk for prostate cancer. *Nat Genet.* 2007; 39 (5):638–644. ng2015 [pii]. 10.1038/ng2015 [PubMed: 17401364]
 33. Severi G, Hayes VM, Padilla EJ, English DR, Southey MC, Sutherland RL, Hopper JL, Giles GG. 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 (3):610–612. 16/3/610 [pii]. 10.1158/1055-9965.EPI-06-0872 [PubMed: 17372260]
 34. Sun J, Lange EM, Isaacs SD, Liu W, Wiley KE, Lange L, Gronberg H, Duggan D, Carpten JD, Walsh PC, Xu J, Chang BL, Isaacs WB, Zheng SL. Chromosome 8q24 risk variants in hereditary and non-hereditary prostate cancer patients. *Prostate.* 2008; 68 (5):489–497.10.1002/pros.20695 [PubMed: 18213635]
 35. Li M, Zhou Y, Chen P, Yang H, Yuan X, Tajima K, Cao J, Wang H. 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 (3):e18251.10.1371/journal.pone.0018251 [PubMed: 21455501]
 36. Tuupanen S, Niittymaki I, Nousiainen K, Vanharanta S, Mecklin JP, Nuorva K, Jarvinen H, Hautaniemi S, Karhu A, Aaltonen LA. Allelic imbalance at rs6983267 suggests selection of the risk allele in somatic colorectal tumor evolution. *Cancer Res.* 2008; 68 (1):14–17. 68/1/14 [pii]. 10.1158/0008-5472.CAN-07-5766 [PubMed: 18172290]
 37. Xiong F, Wu C, Bi X, Yu D, Huang L, Xu J, Zhang T, Zhai K, Chang J, Tan W, Cai J, Lin D. Risk of genome-wide association study-identified genetic variants for colorectal cancer in a Chinese population. *Cancer Epidemiol Biomarkers Prev.* 19(7):1855–1861. 1055-9965.EPI-10-0210 [pii]. 10.1158/1055-9965.EPI-10-0210 [PubMed: 20530476]

38. Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med.* 2008; 359 (21):2208–2219. 359/21/2208 [pii]. 10.1056/NEJMoa0804742 [PubMed: 19020323]
39. Weedon MN, McCarthy MI, Hitman G, Walker M, Groves CJ, Zeggini E, Rayner NW, Shields B, Owen KR, Hattersley AT, Frayling TM. Combining information from common type 2 diabetes risk polymorphisms improves disease prediction. *PLoS Med.* 2006; 3 (10):e374. 06-PLME-RA-0127R2 [pii]. 10.1371/journal.pmed.0030374 [PubMed: 17020404]
40. Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk to disease from genome-wide association studies. *Genome Res.* 2007; 17 (10):1520–1528. gr.6665407 [pii]. 10.1101/gr.6665407 [PubMed: 17785532]
41. Beebe-Dimmer JL, Levin AM, Ray AM, Zuhlke KA, Machiela MJ, Halstead-Nussloch BA, Johnson GR, Cooney KA, Douglas JA. Chromosome 8q24 markers: risk of early-onset and familial prostate cancer. *Int J Cancer.* 2008; 122 (12):2876–2879. 10.1002/ijc.23471 [PubMed: 18360876]
42. Hamano T, Matsui H, Sekine Y, Ohtake N, Nakata S, Suzuki K. Association of SNP rs1447295 and microsatellite marker DG8S737 with familial prostate cancer and high grade disease. *J Urol.* 2010; 184 (2):738–742. S0022-5347(10)03200-3 [pii]. 10.1016/j.juro.2010.03.102 [PubMed: 20639049]
43. Wang L, McDonnell SK, Slusser JP, Hebbring SJ, Cunningham JM, Jacobsen SJ, Cerhan JR, Blute ML, Schaid DJ, Thibodeau SN. Two common chromosome 8q24 variants are associated with increased risk for prostate cancer. *Cancer Res.* 2007; 67 (7):2944–2950. 67/7/2944 [pii]. 10.1158/0008-5472.CAN-06-3186 [PubMed: 17409399]
44. Wokolorczyk D, Gliniewicz B, Stojewski M, Sikorski A, Zlowocka E, Debniak T, Jakubowska A, Gorski B, van de Wetering T, Narod SA, Lubinski J, Cybulski C. The rs1447295 and DG8S737 markers on chromosome 8q24 and cancer risk in the Polish population. *Eur J Cancer Prev.* 19(2): 167–171. 10.1097/CEJ.0b013e32832945c3 [PubMed: 19952762]
45. Zeegers MP, Khan HS, Schouten LJ, van Dijk BA, Goldbohm RA, Schalken J, Shajahan S, Pearlman A, Oddoux C, van den Brandt PA, Ostrer H. Genetic marker polymorphisms on chromosome 8q24 and prostate cancer in the Dutch population: DG8S737 may not be the causative variant. *Eur J Hum Genet.* 19(1):118–120. ejhg2010133 [pii]. 10.1038/ejhg.2010.133 [PubMed: 20700145]
46. Pemberton TJ, Mehta NU, Witonsky D, Di Rienzo A, Allayee H, Conti DV, Patel PI. Prevalence of common disease-associated variants in Asian Indians. *BMC Genet.* 2008; 9:13. 1471-2156-9-13 [pii]. 10.1186/1471-2156-9-13 [PubMed: 18248681]
47. Ahmadiyah N, Pomerantz MM, Grisanzio C, Herman P, Jia L, Almendro V, He HH, Brown M, Liu XS, Davis M, Caswell JL, Beckwith CA, Hills A, Macconail L, Coetzee GA, Regan MM, Freedman ML. 8q24 prostate, breast, and colon cancer risk loci show tissue-specific long-range interaction with MYC. *Proc Natl Acad Sci U S A.* 107(21):9742–9746. 0910668107 [pii]. 10.1073/pnas.0910668107 [PubMed: 20453196]
48. Jia L, Landan G, Pomerantz M, Jaschek R, Herman P, Reich D, Yan C, Khalid O, Kantoff P, Oh W, Manak JR, Berman BP, Henderson BE, Frenkel B, Haiman CA, Freedman M, Tanay A, Coetzee GA. Functional enhancers at the gene-poor 8q24 cancer-linked locus. *PLoS Genet.* 2009; 5 (8):e1000597. 10.1371/journal.pgen.1000597 [PubMed: 19680443]
49. Panagopoulos I, Moller E, Collin A, Mertens F. The POU5F1P1 pseudogene encodes a putative protein similar to POU5F1 isoform 1. *Oncol Rep.* 2008; 20 (5):1029–1033. [PubMed: 18949397]
50. Pomerantz MM, Ahmadiyah N, Jia L, Herman P, Verzi MP, Doddapaneni H, Beckwith CA, Chan JA, Hills A, Davis M, Yao K, Kehoe SM, Lenz HJ, Haiman CA, Yan C, Henderson BE, Frenkel B, Barretina J, Bass A, Tabernero J, Baselga J, Regan MM, Manak JR, Shivdasani R, Coetzee GA, Freedman ML. The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. *Nat Genet.* 2009; 41 (8):882–884. ng.403 [pii]. 10.1038/ng.403 [PubMed: 19561607]
51. Tuupanen S, Turunen M, Lehtonen R, Hallikas O, Vanharanta S, Kivioja T, Bjorklund M, Wei G, Yan J, Niittymaki I, Mecklin JP, Jarvinen H, Ristimaki A, Di-Bernardo M, East P, Carvajal-Carmona L, Houlston RS, Tomlinson I, Palin K, Ukkonen E, Karhu A, Taipale J, Aaltonen LA.

- The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling. *Nat Genet.* 2009; 41 (8):885–890. ng.406 [pii]. 10.1038/ng.406 [PubMed: 19561604]
52. Wasserman NF, Aneas I, Nobrega MA. An 8q24 gene desert variant associated with prostate cancer risk confers differential in vivo activity to a MYC enhancer. *Genome Res.* gr.105361.110 [pii]. 10.1101/gr.105361.110
53. Sotelo J, Esposito D, Duhagon MA, Banfield K, Mehalko J, Liao H, Stephens RM, Harris TJ, Munroe DJ, Wu X. Long-range enhancers on 8q24 regulate c-Myc. *Proc Natl Acad Sci U S A.* 2010; 107 (7):3001–3005. 0906067107 [pii]. 10.1073/pnas.0906067107 [PubMed: 20133699]
54. Wright JB, Brown SJ, Cole MD. Upregulation of c-MYC in cis through a large chromatin loop linked to a cancer risk-associated single-nucleotide polymorphism in colorectal cancer cells. *Mol Cell Biol.* 2010; 30 (6):1411–1420. MCB.01384-09 [pii]. 10.1128/MCB.01384-09 [PubMed: 20065031]
55. Lamb DJ, Tannour-Louet M. In vivo exploration of the functional activity of the non-coding 8q24 prostate cancer risk locus. *Asian J Androl.* 2010; 12 (6):787–789. aja2010102 [pii]. 10.1038/aja.2010.102 [PubMed: 20818410]
56. Talseth-Palmer BA, Brenne IS, Ashton KA, Evans TJ, McPhillips M, Groombridge C, Suchy J, Kurzawski G, Spigelman A, Lubinski J, Scott RJ. Colorectal cancer susceptibility loci on chromosome 8q23.3 and 11q23.1 as modifiers for disease expression in Lynch syndrome. *J Med Genet.* 2010; 48 (4):279–284. jmg.2010.079962 [pii]. 10.1136/jmg.2010.079962 [PubMed: 21097774]

Table 1

Select characteristics of cases and controls.

	Liver Cancer Cases (%)	Stomach Cancer Cases (%)	Esophageal Cancer Cases (%)	Controls (%)
Age in years (mean, SD)	53.9 13.0	61.5 9.8	60.6 9.6	57.7 11.8
Sex				
Female	45 (22.0)	68 (33.0)	77 (35.3)	128 (30.8)
Male	159 (78.0)	138 (67.0)	141 (64.7)	287 (69.2)
BMI in kg/m ² (mean, SD)	21.6 2.5	21.5 2.7	21.9 2.8	22.3 2.5
Hepatitis B serum antigen				
Absent	72 (35.3)			312 (75.2)
Present	132 (64.7)			102 (24.6)
Missing				1 (0.2)
<i>Helicobacter pylori</i>				
Absent		130 (63.1)		251 (60.5)
Present		71 (34.5)		114 (27.5)
Missing		5 (2.4)		50 (12.0)
Education				
Illiterate	44 (21.6)	66 (32.0)	83 (38.1)	73 (17.6)
Primary School	77 (37.8)	107 (51.9)	101 (46.3)	142 (34.2)
Middle School	70 (34.3)	30 (14.6)	28 (12.8)	124 (29.9)
Senior School	13 (6.4)	2 (1.0)	3 (1.4)	66 (15.9)
Bachelor's or higher	0 (0)	1 (0.5)	0 (0)	10 (2.4)
Missing			3 (1.4)	
Ever Smoking				
Never	85 (41.7)	92 (44.7)	94 (43.1)	217 (52.3)
Ever	107 (52.5)	109 (52.9)	117 (53.7)	197 (47.5)
Missing	12 (5.8)	5 (2.4)	7 (3.2)	1 (0.2)
Alcohol Drinking				
Never	87 (42.7)	111 (53.9)	116 (53.2)	207 (49.9)
Occasionally	29 (14.2)	31 (15.1)	18 (8.3)	72 (17.3)
Often	51 (25.0)	32 (15.5)	37 (17.0)	75 (18.1)
Everyday	25 (12.3)	27 (13.1)	40 (18.3)	58 (14.0)
Missing	12 (5.8)	5 (2.4)	7 (3.2)	3 (0.7)

Table 2

Association between family history of cancer and upper gastrointestinal cancers.

Cancer	Family History of Any Cancer		Family History of Index Cancer	
	Ca/Co	OR _{adj} (95% CI)	Ca/Co	OR _{adj} (95% CI)
Liver ^{a,b}				
Without Family History	101/289	1.00	151/376	1.00
With Family History	93/112	2.52 (1.63–3.88)	53/39	3.76 (2.13–6.63) ^d
Unrelateds and Other Relatives	2/10			
Missing	8/4			
Total	204/415			
Stomach ^{a,c}				
Without Family History	127/289	1.00	169/393	1.00
With Family History	63/112	1.41 (0.91–2.18)	37/22	4.56 (2.17–9.58)
Unrelateds and Other Relatives	13/10			
Missing	3/4			
Total	206/415			
Esophagus ^a				
Without Family History	151/289	1.00	187/361	1.00
With Family History	55/112	0.93 (0.61–1.44)	31/54	1.31 (0.74–2.32)
Unrelateds and Other Relatives	5/10			
Missing	7/4			
Total	218/415			

^a Adjusted for age, sex, education, smoking status, pack years, alcohol drinking frequency, and BMI.^b Adjusted for hepatitis B antigen and aflatoxin exposure.^c Adjusted for *Helicobacter pylori* infection.^d Previously reported by Mu LN, Cao W, Zhang ZF et al. 2007. *Cancer Causes and Controls*.

Table 3

Association between 8q24 SNP genotypes and upper gastrointestinal cancers,^d

Cancer Site	rs1447295			rs16901979			rs6983267		
	Ca/Co	OR _{adj} (95% CI)	Ca/Co	OR _{adj} (95% CI)	Ca/Co	OR _{adj} (95% CI)	Ca/Co	OR _{adj} (95% CI)	
Liver^{d,b}									
CC	127/275	1.00	CC	99/203	1.00	TT	53/143	1.00	
CA	52/100	1.33 (0.82–2.15)	CA	71/138	1.16 (0.74–1.81)	TG	86/160	1.39 (0.85–2.27)	
AA	7/9	1.37 (0.43–4.33)	AA	14/30	1.22 (0.54–2.75)	GG	44/71	1.69 (0.93–3.05)	
P _{trend}		0.236			0.465			0.068	
Dom		1.33 (0.84–2.11)	Dom		1.17 (0.76–1.79)	Dom		1.48 (0.94–2.33)	
Rec		1.27 (0.40–4.00)	Rec		1.14 (0.52–2.51)	Rec		1.40 (0.83–2.36)	
Stomach^{d,c}									
CC	140/275	1.00	CC	105/203	1.00	TT	58/143	1.00	
CA	37/100	0.77 (0.47–1.26)	CA	67/138	0.85 (0.55–1.30)	TG	89/160	1.07 (0.67–1.69)	
AA	7/9	1.27 (0.40–4.05)	AA	16/30	1.29 (0.60–2.79)	GG	31/71	0.81 (0.44–1.48)	
P _{trend}		0.599			0.993			0.605	
Dom		0.82 (0.52–1.30)	Dom		0.91 (0.60–1.36)	Dom		0.99 (0.64–1.53)	
Rec		1.35 (0.43–4.27)	Rec		1.38 (0.65–2.92)	Rec		0.78 (0.45–1.33)	
Esophagus^d									
CC	135/275	1.00	CC	112/203	1.00	TT	66/143	1.00	
CA	56/100	1.19 (0.77–1.83)	CA	69/138	0.94 (0.62–1.42)	TG	95/160	0.99 (0.64–1.53)	
AA	2/9	0.31 (0.06–1.56)	AA	14/30	1.15 (0.54–2.44)	GG	39/71	0.91 (0.52–1.60)	
P _{trend}		0.935			0.915			0.794	
Dom		1.09 (0.71–1.66)	Dom		0.98 (0.66–1.44)	Dom		0.97 (0.64–1.42)	
Rec		0.29 (0.06–1.49)	Rec		1.18 (0.57–2.44)	Rec		0.92 (0.56–1.51)	

^a Adjusted for age, sex, education, smoking status, pack years, alcohol drinking frequency, and BMI.

^b Adjusted for hepatitis B antigen and aflatoxin exposure.

^c Adjusted for *Helicobacter pylori* infection.

^d Originally published in Park et al., "Associations between variants of the 8q24 chromosome and nine smoking-related cancer sites." *Cancer Epidemiol Biomarkers Prev.* 2009.

Table 4

Association between 8q24 SNP genotypes and upper gastrointestinal cancers, stratified by family history of cancer.

Cancer Site	FH	rs1447295 (CC=Ref, AC, AA)				rs16901979 (CC=Ref, AC, AA)				rs6983267 (TT=Ref, GT, GG)					
		Ca/Co	With FH OR _{adj} (95% CI)	Ca/Co	No FH OR _{adj} (95% CI)	P	Ca/Co	With FH OR _{adj} (95% CI)	Ca/Co	No FH OR _{adj} (95% CI)	P	Ca/Co	With FH OR _{adj} (95% CI)	Ca/Co	No FH OR _{adj} (95% CI)
Liver ^{a,c}	Any	51/74	1.00	69/198	1.00	49/48	1.00	47/152	1.00	23/47	1.00	27/93	1.00		
		31/27	2.75 (1.10–6.91)	20/72	0.99 (0.51–1.92)	29/40	1.18 (0.51–2.73)	39/97	1.22 (0.69–2.18)	42/35	2.61 (1.00–6.82)	40/124	0.92 (0.48–1.77)		
		3/1	3.31 (0.25–43.4)	4/8	1.06 (0.26–4.29)	7/9	0.97 (0.24–3.80)	6/21	0.91 (0.28–2.94)	17/17	1.31 (0.37–4.61)	26/54	2.05 (0.96–4.38)	0.029	
		Dom.	2.80 (1.15–6.80)	Dom.	1.00 (0.54–1.87)	Dom.	1.13 (0.52–2.48)	Dom.	1.17 (0.67–2.04)	Dom.	2.17 (0.89–5.28)	Dom.	1.20 (0.66–2.18)		
		Rec.	2.61 (0.19–34.1)	Rec.	1.06 (0.26–4.25)	Rec.	0.90 (0.24–3.38)	Rec.	0.83 (0.26–2.62)	Rec.	0.76 (0.24–2.36)	Rec.	2.15 (1.11–4.16)		
Stom ach ^{a,c}	Any	42/74	1.00	95/198	1.00	27/48	1.00	76/152	1.00	18/47	1.00	39/93	1.00		
		14/27	1.11 (0.46–2.67)	23/72	0.69 (0.37–1.26)	26/40	1.03 (0.46–2.32)	41/97	0.74 (0.43–1.25)	30/35	1.77 (0.75–4.19)	58/124	0.79 (0.44–1.40)		
		2/1	8.20 (0.48–139)	5/8	0.87 (0.22–3.31)	5/9	0.75 (0.17–3.22)	11/21	1.81 (0.69–4.74)	11/17	1.22 (0.38–3.95)	19/54	0.55 (0.25–1.20)	0.253	
		Dom.	1.28 (0.55–2.99)	Dom.	0.71 (0.40–1.26)	Dom.	0.98 (0.45–2.12)	Dom.	0.86 (0.52–1.41)	Dom.	1.60 (0.71–3.59)	Dom.	0.72 (0.41–1.26)		
		Rec.	7.93 (0.47–132)	Rec.	0.94 (0.25–3.59)	Rec.	0.74 (0.18–3.01)	Rec.	2.02 (0.79–5.20)	Rec.	0.90 (0.31–2.67)	Rec.	0.64 (0.33–1.27)		
	ROR _{dom}	2.54 (0.94–6.87)	ROR _{dom}	0.065*	ROR _{dom}	0.84 (0.34–2.07)	ROR _{dom}	0.712*	ROR _{dom}	1.81 (0.67–4.85)	ROR _{dom}	2.20 (0.84–5.76)	ROR _{dom}	0.105*	

^a Adjusted for age, sex, education, smoking status, pack years, alcohol drinking frequency, and BMI.

^b Adjusted for hepatitis B antigen and aflatoxin exposure.

^c Adjusted for *Helicobacter pylori* infection.

NAC: Not Able to Calculate

FH: Family History

P : P-value for test of heterogeneity

* P-value for ROR

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 5

Association between 8p24 SNP genotypes and liver cancer, stratified by family history of cancer, in hepatitis B negative subgroup.

Cancer Site	FH	rs1447295 (CC=Ref, AC, AA)				rs16901979 (CC=Ref, AC, AA)				rs6983267 (TT=Ref, GT, GG)						
		Ca/Co	With FH OR _{adj} (95% CI)	Ca/Co	No FH OR _{adj} (95% CI)	P	Ca/Co	With FH OR _{adj} (95% CI)	Ca/Co	No FH OR _{adj} (95% CI)	P	Ca/Co	With FH OR _{adj} (95% CI)	Ca/Co	No FH OR _{adj} (95% CI)	P
Liver ^a	Any	12/ 58	1.00 (1.10–12.8)	25/141	1.00 (0.42–2.65)	0.083	49/ 48	1.00 (0.27–2.45)	47/152	1.00 (0.68–4.00)	0.734	23/47	1.00 (1.00–18.2)	27/ 93	1.00 (0.31–2.43)	0.040
		12/ 23	3.76 (1.10–12.8)	9/54	1.06 (0.42–2.65)		29/ 40	0.82 (0.27–2.45)	39/97	1.65 (0.68–4.00)		42/35	4.28 (1.00–18.2)	40/ 124	0.87 (0.31–2.43)	
		1/1	1.99 (0.06–58.9)	0/7	NAC	0.083	7/9	0.70 (0.11–4.32)	6/21	2.23 (0.50–9.82)	0.734	17/17	1.63 (0.20–13.3)	26/54	2.39 (0.79–7.23)	0.040
		Dom. Rec.	3.52 (1.10–11.1)	Dom. Rec.	0.90 (0.36–2.21)		Dom. Rec.	0.79 (0.28–2.25)	Dom. Rec.	1.73 (0.74–4.05)		Dom. Rec.	3.55 (0.87–14.4)	Dom. Rec.	1.26 (0.50–3.17)	
		1.74 (0.04–62.0)	Rec.	NAC		Rec.	0.77 (0.13–4.41)	Rec.	1.73 (0.42–7.01)		Rec.	0.63 (0.10–3.89)	Rec.	2.59 (1.02–6.57)		

^a Adjusted for age, sex, education, smoking status, pack years, alcohol drinking frequency, BMI, and aflatoxin exposure.

NAC: Not Able to Calculate

FH: Family History

P : P-value for test of heterogeneity

Table 6

Genetic risk score for 8q24 SNP genotypes^b and upper gastrointestinal cancers, stratified by family history of cancer.

Cancer Site	Ca/Co	With Family History OR _{adj} (95% CI)	Ca/Co	No Family History OR _{adj} (95% CI)	Ca/Co	Combined
Liver ^d						
Continuous score	79/94	2.00 (1.15–3.47)	87/258	1.08 (0.78–1.51)	173/356	1.26 (0.97–1.63)
P _{trend}		0.012		0.613		0.076
Categorical score						
0 minor genotypes	9/12	1.00	10/41	1.00	20/56	1.00
1 minor genotype	29/45	1.00 (0.23–4.39)	36/103	1.28 (0.51–3.17)	68/148	1.35 (0.66–2.75)
2 minor genotypes	41/37	2.36 (0.56–9.90)	41/114	1.36 (0.56–3.30)	85/152	1.75 (0.88–3.46)
P _{trend}		0.077		0.518		0.085

^a Adjusted for age, sex, education, smoking status, pack years, alcohol drinking frequency, hepatitis B antigen, aflatoxin exposure, and BMI.

^b Cases and controls missing at least one of the three 8q24 SNP genotypes were excluded: 31 liver cancer cases and 59 controls.