



Alcohol and Cancer Biology Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.

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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Bongaerts, B. W., et al. (2006). "Alcohol and the risk of colon and rectal cancer with mutations in the K-ras gene." *Alcohol* **38**(3): 147-154.

The first metabolite of alcohol, acetaldehyde, may trigger replication errors and mutations in DNA, which may predispose to developing colorectal cancer (CRC). In a prospective study on colon and rectal cancer, we investigated the following hypotheses: alcohol consumption is associated with an increased risk of mutations in the K-ras oncogene, and beer consumption is associated with an increased risk of G->A mutations in this gene. Therefore, we studied the associations between consumption of alcohol and alcoholic beverages and the risk of CRC without and with specific K-ras gene mutations. In 1986, 120,852 men and women, aged 55-69 years, completed a questionnaire on risk factors for cancer. The case-cohort approach was used for data processing and

analyses. After 7.3 years of follow-up, excluding the first 2.3 years, complete data from 4,076 subcohort members, 428 colon and 150 rectal cancer patients, were available for data analyses. Incidence rate ratios (RRs) and corresponding 95% confidence intervals (95% CIs) were estimated using Cox proportional hazards models. Compared to abstaining, a total alcohol consumption of 30.0 g/day and more was associated with the risk of colon and rectal cancer with and without a K-ras mutation in both men and women. Independent from alcohol intake, liquor consumption when compared to nonliquor consumption was associated with an increased risk of rectal cancer with a wild type K-ras in men (RR: 2.25, 95% CI: 1.0-5.0). Beer consumption was not clearly associated with the risk of colon and rectal tumors harboring G->A mutations in the K-ras gene in men. This association could not be assessed in women because of sparse beer consumption. In conclusion, alcohol does not seem to be involved in predisposing to CRC through mutations in the K-ras gene, and specifically beer consumption is not associated with colon and rectal tumors harboring a G->A mutation.

Caceres, D. D., et al. (2005). "Relationship among metabolizing genes, smoking and alcohol used as modifier factors on prostate cancer risk: exploring some gene-gene and gene-environment interactions." *Eur J Epidemiol* **20**(1): 79-88.

BACKGROUND: Prostate cancer (PCa) is one of the most common male cancers, but the burden of this disease shows remarkable worldwide variation. The role of susceptibility low penetrance genes and environmental factors in the etiology of (PCa) is

unclear, but may involve, in some cases, multiple alleles at multiple loci and environmental factors. **STUDY OBJECTIVES:** To assess whether CYP1A1, GSTM1, GSTT1 susceptibility genotypes, smoking status and alcohol consumption factors contribute to PCa risk, gene-gene and gene-environment interactions were analyzed. **DESIGN AND PARTICIPANTS:** We explored interactions on a multiplicative scale conducting a population-based case-control and a case-only study on 103 incident PCa patients and 132 unrelated controls. **MAIN RESULTS:** The interaction odds ratios (IOR) for PCa risk were increased in men who had both susceptibility genotypes GST (M1; T1) null and CYP1A1-M1* in a case-control and case-only design (IOR (cc): 1.11; 95% CI: 0.12-10.02; IOR (co): 6.23; 95% CI: 0.51-75.89; IOR (co): 2.80; 95% CI: 0.44-17.45 and IOR_{co}: 2.65; 95% CI: 0.30-25.40). No clear evidence for interaction on a multiplicative scale between smoking status, alcohol consumption and genetic polymorphisms in PCa risk was observed. **CONCLUSIONS:** Our findings suggest that the interaction between genetic polymorphisms in GST (T1; M1) and CYP1A1-M1* would play a significant role as a modifying factor on PCa risk in Chilean people. However, these preliminary exploratory results should be confirmed in a larger study.

Dashti, S. G., et al. (2017). "Alcohol Consumption and the Risk of Colorectal Cancer for Mismatch Repair Gene Mutation Carriers." *Cancer Epidemiol Biomarkers Prev* **26**(3): 366-375.

Background: People with germline mutation in one of the DNA mismatch repair (MMR) genes have increased colorectal cancer risk. For these high-risk people, study findings of the relationship between alcohol consumption and colorectal cancer risk have been inconclusive. **Methods:** 1,925 MMR gene mutations carriers recruited into the Colon Cancer Family Registry who had completed a questionnaire on lifestyle factors were included. Weighted Cox proportional hazard regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between alcohol consumption and colorectal cancer. **Results:** Colorectal cancer was diagnosed in 769 carriers (40%) at a mean (SD) age of 42.6 (10.3) years. Compared with abstinence, ethanol consumption from any alcoholic beverage up to 14 g/day and >28 g/day was associated with increased colorectal cancer risk (HR, 1.50; 95% CI, 1.09-2.07 and 1.69; 95% CI, 1.07-2.65, respectively; $P_{trend} = 0.05$), and colon cancer risk (HR, 1.78; 95% CI, 1.27-2.49 and 1.94; 95% CI, 1.19-3.18, respectively; $P_{trend} = 0.02$). However, there was no clear evidence for an association with rectal cancer risk. Also, there was no evidence for associations

between consumption of individual alcoholic beverage types (beer, wine, spirits) and colorectal, colon, or rectal cancer risk. **Conclusions:** Our data suggest that alcohol consumption, particularly more than 28 g/day of ethanol (approximately 2 standard drinks of alcohol in the United States), is associated with increased colorectal cancer risk for MMR gene mutation carriers. **Impact:** Although these data suggested that alcohol consumption in MMR carriers was associated with increased colorectal cancer risk, there was no evidence of a dose-response, and not all types of alcohol consumption were associated with increased risk. *Cancer Epidemiol Biomarkers Prev*; **26**(3); 366-75. (c)2016 AACR.

Dennis, J., et al. (2011). "Breast cancer risk in relation to alcohol consumption and BRCA gene mutations--a case-only study of gene-environment interaction." *Breast J* **17**(5): 477-484.

The variable penetrance of the BRCA1 and BRCA2 genes suggests that other genetic or environmental factors may interact with these mutations to modify breast cancer risk. The objective of this study was to measure departures from multiplicative effects of alcohol consumption and BRCA gene mutations. A cohort of French-Canadian breast cancer patients was tested for BRCA gene mutations and completed a food frequency questionnaire. The case-only odds ratio (COR) was calculated. A total of 857 women, including 10 BRCA1 and 33 BRCA2 mutation carriers, participated in the study. No significant interaction between alcohol consumption and BRCA1 mutations was detected, although the interaction with wine consumption suggested a sub-multiplicative effect (COR = 0.38, 95% CI: 0.08-1.81). Consumption of alcohol other than wine interacted significantly with BRCA2 mutations (COR = 2.15, 95% CI: 1.03-4.49). Consumption of wine may protect against BRCA1-associated tumors, while women with BRCA2 mutations may be at greater risk of alcohol-induced breast cancer.

Dotson, C. D., et al. (2012). "Variation in the gene TAS2R13 is associated with differences in alcohol consumption in patients with head and neck cancer." *Chem Senses* **37**(8): 737-744.

Variation in responsiveness to bitter-tasting compounds has been associated with differences in alcohol consumption. One strong genetic determinant of variation in bitter taste sensitivity is alleles of the TAS2R gene family, which encode chemosensory receptors sensitive to a diverse array of natural and synthetic compounds. Members of the TAS2R family, when expressed in the gustatory system, function as bitter taste receptors. To better understand the

relationship between TAS2R function and alcohol consumption, we asked if TAS2R variants are associated with measures of alcohol consumption in a head and neck cancer patient cohort. Factors associated with increased alcohol intake are of strong interest to those concerned with decreasing the incidence of cancers of oral and pharyngeal structures. We found a single nucleotide polymorphism (SNP) located within the TAS2R13 gene (rs1015443 [C1040T, Ser259Asn]), which showed a significant association with measures of alcohol consumption assessed via the Alcohol Use Disorders Identification Test (AUDIT). Analyses with other SNPs in close proximity to rs1015443 suggest that this locus is principally responsible for the association. Thus, our results provide additional support to the emerging hypothesis that genetic variation in bitter taste receptors can impact upon alcohol consumption.

Fernandez-Somoano, A., et al. (2017). "Alcohol Consumption and Lung Cancer According to Ile349Val Polymorphism in ADH3 Gene: Beyond the Tobacco Smoking Effect." *J Cancer* **8**(12): 2296-2302.

Objectives: Smoking is the leading cause of lung cancer. However, several studies have suggested other factors such as alcohol consumption could also play a role through polymorphisms associated with alcohol metabolism. We investigated the association between alcohol consumption and lung cancer according to the Ile349Val polymorphism in the alcohol dehydrogenase 3 ADH3 gene. Methods: We carried out a hospital-based case-control study, a total of 402 incident cases of lung cancer and 383 controls were genotyped for the Ile349Val polymorphism by polymerase chain reaction combined with restriction fragment length polymorphism. Alcohol consumption and other variables were measured using questionnaires in personal interviews. We used multiple logistic regressions to estimate adjusted odd ratios using and 95% confidence intervals. Results: In multivariate analysis, an increased risk of lung cancer was observed for the highest category of alcohol consumption (≥ 30 g/day), although it does not reach statistical significance (OR=1.60, 95% CI: 0.91-2.83). Besides, an increased risk of lung cancer was observed in the highest category of alcohol consumption for the Ile/Val genotype compared with the Ile/Ile genotype (OR=2.35, 95% CI: 1.04-5.33). Conclusions: This study suggests that beyond smoking consumption, a high consumption of alcohol might increase the risk of lung cancer. No clear association was found between alcohol consumption and lung cancer according to the Ile349Val polymorphism in ADH3 gene.

Ferrari, P., et al. (2012). "Alcohol dehydrogenase and aldehyde dehydrogenase gene polymorphisms,

alcohol intake and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition study." *Eur J Clin Nutr* **66**(12): 1303-1308.

BACKGROUND/OBJECTIVES: Heavy alcohol drinking is a risk factor of colorectal cancer (CRC), but little is known on the effect of polymorphisms in the alcohol-metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) on the alcohol-related risk of CRC in Caucasian populations. SUBJECTS/METHODS: A nested case-control study (1269 cases matched to 2107 controls by sex, age, study centre and date of blood collection) was conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC) to evaluate the impact of rs1229984 (ADH1B), rs1573496 (ADH7) and rs441 (ALDH2) polymorphisms on CRC risk. Using the wild-type variant of each polymorphism as reference category, CRC risk estimates were calculated using conditional logistic regression, with adjustment for matching factors. RESULTS: Individuals carrying one copy of the rs1229984(A) (ADH1B) allele (fast metabolizers) showed an average daily alcohol intake of 4.3 g per day lower than subjects with two copies of the rs1229984(G) allele (slow metabolizers) (P (diff)<0.01). None of the polymorphisms was associated with risk of CRC or cancers of the colon or rectum. Heavy alcohol intake was more strongly associated with CRC risk among carriers of the rs1573496(C) allele, with odds ratio equal to 2.13 (95% confidence interval: 1.26-3.59) compared with wild-type subjects with low alcohol consumption (P (interaction)=0.07). CONCLUSIONS: The rs1229984(A) (ADH1B) allele was associated with a reduction in alcohol consumption. The rs1229984 (ADH1B), rs1573496 (ADH7) and rs441 (ALDH2) polymorphisms were not associated with CRC risk overall in Western-European populations. However, the relationship between alcohol and CRC risk might be modulated by the rs1573496 (ADH7) polymorphism.

Gao, C. M., et al. (2014). "Polymorphisms in XRCC1 gene, alcohol drinking, and risk of colorectal cancer: a case-control study in Jiangsu Province of China." *Asian Pac J Cancer Prev* **14**(11): 6613-6618.

To evaluate the relationship between alcohol drinking, XRCC1 codon 194 and 399 polymorphisms and risk of colorectal cancer, we conducted a case-control study with 315 colorectal cancer cases (105 colon, 210 rectal) and 439 population-based controls in Jiangsu Province of China. The XRCC1 codon 194 and 399 genotypes were identified using polymerase chain reaction and restriction fragment length polymorphism methods (PCR-RFLP). A structured questionnaire was used to elicit detailed information.

Odds ratios (ORs) were estimated with an unconditional logistic model. In this study no significant differences were observed among the studied groups with regard to the genotype distribution of the XRCC1 codons 194 and 399 and the risk of colorectal cancer did not appear to be significantly influenced by genotype alone, whereas alcohol consumption showed a positive association (P for trend <0.01). When combined effects of XRCC1 polymorphisms and alcohol consumption were analyzed, we found that the 194Trp or 399Gln alleles further increased the colorectal cancer risk due to high alcohol intake. These findings support the conclusion that colorectal cancer susceptibility may be altered by gene-environment interactions.

Hiraki, A., et al. (2007). "Gene-gene and gene-environment interactions between alcohol drinking habit and polymorphisms in alcohol-metabolizing enzyme genes and the risk of head and neck cancer in Japan." *Cancer Sci* **98**(7): 1087-1091.

Alcohol consumption is a strong risk factor for squamous cell carcinoma of the head and neck (SCCHN). The genetic polymorphisms aldehyde dehydrogenase2 (ALDH2) Glu487Lys and alcohol dehydrogenase 2 (ADH2) His47Arg, which have a strong impact on alcohol metabolism, are common in the Japanese population. To clarify the significance of these polymorphisms in SCCHN carcinogenesis, we conducted a matched case-control study with 239 incident SCCHN subjects and 716 non-cancer controls. Both ADH2 Arg/Arg and ALDH2 Glu/Lys were found to be independently associated with increased risk, with odds ratios (OR) of 2.67 (95% confidence interval [CI] 1.51-4.57) and 1.66 (95% CI 1.20-2.31), respectively. Further, compared with subjects having both ADH2 His/His and ALDH2 Glu/Glu, the adjusted OR and its 95% CI for those with both ADH2 Arg/Arg and ALDH2 Glu/Lys was 5.00 (2.32-10.71) in all subjects. This combination effect was evident in heavy drinkers (OR 11.3, 95% CI 2.97-43.3) but not in moderate or non-drinkers. Statistically significant gene-environment interactions between the two polymorphisms and drinking level were seen (ADH2 P = 0.035, ALDH2, P = 0.013). Furthermore, we also found a statistically significant gene-gene interaction between the two polymorphisms (P = 0.042). In conclusion, this case-control study showed a significantly increased risk of SCCHN in subjects with the ADH2 Arg/Arg and ALDH2 Glu/Lys polymorphisms in a Japanese population. In addition, our results also demonstrated that this risk was associated with significant gene-gene interactions between ADH2 and ALDH2 polymorphisms, as well as gene-environment interactions between these polymorphisms and alcohol drinking.

Hong, Y. C., et al. (2005). "Polymorphisms of XRCC1 gene, alcohol consumption and colorectal cancer." *Int J Cancer* **116**(3): 428-432.

To evaluate contribution of polymorphisms of the XRCC1 gene to the risk of colorectal cancer, we conducted a case-control study of 209 colorectal cancer cases and 209 age- and gender-matched controls in the Korean population. We tested the hypothesis by constructing allele combinations with known SNP. Allelic variants of the XRCC1 gene at codons 194, 280 and 399 were analyzed in lymphocyte DNA by PCR-RFLP. We observed an increased risk of colorectal cancer associated with the 399Gln allele. The odds ratio (OR) was 1.61 (95% confidence interval [CI] 1.09-2.39) for the 399Gln allele. When combined allele-specific OR were calculated after estimating frequencies, 3 common allele combinations were found to be associated with an increased risk of colorectal cancer. The OR for the 194Trp-280Arg-399Arg was 1.48 (95% CI = 1.06-2.07) using 194Arg-280Arg-399Arg as the reference. The OR for the 194Arg-280His-399Arg and the 194Arg-280Arg-399Gln were 1.78 (95% CI = 1.09-2.89) and 1.78 (95% CI = 1.23-2.59), respectively. Analysis after controlling for smoking, exercise and dietary habits indicated that alcohol consumption (> or =80 g/week) is a significant risk factor of colorectal cancer (OR = 2.60, 95% CI = 1.46-4.62). An increased risk for colorectal cancer was identified in alcohol drinkers with the risky allele combinations. Our results suggest that polymorphisms in the XRCC1 genes may contribute to colorectal cancer susceptibility, and some evidence was obtained of a genetic modification for the relationship between alcohol intake and colorectal cancer.

Kobayashi, L. C., et al. (2012). "Folate intake, alcohol consumption, and the methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism: influence on prostate cancer risk and interactions." *Front Oncol* **2**: 100.

PURPOSE: Folate is essential to DNA methylation and synthesis and may have a complex dualistic role in prostate cancer. Alcohol use may increase risk and epigenetic factors may interact with lifestyle exposures. We aimed to characterize the independent and joint effects of folate intake, alcohol consumption, and the MTHFR C677T gene polymorphism on prostate cancer risk, while accounting for intakes of vitamins B (2), B (6), B (12), methionine, total energy, and confounders. METHODS: A case-control study was conducted at Kingston General Hospital of 80 incident primary prostate cancer cases and 334 urology clinic controls, all with normal age-specific PSA levels (to exclude

latent prostate cancers). Participants completed a questionnaire on folate and alcohol intakes and potential confounders prior to knowledge of diagnosis, eliminating recall bias, and blood was drawn for MTHFR genotyping. Joint effects of exposures were assessed using unconditional logistic regression and significance of multiplicative and additive interactions using general linear models. RESULTS: Folate, vitamins B (2), B (6), B (12), methionine, and the CT and TT genotypes were not associated with prostate cancer risk. The highest tertile of lifetime alcohol consumption was associated with increased risk (OR = 2.08; 95% CI: 1.12-3.86). Consumption of >5 alcoholic drinks per week was associated with increased prostate cancer risk among men with low folate intake (OR = 2.38; 95% CI: 1.01-5.57), and higher risk among those with the CC MTHFR genotype (OR = 4.43; 95% CI: 1.15-17.05). Increased risk was also apparent for average weekly alcohol consumption when accounting for the multiplicative interaction between folate intake and MTHFR C677T genotype (OR = 3.22; 95% CI: 1.36-7.59). CONCLUSION: Alcohol consumption is associated with increased prostate cancer risk, and this association is stronger among men with low folate intake, with the CC MTHFR genotype, and when accounting for the joint effect of folate intake and MTHFR C677T genotype.

Lebedeva, I. V., et al. (2008). "Chemoprevention by perillyl alcohol coupled with viral gene therapy reduces pancreatic cancer pathogenesis." *Mol Cancer Ther* 7(7): 2042-2050.

Pancreatic cancer is one of the deadliest of cancers. Even with aggressive therapy, the 5-year survival rate is <5%, mandating development of more effective treatments. Melanoma differentiation-associated gene-7/interleukin-24 (mda-7/IL-24) shows potent antitumor activity against most cancers displaying safety with significant clinical efficacy. However, pancreatic cancer cells display inherent resistance to mda-7/IL-24 that is the result of a "protein translational block" of mda-7/IL-24 mRNA in these tumor cells. We now show that a dietary supplement perillyl alcohol (POH) has significant chemopreventive effects for pancreatic cancer and, when coupled with adenovirus-mediated mda-7/IL-24 gene therapy (Ad.mda-7), effectively eliminates s.c. and i.p. xenografts of human pancreatic cancer cells in nude mice, promoting enhanced survival. The combination of POH and Ad.mda-7 efficiently abrogates the mda-7/IL-24 protein translational block, resulting in MDA-7/IL-24 protein production and growth suppression. Of direct translational relevance, clinically achievable concentrations of POH with Ad.mda-7, both of which have been found safe and

without toxic effects in human trials, were used. This novel and innovative approach combining a dietary agent and a virally delivered therapeutic cytokine provides a means of both preventing and treating human pancreatic cancer with significant clinical translational potential.

Lebedeva, I. V., et al. (2008). "Mechanism of in vitro pancreatic cancer cell growth inhibition by melanoma differentiation-associated gene-7/interleukin-24 and perillyl alcohol." *Cancer Res* 68(18): 7439-7447.

The death rate for pancreatic cancer approximates the number of new cases each year, and when diagnosed, current therapeutic regimens provide little benefit in extending patient survival. These dire statistics necessitate the development of enhanced single or combinatorial therapies to decrease the pathogenesis of this invariably fatal disease. Melanoma differentiation-associated gene-7/interleukin-24 (mda-7/IL-24) is a potent cancer gene therapeutic because of its broad-spectrum cancer-specific apoptosis-inducing properties as well as its multipronged indirect antitumor activities. However, pancreatic cancer cells show inherent resistance to mda-7/IL-24 that is caused by a block of translation of mda-7/IL-24 mRNA in these tumor cells. We now reveal that a dietary agent perillyl alcohol (POH) in combination with Ad.mda-7 efficiently reverses the mda-7/IL-24 "protein translational block" by inducing reactive oxygen species, thereby resulting in mda-7/IL-24 protein production, growth suppression, and apoptosis. Pharmacologic inhibitor and small interfering RNA studies identify xanthine oxidase as a major source of superoxide radical production causing these toxic effects. Because both POH and Ad.mda-7 are being evaluated in clinical trials, combining a dietary agent and a virally delivered therapeutic cytokine provides an innovative approach for potentially treating human pancreatic cancer.

Lopez, R. V., et al. (2011). "Education, tobacco smoking, alcohol consumption, and IL-2 and IL-6 gene polymorphisms in the survival of head and neck cancer." *Braz J Med Biol Res* 44(10): 1006-1012.

The association of education, tobacco smoking, alcohol consumption, and interleukin-2 (IL-2 +114 and -384) and -6 (IL-6 -174) DNA polymorphisms with head and neck squamous cell carcinoma (HNSCC) was investigated in a cohort study of 445 subjects. IL-2 and IL-6 genotypes were determined by real-time PCR. Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals (95%CI) of disease-specific survival according to anatomical sites of the head and neck. Mean age was 56 years and most patients were males (87.6%). Subjects with 5 or more

years of schooling had better survival in larynx cancer. Smoking had no effect on HNSCC survival, but alcohol consumption had a statistically significant effect on larynx cancer. IL-2 gene +114 G/T (HR = 0.52; 95%CI = 0.15-1.81) and T/T (HR = 0.22; 95%CI = 0.02-3.19) genotypes were associated with better survival in hypopharynx cancer. IL-2 +114 G/T was a predictor of poor survival in oral cavity/oropharynx cancer and larynx cancer (HR = 1.32; 95%CI = 0.61-2.85). IL-2 -384 G/T was associated with better survival in oral cavity/oropharynx cancer (HR = 0.80; 95%CI = 0.45-1.42) and hypopharynx cancer (HR = 0.68; 95%CI = 0.21-2.20), but an inverse relationship was observed for larynx cancer. IL-6 -174 G/C was associated with better survival in hypopharynx cancer (HR = 0.68; 95%CI = 0.26-1.78) and larynx cancer (HR = 0.93; 95%CI = 0.42-2.07), and C/C reduced mortality in larynx cancer. In general, our results are similar to previous reports on the value of education, smoking, alcohol consumption, and IL-2 and IL-6 genetic polymorphisms for the prognosis of HNSCC, but the risks due to these variables are small and estimates imprecise.

Mao, N., et al. (2016). "Association between alcohol dehydrogenase-2 gene polymorphism and esophageal cancer risk: a meta-analysis." *World J Surg Oncol* **14**(1): 191.

BACKGROUND: It has been shown that gene polymorphisms may play an important role in the carcinogenesis of esophageal cancer. This study is to investigate the role of alcohol dehydrogenase 1B (ADH1B) gene Arg47His polymorphism in esophageal cancer susceptibility. **METHODS:** Case-control studies published between January 2000 and June 2015 were searched to retrieve relevant articles. The pooled odds ratio (OR) and 95 % confidence interval (CI) were employed to calculate the strength of association. **RESULTS:** A total of 23 relevant articles were finally selected for the analysis, including 9338 esophageal cancer patients and 14,896 matched controls. Overall, we found that the 47His allele was significant associated with the decreased risk of esophageal cancer when compared with the 47Arg allele in total populations (A vs. G: OR = 0.67, 95 % CI = 0.59-0.76, P < 0.00001). This protective relationship was observed under other genetic models as well (P < 0.00001). Subgroup analysis by ethnicity showed that ADH1B Arg47His variant was associated with the decreased esophageal cancer risk under all the genetic models (P < 0.00001) among Asians, especially in Chinese and Japanese; while in non-Asians, no significant correlation was detected in any genetic models (P > 0.05). Furthermore, Arg/Arg genotype of ADH1B Arg47His variant combined with drinking, smoking and males appeared to show a high

risk in patients with esophageal cancer. **CONCLUSIONS:** Our results suggested that ADH1B gene Arg47His variant was associated with the decreased esophageal cancer risk. Genetic-environmental interaction should be further considered in the future researches.

Masaoka, H., et al. (2016). "Aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 1B (ADH1B) polymorphisms exacerbate bladder cancer risk associated with alcohol drinking: gene-environment interaction." *Carcinogenesis* **37**(6): 583-588.

Although a range of chemical exposures (cigarette smoking and occupational exposure) are recognized risk factors for the development of bladder cancer (BCa), many epidemiological studies have demonstrated that alcohol drinking is not associated with BCa risk. Aldehyde dehydrogenase 2 (ALDH2; rs671, Glu504Lys) and alcohol dehydrogenase 1B (ADH1B; rs1229984, His47Arg) polymorphisms impact the accumulation of acetaldehyde, resulting in an increased risk of various cancers. To date, however, no studies evaluating the association between BCa risk and alcohol drinking have considered these polymorphisms. Here, we conducted a matched case-control study to investigate whether ALDH2 and ADH1B polymorphisms influence BCa risk associated with alcohol drinking. Cases were 74 BCa patients and controls were 740 first-visit outpatients without cancer at Aichi Cancer Center Hospital between January 2001 and December 2005. Odds ratio (OR), 95% confidence interval (CI) and gene-environment interaction were assessed by conditional logistic regression analysis with adjustment for potential confounders. Results showed that ALDH2 Glu/Lys was associated with a significantly increased risk of BCa compared with Glu/Glu (OR 2.03, 95% CI 1.14-3.62, P = 0.017). In contrast, ALDH2 Glu/Lys showed no increase in risk among the stratum of never drinkers compared with Glu/Glu, indicating a gene-environment interaction. ADH1B His/Arg had an OR of 1.98 (1.20-3.24, P = 0.007) compared with His/His. ADH1B Arg+ showed a similar OR and 95% CI. Individuals with ALDH2 Glu/Lys and ADH1B Arg+ had the highest risk of BCa compared with ALDH2 Glu/Glu and ADH1B His/His [OR 4.00 (1.81-8.87), P = 0.001].

Matsuo, K., et al. (2001). "Gene-environment interaction between an aldehyde dehydrogenase-2 (ALDH2) polymorphism and alcohol consumption for the risk of esophageal cancer." *Carcinogenesis* **22**(6): 913-916.

Aldehyde dehydrogenase-2 (ALDH2) degrades acetaldehyde metabolized from ethanol. Its encoding gene ALDH2 has a functional polymorphism: ALDH2

Glu487LYS: An association between this polymorphism and esophageal cancer among alcoholics has been reported. To further evaluate the gene-environment interaction, a hospital-based case-control study was conducted. Cases were 102 patients with histologically confirmed esophageal cancer and controls were 241 non-cancer outpatients of Aichi Cancer Center. ALDH2 genotypes were examined by a PCR-CTPP method developed in our laboratory, which does not require a digestion stage. Logistic regression analysis was employed for estimation of relative risk and gene-environment interaction. The allele frequency for ALDH2 Lys487 was 0.28, consistent with previous reports. The age, sex, smoking and drinking status adjusted odds ratio for the ALDH2 Glu/Lys and Lys/Lys genotypes as compared with the Glu/Glu genotype was 3.43 (95% CI 1.74-6.75). The odds ratio for heavy drinking was 49.6 (14.5-169.4) among Lys487 carriers and 7.84 (2.77-22.2) for the Glu/Glu genotype. The gene-environment interaction between alcohol drinking and the ALDH2 Lys487 allele was 6.84 (2.39-19.6), whereas no significant interaction was obtained with smoking status. Although limited because of its prevalent case-control design, our study revealed a strong gene-environment interaction between ALDH2 polymorphism and heavy alcohol consumption. Taking the observed high risk of esophageal cancer in association with the ALDH2 Lys487 allele into consideration, reducing alcohol intake may be most protective among Lys487 allele carriers of this polymorphism.

Matsuo, K., et al. (2005). "One-carbon metabolism related gene polymorphisms interact with alcohol drinking to influence the risk of colorectal cancer in Japan." *Carcinogenesis* **26**(12): 2164-2171.

One-carbon metabolism, in which folate plays an essential role, is involved in DNA methylation and synthesis, and is suspected of impacting on colorectal carcinogenesis. Alcohol is well recognized as a risk factor for colorectal cancer (CRC) and interactions with one-carbon metabolism have also been suggested. Therefore, functional polymorphisms in genes encoding members of this pathway, MTHFR C677T and A1298C (genes for methylenetetrahydrofolate reductase), MTR A2756G (gene for methionine synthase) and TS (gene for thymidylate synthase) tandem repeats polymorphisms, have attracted attention. We conducted a matched case-control study with 257 incident CRC cases and 771 non-cancer controls at the Aichi Cancer Center to clarify associations among folate intake and four polymorphisms with reference to CRC risk. Gene-environment interaction between polymorphisms, drinking and folate consumption was also evaluated.

None of the polymorphisms showed any significant impact on CRC risk by genotype alone, but when combined with alcohol consumption the MTHFR 677CC type showed a significantly reduced risk (odds ratio (OR) = 0.45, 95% confidence interval (CI): 0.23-0.86) (P = 0.01). MTR GG showed increased risk only among drinkers (OR = 3.35, 1.40-8.05) (P = 0.047). TS polymorphism did not show statistical significance by genotype alone, while interaction with drinking was significant (P = 0.028). The association was not changed even after stratification by daily folate consumption and drinking habit. In conclusion, we found consistently significant interactions between one-carbon metabolism-related polymorphisms and alcohol drinking.

Murata, M., et al. (1999). "Genotype difference of aldehyde dehydrogenase 2 gene in alcohol drinkers influences the incidence of Japanese colorectal cancer patients." *Jpn J Cancer Res* **90**(7): 711-719.

A case-control study was conducted to explore the possible etiologic role of alcohol and aldehyde dehydrogenase 2 (ALDH2) gene among Japanese colorectal cancer patients. Information on their drinking, smoking and dietary habits was collected from 265 colon and 164 rectum cancer patients, and 794 non-cancer patients as a control group. Genotypes of the ALDH2 gene at codon 487, glutamic acid (ALDH2*1) as a wild-type or lysine (ALDH2*2) as a mutated type with reduced enzyme activity, were analyzed by polymerase chain reaction in 160 colon and 110 rectum cancer patients and 121 control persons. Univariate analysis with the chi 2 statistical test showed that heavy alcohol drinking (P < 0.01), frequent meat intake (P < 0.001), and irregular (P < 0.01), hasty (P < 0.01) and excessive (P < 0.001) eating habits were associated with the incidence of both colon and rectum cancers, whereas heavier smoking (P < 0.05) and infrequent fish (P < 0.03) and fruit (P < 0.01) intake were solely associated with incidence of rectum cancer. Infrequent green vegetable intake was not correlated with the incidence of colorectal cancer. Multivariate unconditional logistic regression analysis confirmed the association of alcohol consumption (P < 0.01) and meat intake (P < 0.05). Homozygous and heterozygous carriers of ALDH2*2 allele tended to be found in colon (trend P = 0.04) but not in rectum cancer patients compared to controls. Risk elevation for colon cancer due to alcohol consumption was pronounced among the heterozygotes and it was statistically significant especially for distal colon cancer (trend P = 0.02). We conclude that alcohol consumption is a risk factor for colorectal cancer and the risk can be enhanced in ALDH2 heterozygotes.

Sarkar, S., et al. (2014). "Chemoprevention gene therapy (CGT) of pancreatic cancer using perillyl alcohol and a novel chimeric serotype cancer terminator virus." *Curr Mol Med* **14**(1): 125-140.

Conditionally replication competent adenoviruses (Ads) that selectively replicate in cancer cells and simultaneously express a therapeutic cytokine, such as melanoma differentiation associated gene-7/Interleukin-24 (mda-7/IL-24), a Cancer Terminator Virus (CTV-M7), hold potential for treating human cancers. To enhance the efficacy of the CTV-M7, we generated a chimeric Ad.5 and Ad.3 modified fiber bipartite CTV (Ad.5/3-CTV-M7) that can infect tumor cells in a Cocksackie Adenovirus receptor (CAR) independent manner, while retaining high infectivity in cancer cells containing high CAR. Although mda-7/IL-24 displays broad-spectrum anticancer properties, pancreatic ductal adenocarcinoma (PDAC) cells display an intrinsic resistance to mda-7/IL-24-mediated killing due to an mda-7/IL-24 mRNA translational block. However, using a chemoprevention gene therapy (CGT) approach with perillyl alcohol (POH) and a replication incompetent Ad to deliver mda-7/IL-24 (Ad.mda-7) there is enhanced conversion of mda-7/IL-24 mRNA into protein resulting in pancreatic cancer cell death in vitro and in vivo in nude mice containing human PDAC xenografts. This combination synergistically induces mda-7/IL-24-mediated cancer-specific apoptosis by inhibiting anti-apoptotic Bcl-xL and Bcl-2 protein expression and inducing an endoplasmic reticulum (ER) stress response through induction of BiP/GRP-78, which is most evident in chimeric-modified non-replicating Ad.5/3- mda-7- and CTV-M7-infected PDAC cells. Moreover, Ad.5/3-CTV-M7 in combination with POH sensitizes therapy-resistant MIA PaCa-2 cell lines over-expressing either Bcl-2 or Bcl-xL to mda-7/IL-24-mediated apoptosis. Ad.5/3-CTV-M7 plus POH also exerts a significant antitumor 'bystander' effect in vivo suppressing both primary and distant site tumor growth, confirming therapeutic utility of Ad.5/3-CTV-M7 plus POH in PDAC treatment, where all other current treatment strategies in clinical settings show minimal efficacy.

Sturmer, T., et al. (2002). "Interaction between alcohol dehydrogenase II gene, alcohol consumption, and risk for breast cancer." *Br J Cancer* **87**(5): 519-523.

MaeIII Restriction Fragment Length Polymorphism in exon 3 of the alcohol dehydrogenase II was assessed in serum from 467 randomly selected German women and 278 women with invasive breast cancer to evaluate the interaction between a polymorphism of the alcohol dehydrogenase II gene, alcohol consumption and risk for breast cancer. In both groups, usual consumption of different alcoholic

beverages was asked for using semiquantitative food frequency questionnaires. We used multivariable logistic regression to separately estimate the association between alcohol consumption and alcohol dehydrogenase II polymorphism in the population sample and women with breast cancer. The alcohol dehydrogenase II polymorphism was detected in 14 women from the population sample (3.0%) and in 27 women with invasive breast cancer (9.7%). Frequency of alcohol consumption was independent of the genotype in the population sample. In women with breast cancer, there was a significant inverse association between the alcohol dehydrogenase II polymorphism and frequency of alcohol consumption (adjusted case-only odds ratio over increasing frequency of alcohol consumption=0.5; P for interaction=0.02). We observed a gene-environment interaction between the alcohol dehydrogenase II polymorphism, alcohol consumption, and risk for breast cancer. Breast cancer risk associated with alcohol consumption may vary according to the alcohol dehydrogenase II polymorphism, probably due to differences in alcohol metabolism.

Suzuki, T., et al. (2008). "Alcohol drinking and one-carbon metabolism-related gene polymorphisms on pancreatic cancer risk." *Cancer Epidemiol Biomarkers Prev* **17**(10): 2742-2747.

Effect of alcohol consumption on pancreatic cancer risk has been investigated in many studies, but results have been inconsistent. We conducted a case-control study to assess the effect of alcohol on pancreatic cancer in conjunction with polymorphisms in one-carbon metabolism enzymes, methylenetetrahydrofolate reductase (MTHFR C677T), methionine synthase (MTR A2756G), methionine synthase reductase (MTRR A66G), and thymidylate synthase (TS) variable number of tandem repeat. A total of 157 pancreatic cancer patients and 785 age- and sex- matched control subjects were genotyped for polymorphisms. Odds ratios (OR) with 95% confidence intervals (95% CI) were estimated using unconditional logistic models adjusted for potential confounders. Heavy alcohol drinking was marginally associated with an increased risk of pancreatic cancer (OR, 1.90; 95% CI, 1.00-3.62). None of the polymorphisms showed any significant effect on pancreatic cancer risk by genotype alone. In stratified analysis, effect of alcohol consumption on pancreatic cancer was observed in individuals with the MTHFR 667 CC, MTR 2756 AA, or MTRR 66 G allele. OR (95% CI) of pancreatic cancer for heavy drinkers compared with never drinkers was 4.50 (1.44-14.05) in the MTHFR 667 CC genotype, 2.65 (1.17-6.00) in the MTR 2756 AA genotype, and 3.35 (1.34-8.36) in the MTRR 66 G allele carriers. These results suggest that

the folate-related enzyme polymorphism modifies the association between drinking habit and pancreatic cancer risk.

Tsai, S. M., et al. (2012). "Oxidative stress-related enzyme gene polymorphisms and susceptibility to breast cancer in non-smoking, non-alcohol-consuming Taiwanese women: a case-control study." *Ann Clin Biochem* **49**(Pt 2): 152-158.

BACKGROUND: Mitochondrial manganese superoxide dismutase (MnSOD) converts superoxide anion into H₂O₂, which is neutralized sequentially by either catalase (CAT) or glutathione peroxidase 1 (Gpx 1) into water or converted into highly reactive hypochlorous acid by myeloperoxidase (MPO). We hypothesize that gene variants for these enzymes might be associated with the risk of breast cancer in non-smoking, non-alcohol-consuming women. **METHODS:** Genotypes of oxidative stress-related enzymes (MnSOD1183T>C, MPO-463G>A, GPx1Pro198Leu and CAT-262C>T) were analysed in 260 non-smoking and non-alcohol-consuming female patients with breast cancer and 224 habit-matched controls. **RESULTS:** Subjects with the MnSOD1183T>C C carrier or those with the GPx1Pro198Leu CT genotype had significantly decreased age-adjusted risks (odds ratio [OR]: 0.56 and 0.16 with 95% confidence intervals [95% CI]: 0.38-0.83 and 0.08-0.29, respectively) for breast cancer. Certain combined genotypes of the polymorphisms also significantly modulated the age-adjusted risk. **CONCLUSIONS:** We conclude that oxidative stress-related enzyme genetic variants, especially GPx1Pro198Leu CT, modify the risk of breast cancer development in non-smoking and non-alcohol-consuming women. The role of unidentified environmental factors predisposing to breast cancer development through an oxidative stress mechanism merits further investigation.

Yang, C. X., et al. (2005). "Esophageal cancer risk by ALDH2 and ADH2 polymorphisms and alcohol consumption: exploration of gene-environment and gene-gene interactions." *Asian Pac J Cancer Prev* **6**(3): 256-262.

Alcohol drinking is a major risk factor for esophageal cancer in Japan and its impact may be modulated by levels of ALDH2, ADH2 and CYP2E1, three representative alcohol-metabolizing enzymes which display genetic polymorphisms altering individual alcohol-oxidizing capacity and drinking behavior. To assess the actual influence of ADH2 Arg47His, ALDH2 Glu487Lys and CYP2E1 variant c2 allele polymorphisms on esophageal cancer risk with conjunction with alcoholic consumption, the present 1:3 matched case-control study was conducted.

The 165 histologically diagnosed Japanese esophageal cancer cases were here compared with 495 randomly selected controls, matched with respect to sex and age. Conditional logistic regression was used to calculate Odds Ratios (ORs) and 95% confidence intervals (95% CI). Significant gene-environment interactions between alcohol drinking and both ADH2 and ALDH2 were observed regarding esophageal cancer risk. The ADH2 Arg47His polymorphism showed moderately increased risk (OR for Arg/His and Arg/Arg relative to His/His: 2.01 (1.39-2.90)). In the ALDH2 case, comparing the Glu/Lys with the Glu/Glu genotype, ORs were markedly increased to 9.64 (3.23-28.8) and 95.4 (28.7-317) from 1.88 (0.42-8.37) and 4.62 (0.93-23.1) for moderate drinking and heavy drinking, respectively. No significant alteration in risk was observed with the CYP2E1 polymorphism. In conclusion, the present study revealed a significant gene-environment interaction between alcohol drinking and the ALDH2 polymorphism regarding esophageal cancer risk among a general population in Japan, providing concrete evidence of a role for acetaldehyde in neoplastic development. Interactions between ALDH2 and ADH2 need further clarification.

Yang, C. X., et al. (2005). "Gene-environment interactions between alcohol drinking and the MTHFR C677T polymorphism impact on esophageal cancer risk: results of a case-control study in Japan." *Carcinogenesis* **26**(7): 1285-1290.

Folate takes part in two biological pathways involved in DNA methylation and synthesis, and a potential protective influence of this nutrient chemical against carcinogenicity has been recognized in several sites, including the esophagus. Therefore, the functional polymorphisms in genes encoding folate metabolizing enzymes, MTHFR C677T and MTR A2756G, might be suspected of impacting on esophageal cancer risk. We therefore conducted a matched case-control study of 165 esophageal cancer cases and 495 non-cancer controls to clarify associations among folate intake, MTHFR C677T and MTR A2756G polymorphisms, and esophageal cancer risk. Gene-environment interactions between the two polymorphisms, and drinking and smoking were also evaluated. Folate consumption and MTHFR 677TT were associated with a non-significant tendency for decreased risk while the MTR genotypes did not show any links in themselves; further, when analysis was limited to heavy drinkers, the MTHFR TT genotype significantly decreased esophageal cancer risk [odds ratio (OR) = 0.27, 95% confidence interval (CI), 0.09-0.76]. The OR for the gene-environment interaction between heavy drinking and the 677TT genotype in the case-only design was 0.31 (95% CI, 0.10-0.94), indicating risk with heavy drinking to be 69%

decreased in individuals harboring the 677TT genotype. We failed to find any significant interaction between either of the polymorphisms and smoking.

Yang, P. Y., et al. (2016). "Impact of Maspin Polymorphism rs2289520 G/C and Its Interaction with Gene to Gene, Alcohol Consumption Increase Susceptibility to Oral Cancer Occurrence." *PLoS One* **11**(8): e0160841.

BACKGROUND: The purpose of this study was to identify gene polymorphisms of mammary serine protease inhibitor (Maspin) specific to patients with oral cancer susceptibility and clinicopathological status. **METHODOLOGY/PRINCIPAL FINDINGS:** Three single-nucleotide polymorphisms (SNPs) of the Maspin gene from 741 patients with oral cancer and 601 non-cancer controls were analyzed by real-time PCR. The participants with G/G homozygotes or with G/C heterozygotes of Maspin rs2289520 polymorphism had a 2.07-fold ($p = 0.01$) and a 2.01-fold ($p = 0.02$) risk of developing oral cancer compared to those with C/C homozygotes. Moreover, gene-gene interaction increased the risk of oral cancer susceptibility among subjects expose to oral cancer related risk factors, including areca, alcohol, and tobacco consumption. **CONCLUSION:** G allele of Maspin rs2289520 polymorphism may be a factor that increases the susceptibility to oral cancer. The interactions of gene to oral cancer-related environmental risk factors have a synergetic effect that can further enhance oral cancer development.

Yokoyama, A., et al. (1999). "Alcohol and aldehyde dehydrogenase gene polymorphisms influence susceptibility to esophageal cancer in Japanese alcoholics." *Alcohol Clin Exp Res* **23**(11): 1705-1710.

BACKGROUND: Studies have consistently demonstrated that inactive aldehyde dehydrogenase-2 (ALDH2), encoded by ALDH2*1/2*2, is closely associated with alcohol-related carcinogenesis. Recently, the contributions of alcohol dehydrogenase-2 (ADH2) polymorphism to alcoholism, esophageal cancer, and the flushing response have also been described. **METHODS:** To determine the effects of ALDH2 and ADH2 genotypes in genetically based cancer susceptibility, lymphocyte DNA samples from 668 Japanese alcoholic men more than 40 years of age (91 with and 577 without esophageal cancer) were genotyped and the results were expressed as odds ratios (ORs). This study also tested 82 of the alcoholics with esophageal cancer to determine whether cancer susceptibility is associated with patients' responses to simple questions about current or former flushing after drinking a glass of beer. **RESULTS:** The frequencies of ADH2*1/2*1 and

ALDH2*1/2*2 were significantly higher in alcoholics with, than in those without, esophageal cancer (0.473 vs. 0.289 and 0.560 vs. 0.099, respectively). After adjustment for drinking and smoking, the analysis showed significantly increased cancer risk for alcoholics with either ADH2*1/2*1 (OR = 2.03) or ALDH2*1/2*2 (OR = 12.76). For those having ADH2*1/2*1 combined with ALDH2*1/2*2, the esophageal cancer risk was enhanced in a multiplicative fashion (OR = 27.66). Responses to flushing questions showed that only 47.8% of the ALDH2*1/2*2 heterozygotes with ADH2*1/2*1, compared with 92.3% of those with ALDH2*1/2*2 and the ADH2*2 allele, reported current or former flushing. Genotyping showed that for alcoholics who reported ever flushing, the questionnaire was 71.4% correct in identifying ALDH2*1/2*2 and 87.9% correct in identifying ALDH2*1/2*1. **CONCLUSION:** Japanese alcoholics can be divided into cancer susceptibility groups on the basis of their combined ADH2 and ALDH2 genotypes. The flushing questionnaire can predict high risk ALDH2*1/2*2 fairly accurately in persons with ADH2*2 allele, but a reliable screening procedure for the highest risk gene combination (ADH2*1/2*1 and ALDH2*1/2*2) will require further investigation.

Zavras, A. I., et al. (2002). "Interaction between a single nucleotide polymorphism in the alcohol dehydrogenase 3 gene, alcohol consumption and oral cancer risk." *Int J Cancer* **97**(4): 526-530.

We investigated effects on oral cancer (OC) risk of an interaction between a single nucleotide polymorphism (SNP) in the alcohol dehydrogenase 3 (ADH3) gene and alcohol consumption levels using a hospital-based study of 93 cases and 99 controls conducted in Athens, Greece. This SNP affects ethanol metabolism in vitro and appeared to interact with alcohol consumption in a previous OC study. We also evaluated a SNP in CYP2E1, another gene involved in ethanol metabolism, reported to be associated with OC risk in a European population. Data on genotypes and risk factors obtained from interviews were analyzed using multivariate logistic regression, accounting for potential confounders. No overall (marginal) association was found between OC risk and ADH3 genotypes. An interaction between ADH3 genotypes and alcohol consumption levels, however, was suggested. In non-drinkers, the ADH3(1-1) genotype has higher risk than ADH3(1-2) or ADH3(2-2) genotypes, but for subjects consuming alcohol, lower risk was observed for ADH3. We fit a logistic regression model to estimate the increase in OC risk associated with each alcohol drink consumed per week. We estimated that OC risk increased by 31.5% per drink/week for the ADH3(2-2) genotype, 4.1% for the

ADH3(1-2) genotype and 1.6% for the ADH3(1-1) genotype. Evidence of genotype-environment interaction was suggestive ($p = 0.048$, Wald chi $p = 0.145$, likelihood ratio). This finding is opposite to that reported for a population in Puerto Rico, where the ADH3(1-1) genotype seemed more sensitive to ethanol exposure. In Greece, genetic variation at the CYP2E1 SNP is almost entirely absent, with only 1 case and 1 control heterozygous for the variant. By contrast, in a population in France where an OC association was reported, the frequency of CYP2E1 heterozygotes was 5% in controls and 9% in OC cases. These findings illustrate the importance of replicating SNP associations both within and between different racial and ethnic groups and geographic regions.

Zhang, L., et al. (2014). "Gene-environment interactions on the risk of esophageal cancer among Asian populations with the G48A polymorphism in the alcohol dehydrogenase-2 gene: a meta-analysis." *Tumour Biol* **35**(5): 4705-4717.

The aim of this study is to investigate the gene-environment interactions between the G48A polymorphism in the alcohol dehydrogenase-2 (ADH2) gene and environmental factors in determining the risk of esophageal cancer (EC). A literature search was conducted in the PubMed, Embase, Web of Science, Cochrane Library, and Google Scholar databases to identify eligible studies published before November 1, 2013. We performed a meta-analysis of 18 case-control studies with a total of 8,906 EC patients and 13,712 controls. The overall analysis suggested that individuals with the GG genotype were associated with a 2.77-fold increased risk of EC, compared with carriers of the GA and AA genotypes. In a stratified analysis by ethnic group, Japanese, Mainland Chinese, and Taiwan Chinese with the GG genotype had a significantly higher risk of EC, compared with Thai and Iranian populations, indicating ethnic variance in EC susceptibility. An analysis of combined effect indicated that GG genotype of ADH2 G48A was associated with the highest risk of EC in heavy drinkers and smokers. A striking difference was found to exist between males and females, showing gender variance for the association between ADH2 G48A and EC risk. This meta-analysis shows that the GG genotype of ADH2 G48A may be associated with an increased risk of EC in Asian populations. In addition, significant gene-environment interactions were found. Heavy drinkers, smokers, and males with the GG genotype may have a higher EC risk. Thus, our results shed new light on the complex gene-environment interactions that exist between environmental factors and ADH2 G48A polymorphism in EC risk.

Zhao, H., et al. (2013). "[Role of alcohol-metabolizing enzymes gene polymorphisms and environmental exposure on colorectal cancer: a case-only study]." *Zhonghua Liu Xing Bing Xue Za Zhi* **34**(10): 1013-1017.

OBJECTIVE: This study was designed to explore the interactions of alcohol dehydrogenase 1B (ADH1B) rs1229984, aldehyde dehydrogenase 2 (ALDH2) (rs671) and cytochrome P4502E1(CYP2E1)rs1329149 with environmental factors and the interactions between genetic factors in the susceptibility of colorectal cancer (CRC). Roles of genetic factors in the development of colorectal cancer were also studied. **METHODS:** With a case-only study design, 472 colorectal cancer cases were enrolled between 2007 and 2009 in this study. Data on demographic characteristics, histories of environmental exposure and clinico-pathological parameters were obtained from all the participants through written questionnaires. Genotypes were determined by Sequenom MassARRAY system. Unconditional logistic regression analysis was employed to explore the gene-environment interactions and gene-gene interactions. chi (2) test and unconditional logistic regression were used to evaluate the roles of polymorphisms on the risk of metastasis to CRC. **RESULTS:** Overweighted individuals that carrying at least one of the ADH1B rs1229984 G alleles presented significant increase on the risk to colorectal cancer (OR = 1.720, 95%CI:1.038-2.848,ORadj = 1.785, 95%CI:1.061-3.002). Modest interaction was seen between smoking and ADH1B (rs1229984) only before the adjustment of data, by sex, age and drinking status (OR = 0.597, 95% CI:0.387-0.921, ORadj = 0.922, 95%CI:0.509-1.669). Correlations between polymorphisms and the Dukes stage were not found. **CONCLUSION:** Overweight presented significant interaction with G allele of ADH1B rs1229984 in the susceptibility of CRC. None of the rs1229984, rs671 and rs1329149 exhibited significant influence on the development of CRC.

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