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Chapter

Genetic Polymorphism and Alcohol Metabolism

Subodh Kumar Jain, Sapna Sedha and Meeta Mishra

Abstract

Throughout the world, human population experiment with alcohol, result into short- and long-term consequences including increased risk of accidental injuries, risky sexual behavior and lower education attainment. Due to polymorphism in the gene whose product enzymes are responsible for alcohol metabolism, serious health consequences including liver cirrhosis and hepatocarcinoma can occur. Enzyme alcohol dehydrogenase, CYP450 and catalase are alcohol metabolizing enzymes. Polymorphism in any one or all of the enzymes will result in defective alcohol metabolism and acetaldehyde accumulation cause serious health problems. This article mainly focuses on the consequences of alcohol consumption at genetic level that ultimately affect alcohol metabolism resulting in various health disorders.

Keywords: alcohol, alcohol dehydrogenase, cytochrome P450, catalase

1. Introduction

Alcohol abuse and alcoholism represent substantial problems that affect a large portion of individuals throughout the world. More than 200 disease and injury conditions are caused by alcohol consumption due to liver cirrhosis, cancer and various injuries [1]. According to Organization for Economic Cooperation and Development (OECD) report released in May 2015, alcoholism has been increased by about 55% between 1992 and 2012. It is a quickly rising concern among the youth of the country. According to WHO [2], alcohol per capita consumption increased in China and India (China: 4.1, 7.1 and 7.2 liters in 2005, 2010 and 2016 respectively; India: 2.4, 4.3 and 5.7 liters in 2005, 2010 and 2016 respectively). By 2025, the highest increase in per capita alcohol consumption is expected in India and China covering largest population of South-East Asia and Western Pacific region. **Table 1** indicates Indian scenario of alcohol consumption.

Approximately 80% of the college students consume alcohol which can have short- and long-term consequences including increased risk of accidental injury, risky sexual behavior, and lower education attainment. Alcohol use stimulates the Hypothalamic-Pituitary-Adrenal (HPA) axis and causes stress-like cortisol responses [3, 4]. Frequent stimulation of the HPA by alcohol may alter the function of the system, setting the stage for reduced activity to stressors and increased likelihood of alcohol use disorder. Moreover, abnormal stress physiology is related to greater addiction severity, cravings, and poor treatment outcome alcohol use disorder [5]. More than 90% of people who drink heavily develop fatty liver, a type of liver disease. Yet only 20% will go on to develop the more severe alcoholic liver disease and liver cirrhosis [6]. Environmental factors and genetic differences in the

State/UT	Toddy and country liquor (ml)	Beer, imported alcohol, wine (ml)	State/UT	Toddy and country liquor (ml)	Beer, imported alcohol, wine (ml)
Andaman and Nicobar Island	656	532	Lakshadweep	0	0
Andhra Pradesh	561	104	Madhya Pradesh	133	12
Arunachal Pradesh	749	346	Maharashtra	65	19
Assam	304	19	Manipur	155	6
Bihar	266	17	Meghalaya	74	49
Chandigarh	37	42	Mizoram	29	2
Chhattisgarh	120	27	Nagaland	159	23
Dadra and Nagar Haveli	2533	498	Orissa	146	20
Daman and Diu	252	1079	Pondicherry	154	144
Delhi	55	86	Punjab	141	50
Goa	47	108	Rajasthan	80	43
Gujarat	53	3	Sikkim	41	307
Haryana	89	43	Tamil Nadu	20	85
Himachal Pradesh	149	73	Tripura	163	2
Jammu and Kashmir	32	7	Uttar Pradesh	34	5
Jharkhand	320	14	Uttarakhand	38	43
Karnataka	23	102	West Bengal	74	12
Kerala	94	102			

Table 1.
State-wise alcohol consumption per capita per week in India [7].

way alcohol is metabolized, also contribute to the development of alcoholic pancreatitis [8]. Genetic factors, for example, variation in enzyme activity that metabolize alcohol and environmental factors, for example, quantity of alcohol and overall nutrition a person consume play an important role in the etiology of alcoholic liver disorders including liver cancer. It has been reported that in the population of Central India who consume alcohol are at risk for liver disorders due to ALDH2, GSTM1 and GSTT1 gene polymorphism [9, 10].

This article mainly focuses on the consequences of alcohol consumption at genetic level that ultimately affect alcohol metabolism resulting in various health disorders.

2. Alcohol types and components

There are two categories of alcoholic beverages, fermented (beer and wine) and distilled (whiskey, rum, gin, vodka etc.) and the concentration of ethanol differs across preparation. Yeast fermented alcoholic drinks generally contain less concentration of alcohol since yeast stops growing at about 15% ethanol concentration while strong alcoholic drinks/liquors are prepared through distillation [11].

Most alcoholic beverages mainly contain ethanol and water. Some beverages like beer, wine, spirit contain volatile and non-volatile substances along with ethanol. Volatile compounds include hydrocarbons, aliphatic carbon compounds, monocarboxylic acids esters, compounds having sulfur and nitrogen, benzene etc. Dibasic carboxylic acids, tribasic carboxylic acids, coloring agents, inorganic salts polyphenols, tannic acid etc. are the non-volatile substances [12]. Contaminants and toxins found are nitrosamines, mycotoxins, ethyl carbamate, pesticides, thermal processing contaminants, benzene, and inorganic contaminants include lead, cadmium, arsenic, copper, chromium, inorganic anions, and organometals [12].

Regardless of how much a person consume, the body can only metabolize a certain amount of alcohol every hour. That amount varies widely among individuals and depending on liver size and body mass [13]. The effects of alcohol on various tissues depend on blood alcohol concentration (BAC) over time. The time of alcohol absorption, distribution, metabolism and excretion determines BAC [14]. After absorption from small intestine, alcohol reaches liver for metabolism. The rate of BAC rise depends on how quickly alcohol is emptied from the stomach and its metabolism during first pass through stomach and liver [15, 16]. BAC depends on various factors viz. the presence of food in the stomach, alcoholic beverages, the rate of alcohol drinking and genetic polymorphism of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Depending upon age, diet, alcohol consumption and smoking, the rate of alcohol elimination varies from individual to individual [17].

In the developing world, alcohol use is one of the prevalent habit and is responsible for liver cancer [18–20]. Heavy drinking along with smoking increase the risk of developing cancers [21]. Observations suggest that some people develop cancer even at moderate daily alcohol consumption indicating that alcohol metabolism is genetically determined [22]. Also, those who typically consumed more than two drinks per drinking day were at increased risk of high blood pressure, high triglycerides, increased abdominal girth, and elevated blood glucose. Further, excessive per-occasion consumption is the primary risk factor for both acute and chronic alcohol-related problems [23].

3. Alcohol metabolism

The pharmacologic and potentially pathologic effects of alcohol depend on the concentration of ethanol and its metabolites in the body, and on the duration of exposure to these substances. Alcohol is metabolized in the body by various mechanisms, that is, oxidative pathways involving alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), cytochrome P450, and catalase enzymes (which either add oxygen or remove hydrogen) and non-oxidative pathways.

4. Oxidative metabolism

Most of the alcohol that people drink is metabolized in the liver. First, alcohol is oxidized to acetaldehyde by alcohol dehydrogenase (ADH). Acetaldehyde is highly toxic to the body, even in low concentrations. In the second step, acetaldehyde is further metabolized by ALDH to acetate and eventually to acetyl CoA, which then is broken down into water and carbon dioxide for easy elimination (**Figure 1**). Thus depending on the nutritional, hormonal, energetic status, the acetyl CoA is converted to CO_2, ketone bodies, fatty acid and Cholesterol [14].

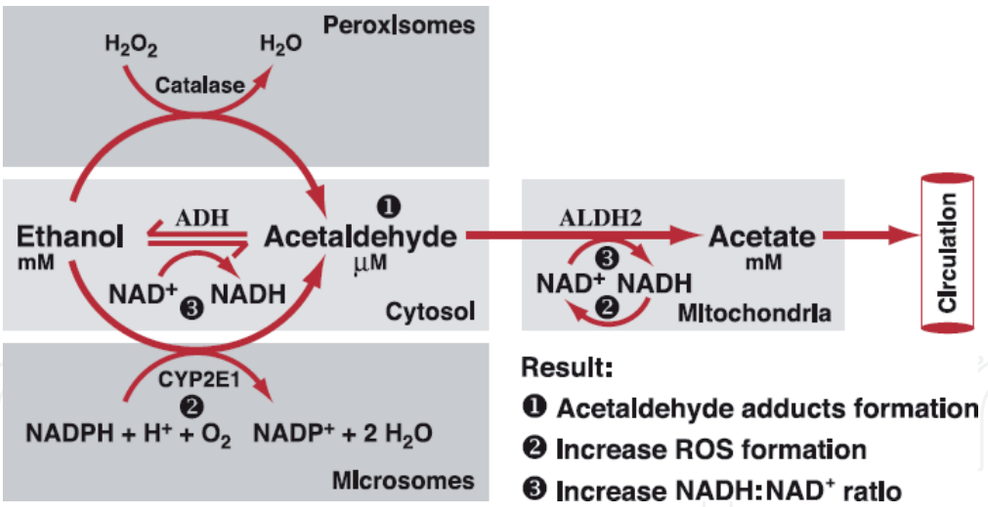

Figure 1.
Oxidative pathway of alcohol metabolism [17].

5. Byproducts of oxidative metabolism

5.1 Acetaldehyde

Acetaldehyde has the power to cause tremendous damage regardless of its short life. This is particularly evident in the liver, where major alcohol metabolism occurs [17]. Minor alcohol metabolism also takes place in the pancreas [24] and the brain, causing damage to cells and tissues [13]. Additionally, small amount of alcohol is metabolized to acetaldehyde in the gastrointestinal tract, exposing it to damaging effects [22]. The International Agency for Research on Cancer [25] asserts that acetaldehyde should be classified as a carcinogen, it promotes cancer in several ways, for example, by interfering with replication of DNA and by inhibiting a process by which the body repairs damaged DNA [22]. Studies have shown that people who are exposed to large amounts of acetaldehyde are at greater risk for developing cancer of the mouth and throat [22].

Acetaldehyde possesses the ability to bind to various proteins like enzymes, microsomal proteins and microtubules. It combines with neurotransmitter dopamine and form salsolinol that cause alcohol dependence and also form DNA adducts, for example, 1,N^2-propanodeoxyguanosine which is carcinogenic [17]. However it is also reported that acetaldehyde concentrations in the brain are not high enough to produce these effects [26]. This is because the brain has a unique blood–brain barrier, which protects it from toxic products circulating in the bloodstream. However, it is possible that due to alcohol metabolism, acetaldehyde is produced in the brain by catalase [27, 28] and CYP2E1 [29].

Acetaldehyde may also be responsible for some of the behavioral and physiological effects previously attributed to alcohol [30]. For example, when acetaldehyde is administered to lab animals, it leads to in-coordination, memory impairment and sleepiness effects often associated with alcohol [26]. Deficiency of aldehyde dehydrogenase (ALDH2) leads to accumulation of acetaldehyde which results in facial flushing or blotches associated with erythema on the face, neck, shoulders, and in some cases, the entire body [31].

5.2 Acetate

Oxidation of acetaldehyde produce acetate which is later oxidized to carbon dioxide (CO_2) in the heart, brain and skeletal muscles. Acetate is also metabolized

to acetyl CoA, which is involved in lipid and cholesterol biosynthesis in the mitochondria of peripheral and brain tissues. Acetate causes depression in the central nervous system and also affects various metabolic processes [17].

6. Non-oxidative metabolism

Ethanol is non-oxidatively metabolized by two pathways; first reaction is catalyzed by the enzyme fatty acid ethyl ester (FAEE) synthase leads to the formation of molecules known as FAEEs. In the second pathway, reaction with the enzyme phospholipase D (PLD) results in the formation of a phospholipid known as phosphatidyl ethanol [32]. This pathway is a critical component in cellular communication.

Alcohol metabolism involves both oxidative and non-oxidative inter related pathways. When ethanol oxidation is inhibited through enzyme inhibition, non-oxidative metabolism is increased along with increase in FAEEs in the liver and pancreas [33].

7. The genetics of alcohol metabolism

Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are the main enzymes of alcohol metabolism. Both the enzymes have several forms encoded by different genes. Enzymes with different characteristics having different ethnic distributions are because of variants of these genes. Since these enzyme variants work efficiently than others suggesting some people can metabolize alcohol more quickly, for example, a fast ADH enzyme or a slow ALDH enzyme may increase acetaldehyde level resulting in deleterious health effects including alcohol dependence [34].

A null allele is a mutant copy of a gene at a locus that completely lack normal function. This can result in to complete absence of the gene product (protein, RNA), or the expression of a non-functional gene product. At the phenotypic level, a null allele is indistinguishable from a deletion of the entire locus [35].

Because of genetic difference in these enzymes, alcohol related problems are either higher or lower in some ethnic groups, for example, *ADH1B*2*, a variant of ADH is common in people of China, Japan and Korea but rare in Europe and Africa [36]. Another version of the ADH enzyme *ADH1B*3*, occurs in 15–25% of African Americans [37]. These enzymes protect against alcoholism [38] by elevating the level of acetaldehyde that make drinking unpleasant [39]. Two variations of the ALDH enzyme, *ALDH1A1*2* and *ALDH1A1*3*, may be associated with alcoholism in African-American people [40].

Along with genetic factors, environmental factors are also important for alcoholism and alcohol-related health problems, for example, alcohol consumption increased from 2.5 to 13% in Japanese alcoholics who carried the protective ADH1B*2 gene [41]. There is no difference in the rate of alcohol metabolism and enzyme pattern between Native Americans and Whites, more Native American people die of alcoholism than any other ethnic group in the United States [42]. This suggests that a rate of alcoholism and alcohol-related problems depends on environmental and genetic factors.

8. Genetic polymorphism

8.1 Alcohol dehydrogenase (ADH)

The major pathway of oxidative metabolism of ethanol in the liver involves ADH present in the cytosol. During oxidation an electron carrier nicotinamide adenine

dinucleotide (NAD) is reduced to NADH providing reduced cytosolic environment in the liver cells. Because of byproduct like highly reactive and toxic free radicals and acetaldehyde, the liver cells become more vulnerable to damage [17]. Control of ADH activity is complex and involves: (a) dissociation of the product NADH which is a rate limiting step and (b) product inhibition by NADH and acetaldehyde [14].

ADH comprises of a complex family. In humans on the basis of kinetic and structural properties, enzyme ADH has been categorized into five classes. Most of them are found in liver, stomach and lungs except ADH5 found in most tissues [17]. If alcohol concentration is high, it is eliminated at a higher rate because of high activity of enzymes viz. class II ADH encoded by *ADH4* gene and β3-ADH encoded by *ADH1B*3* gene [43].

Aldehyde dehydrogenase (ALDH2) rapidly metabolizes acetaldehyde (produced by alcohol oxidation) to acetate and NADH. NADH is then oxidized through electron transport chain, or respiratory chain enzymes [17]. Among various isozymes of ALDH, only the cytosolic ALDH1 and the mitochondrial ALDH2 can metabolize acetaldehyde [44, 45].

9. Genetic Polymorphism in ADH and ALDH2

9.1 ADH

Genetic polymorphism in *ADH1B* and *ADH1C* gene locations is associated with different levels of enzyme activity [46]. In different population *ADH1B* occur at different frequencies. For example, in Caucasian and black populations it is predominant, whereas in Chinese, Japanese and in some people of Jewish ancestry *ADH1B*2* frequency is higher. In case of Caucasian populations, *ADH1C*1* and *ADH1C*2* appear with equal frequency [47]. People of Jewish descent carrying the *ADH1B*2* allele show only marginally (<15%) higher alcohol elimination rates compared to people with *ADH1B*1*. Also, African Americans [48] and native Americans with the *ADH1B*3* allele metabolize alcohol at a faster rate than those with *ADH1B*1* [49].

Variants in both ADH and ALDH2 genes can influence alcohol metabolism by either increasing turnover of ethanol to acetaldehyde or deactivating oxidization function of acetaldehyde to harmless acetic acid [34, 50]. This can result in accumulation of acetaldehyde, which is a known mutagen and carcinogen that cause DNA damage and promote esophageal squamous cell carcinoma (ESCC) development [51]. In addition, ADH and ALDH2 alleles may influence individual alcohol consumption habits and risk of alcoholism development.

Information on alcohol consumption, sex, and family history is essential in risk analyses of alcohol-related variants for several reasons. First, alcohol consumption could be a strong confounding variable and effect modifier in comparing genotypes and the risk of ESCC because genotypes and alcohol consumption are interrelated. Second, alcohol-related enzymes do not play a major role in ESCC development among alcohol nondrinkers, or females who drink lesser alcohol than males. Also the adverse role of loss-of-functional *ADH* and ALDH variants will increase in alcohol drinkers. Third, the mechanism of tumorigenesis may not be same with and without a family history of the esophageal cancer [52, 53].

9.2 ALDH

The allelic variants *ALDH2*1* and *ALDH2*2* resulted from genetic polymorphism of *ALDH2* gene is inactive showing no acetaldehyde metabolism *in vitro*.

After alcohol consumption level of acetaldehyde is high in people having heterozygous or homozygous condition for *ALDH2*2* allele [44, 45] and therefore experience negative physiological responses to alcohol.

10. Cytochrome P450

Cytochrome P450 enzymes are present in almost all tissues of the body and play important roles in hormone synthesis and breakdown including estrogen and testosterone, cholesterol synthesis and vitamin D metabolism. Cytochrome P450 enzymes also function to metabolize potentially toxic compounds, for example, drugs and bilirubin, principally in the liver [54]. The cytochrome P450 isozymes, including CYP2E1, 1A2, and 3A4 which are present predominantly in the microsomes or endoplasmic reticulum, also contribute to alcohol oxidation in the liver. However, CYP2E1 is active only after a person consume large amount of alcohol, and catalase metabolizes only a small fraction of alcohol in the body [47]. This enzyme is induced when alcohol concentration is high and it metabolizes alcohol in to acetaldehyde. It also oxidizes alcohol in tissue like brain where ADH activity is low. It produces ROS which increase the risk of tissue damage [17]. When alcohol is metabolized by CYP2E1, highly reactive oxygen containing molecules or reactive oxygen species (ROS) is produced. ROS can damage proteins and DNA or interact with other substances to create carcinogenic compounds [55].

11. Genetic polymorphism in CYP2E1

CYP2E1 enzyme is an important member of the cytochrome P450 family. It is a naturally ethanol-inducible enzyme involved in alcohol metabolism. Polymorphism in *Rsa*I/*Pst*I in the promoter gene region increases transcriptional activity of the gene which may play an important role in the development of esophageal carcinoma [56].

CYP2E1 c1/c1 genotype found at increased risk for gastric cardia cancer (GCC). Individuals with this genotype and have a history of heavy cigarette smoking were at increased risk for GCC. This suggests that the interaction of the *CYP2E1* polymorphism with smoking has a great influence on susceptibility to GCC [57]. Polymorphisms in *CYP2E1* involved in the metabolism of carcinogens tobacco and alcohol, leads to Head and Neck Squamous Cell Carcinoma (HNSCC). Haplotype analysis revealed that haplotype T-A was associated with a greater than 10-fold increase in risk for HNSCC. Use of alcohol or tobacco interact with *CYP2E1* variant genotypes or with *GSTM1* or *XRCC1 and increases the* risk of HNSCC suggest the importance of gene–gene and gene–environment interactions in the development of HNSCC [58].

There was no risk of ESCC found associated with CYP2A6, CYP2E1, GSTM1 polymorphism suggest an opposite role of GSTP1 and GSTT1 polymorphisms for ESCC [59]. Gene polymorphism in GSTM1, GSTT1, GSTP1, CYP1A1 and CYP2E1 represent risk-modifying factors for ethanol related diseases in Brazilian alcoholics and controls with similar ethnic backgrounds. Also the persons with these genotypes are genetically more prone to the development of alcoholic pancreatitis and alcoholic cirrhosis, respectively [60–63].

12. Catalase

Catalase (in peroxisomes) is capable of oxidizing ethanol *in vitro* in the presence of a hydrogen peroxide (H_2O_2) generating system, such as the enzyme complex

NADPH oxidase or the enzyme xanthine oxidase. It converts hydrogen peroxide into water and molecular oxygen. Quantitatively, however, this is considered a minor pathway of alcohol oxidation, except in the fasted state [64].

12.1 Genetic polymorphism in catalase

CAT pathway plays a prominent role in the oxidation of ethanol in the brain [17]. A common polymorphism in the promoter region of the catalase gene CAT c.-262C > T (rs1001179) influences the susceptibility to alcohol dependence and severity of alcohol dependence [65]. It was found that CAT levels were significantly higher in subjects carrying CAT -262 T allele [66, 67]. There is one study showing CAT activity and alcohol intake are interrelated [68], but the impact of this polymorphism in alcohol dependence needs to be investigated for proper conclusions [67].

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References

[1] World Health Organization (WHO). Global Status Report on Alcohol and Health. Geneva, Switzerland: World Health Organization; 2014. pp. 1-376

[2] World Health Organization (WHO). Global Status Report on Alcohol and Health. Geneva, Switzerland: World Health Organization; 2018. pp. 1-450. ISBN: 978-92-4-156563-9

[3] Gianoulakis C, Dai X, Brown T. Effect of chronic alcohol consumption on the activity of the hypothalamic-pituitary-adrenal axis and pituitary-endorphin as a function of alcohol intake, age, and gender. Alcoholism, Clinical and Experimental Research. 2003;**27**:410-423

[4] Thayer JF, Hall M, Sollers JJ III, Fischer JE. Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. International Journal of Psychophysiology. 2006;**59**:244-250

[5] Lovallo WR. Cortisol secretion patterns in addiction and addiction risk. International Journal of Psychophysiology. 2006;**59**(3):195-202

[6] McCullough AJ, O'Connor JF. Alcoholic liver disease: Proposed recommendations for the American College of Gastroenterology. American Journal of Gastroenterology. 1998;**93**(11):2022-2036. PMID: 9820369

[7] National Sample Survey Office (NSSO) 68th report on Household Consumption in India in 2011-2012. The Hindu News Report, India

[8] Ammann RW. The natural history of alcoholic chronic pancreatitis. Internal Medicine. 2001;**40**(5):368-375. PMID: 1393404

[9] Mansoori AA, Jain SK. ADH1B, ALDH2, GSTM1 and GSTT1 gene polymorphic frequencies among alcoholics and controls in the Arcadian population of Central India. The Asian Pacific Journal of Cancer Prevention. 2018;**19**(3):725-731

[10] Mansoori AA, Jain SK. Molecular links between alcohol and tobacco induced DNA damage, gene polymorphism and patho-physiological consequences: A systematic review of hepatic carcinogenesis. Asian Pacific Journal of Cancer Prevention. 2015;**16**(12):4803-4812

[11] World Health Organization (WHO). Global Status Report on Alcohol. Geneva: Department of Mental Health and Substance Abuse; 2004. ISBN: 92 4 156272 2

[12] International Agency for Research on Cancer (IARC). Alcohol consumption and ethyl carbamate. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2010;**96**:1-1428

[13] Edenberg HJ. The genetics of alcohol metabolism: Role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Research and Health. 2007;**30**(1):5-13

[14] Cederbaum AI. Alcohol metabolism. Clinics in Liver Disease. 2012;**16**(4): 667-685. DOI: 10.1016/j.cld.2012.08.002

[15] Baraona E, Abittan CS, Dohmen K, Moretti M, Pozzato G, Chayes ZW, et al. Gender differences in pharmacokinetics of alcohol. Alcoholism, Clinical and Experimental Research. 2001;**25**(4):502-507

[16] Lee SL, Wang MF, Lee AI, Yin SJ. The metabolic role of human ADH3 functioning as ethanol dehydrogenase. FEBS Letters. 2003;**544**:143-147. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&cmd=search&term=12782305. PMID: 12782305

[17] Samir Z. Overview: How is alcohol metabolized by the body? Alcohol Research and Health: The Journal of the National Institute on Alcohol Abuse and Alcoholism. 2006;**29**(4):245-254

[18] Arora D, Marya CM, Menon I. Cross sectional survey on association between alcohol, betel-nut, cigarette consumption and health promoting behavior of industrial workers in Ghaziabad. Asian Pacific Journal of Cancer Prevention. 2015;**16**:139-144

[19] Gao J, Xie L, Yang WS, Zhang W, Gao S, Wang J, et al. Risk factors of hepatocellular carcinoma—Current status and perspectives. Asian Pacific Journal of Cancer Prevention. 2012;**13**:743-752

[20] Hamed MA, Ali SA. Non-viral factors contributing to hepatocellular carcinoma. World Journal of Hepatology. 2013;**5**:311-322. PMID: 23805355

[21] Tong GX, Liang H, Chai J, Cheng J, Feng R, Chen PL, et al. Association of risk of gastric cancer and consumption of tobacco, alcohol and tea in the Chinese population. The Asian Pacific Journal of Cancer Prevention. 2014;**15**:8765-8774

[22] Seitz HK, Becker P. Alcohol metabolism and cancer risk. Alcohol Research and Health. 2007;**30**(1):38-47

[23] O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: The razor-sharp double-edged sword. Journal of the American College of Cardiology. 2007;**50**:1009-1014

[24] Vonlaufen A, Wilson JS, Pirola RC, Apte MV. Role of alcohol metabolism in chronic pancreatitis. Alcohol Research and Health. 2007;**30**(1):48-54

[25] International Agency for Research on Cancer (IARC). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. In: Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Acetaldehyde No. 77. Lyon, France: IARC; 1999. pp. 319-335

[26] Quertemont E, Didone V. Role of acetaldehyde in mediating the pharmacological and behavioral effects of alcohol. Alcohol Research and Health. 2006;**29**(4):258-265

[27] Aragon CM, Rogan F, Amit Z. Ethanol metabolism in rat brain homogenates by a catalase–H_2O_2 system. Biochemical Pharmacology. 1992;**44**: 93-98. PMID: 1632841

[28] Gill K, Menez JF, Lucas D, Deitrich RA. Enzymatic production of acetaldehyde from ethanol in rat brain tissue. Alcoholism: Clinical and Experimental Research. 1992;**16**: 910-915. PMID: 1443429

[29] Warner M, Gustafsson JA. Effect of ethanol on cytochrome P450 in the rat brain. Proceedings of the National Academy of Sciences of the United States of America. 1994;**91**:1019-1023. PMID: 8302826

[30] Deitrich R, Zimatkin S, Pronko S. Oxidation of ethanol in the brain and its consequences. Alcohol Research and Health. 2006;**29**(4):266-273

[31] Brooks PJ, Enoch MA, Goldman D, Li TK, Yokoyama A. The alcohol flushing response: An unrecognized risk factor for esophageal cancer from alcoholconsumption. PLoS Medicine. 2009;**6**(3):e50. DOI: 10.1371/journal.pmed.1000050. PMC 2659709. PMID: 19320537

[32] Laposata M. Assessment of ethanol intake current tests and new assays on the horizon. American Journal of Clinical Pathology. 1999;**112**:443-450. PMID: 10510667

[33] Werner J, Saghir M, Warshaw AL, Lewandrowski KB, Laposata M,

Iozzo RV, et al. Alcoholic pancreatitis in rats: Injury from nonoxidative metabolites of ethanol. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2002;**283**:G65-G73. PMID: 12065293

[34] Hurley TD, Edenberg HJ, Li TK. Pharmacogenomics of alcoholism. In: Lucinio J, Wong ML, editors. Pharmacogenomics: The Search for Individualized Therapies. Weinheim, Germany: Wiley-VCH; 2002. pp. 417-441

[35] Reszka E, Wasowicz W. Significance of genetic polymorphisms in glutathione S-transferase multigene family and lung cancer risk. International Journal of Occupational Medicine and Environmental Health. 2001;**14**(2):99-113

[36] Oota, H, Pakstis, AJ and Bonne-Tamir B. The evolution and population genetics of the ALDH2 locus: Random genetic drift, selection, and low levels of recombination. Annals of Human Genetics 68(Pt. 2):93-109, 2004. PMID: 15008789

[37] Bosron WF, Li TK. Catalytic properties of human liver alcohol dehydrogenase isoenzymes. Enzyme. 1987;**37**:19-28. PMID: 3569190

[38] Ehlers CL, Gilder DA, Harris L, Carr L. Association of the *ADH2*3* allele with a negative family history of alcoholism in African American young adults. Alcoholism: Clinical and Experimental Research. 2001;**25**:1773-1777. PMID: 11781511

[39] Crabb DW. Ethanol oxidizing enzymes: Roles in alcohol metabolism and alcoholic liver disease. Progress in Liver Diseases. 1995;**13**:151-172. PMID: 9224501

[40] Spence JP, Liang T, Eriksson CJ, Taylor RE, Wall TL, Ehlers CL, et al. Evaluation of aldehyde dehydrogenase 1 promoter polymorphisms identified in human populations. Alcoholism: Clinical and Experimental Research. 2003;**27**:1389-1394. PMID: 14506398

[41] Higuchi S, Matsushita S, Imazeki H, Kinoshita T, Takagi S, Kono H. Aldehyde dehydrogenase genotypes in Japanese alcoholics. Lancet. 1994;**343**:741-742. PMID: 7907720

[42] Bennion LJ, Li TK. Alcohol metabolism in American Indians and whites: Lack of racial differences in metabolic rate and liver alcohol dehydrogenase. New England Journal of Medicine. 1976;**294**:9-13. PMID: 1244489

[43] Bosron WF, Ehrig T, Li TK. Genetic factors in alcohol metabolism and alcoholism. Seminars in Liver Disease. 1993;**13**:126-135. PMID: 8337601

[44] Lu SU, Wang MF, Lin DL, Kao MH, Chen ML, Chiang CH, et al. Ethanol and acetaldehyde metabolism in Chinese with different aldehyde dehydrogenase-2 genotypes. Proceedings of the National Science Council of the Republic of China B. 1995;**19**:129-136. PMID: 7480358

[45] Wall TL, Peterson CM, Peterson KP, Johnson ML, Thomasson HR, Cole M, et al. Alcohol metabolism in Asian-American men with genetic polymorphisms of aldehyde dehydrogenase. Annals of Internal Medicine. 1997;**127**(5):376-379. PMID: 9273829

[46] Agarwal DP. Genetic polymorphisms of alcohol metabolizing enzymes. Pathologie-Biologie (Paris). 2001;**49**:703-709. PMID: 11762132

[47] Lee SL, Chau GY, Yao CT, Wu CW, Yin SJ. Functional assessment of human alcohol dehydrogenase family in ethanol metabolism: Significance of first-pass metabolism. Alcoholism: Clinical and Experimental Research. 2006;**30**:1132-1142. PMID: 16792560

[48] Thomasson HR, Beard JD, Li TK. ADH2 gene polymorphisms are determinants of alcohol pharmacokinetics. Alcoholism: Clinical and Experimental Research. 1995;**19**:1494-1499. PMID: 8749816

[49] Wall TL, Garcia-Andrade C, Thomasson HR, Cole M, Ehlers CL. Alcohol elimination in native American Mission Indians: An investigation of interindividual variation. Alcoholism: Clinical and Experimental Research. 1996;**20**:1159-1164. PMID: 8904964

[50] Birley AJ, James MR, Dickson PA, Montgomery GW, Heath AC, Martin NG, et al. ADH single nucleotide polymorphism associations with alcohol metabolism in vivo. Human Molecular Genetics. 2009;**18**:1533-1542. DOI: 10.1093/hmg/ddp060

[51] Tan SLW, Chadha S, Liu Y, Gabasova E, Perera D, Ahmed K, et al. A class of environmental and endogenous toxins induces BRCA2 haploin sufficiency and genome instability. Cell. 2017;**169**:105-118. e15

[52] Suo C, Yang Y, Ziyu Y, Tiejun Z, Yang X, Tao Q, et al. Alcohol intake interacts with functional genetic polymorphisms of aldehyde dehydrogenase (ALDH2) and alcohol dehydrogenase (ADH) to increase esophageal squamous cell cancer risk. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2019;**14**(4):712-725. ISSN: 1556-1380

[53] Chen X, Z Yuan ML, Zhang Y, Jin L, Ye W. Poor oral health is associated with an increased risk of esophageal squamous cell carcinoma—A population-based case-control study in China. International Journal of Cancer. 2017;**140**:626-635

[54] Bernhardt R. Cytochromes P450 as versatile biocatalysts. Journal of Biotechnology. 2006;**124**:128-145

[55] Seitz HK, Stickel F. Risk factors and mechanisms of hepatocarcinogenesis with special emphasis on alcohol and oxidative stress. Biological Chemistry. 2006;**387**:349-360. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=PubMed&Cmd=ShowDetailView&TermToSearch=16606331. PMID: 16606331

[56] Leng WD, Zeng XT, Chen YJ, Duan XL, Niu MY, Long RP, et al. Cytochrome P450 2E1 RsaI/PstI polymorphism and risk of esophageal cancer: A meta-analysis of 17 case-control studies. Experimental and Therapeutic Medicine. 2012;**4**:938-948

[57] Cai L, Zheng ZL, Zhang ZF. Cytochrome p450 2E1 polymorphisms and the risk of gastric cardia cancer. World Journal of Gastroenterology. 2005;**11**(12):1867-1871. PMCID: PMC4305893

[58] Ruwali M, Khan AJ, Shah PP, Singh AP, Pant MC, Parmar D. Cytochrome P450 2E1 and head and neck cancer: Interaction with genetic and environmental risk factors. Environmental and Molecular Mutagenesis. 2009;**50**(6):473-482. DOI: 10.1002/em.20488

[59] Rossini A, Rapozo DC, Soares Lima SC, Guimarães DP, Ferreira MA, Teixeira R, et al. Polymorphisms of GSTP1 and GSTT1, but not of CYP2A6, CYP2E1 or GSTM1, modify the risk for esophageal cancer in a western population. Carcinogenesis. 2007;**28**:2537-2542

[60] Burim RV, Canalle R, Martinelli Ade L, Takahashi CS. Polymorphisms in glutathione S-transferases GSTM1, GSTT1 and GSTP1 and cytochromes P450 CYP2E1 and CYP1A1 and susceptibility to cirrhosis or pancreatitis in alcoholics. Mutagenesis. 2004;**19**:291-298

[61] Lakkakula S, Maram R, Munirajan AK, Pathapati RM, Visveswara SB, Lakkakula BV.

Functional PstI/RsaI polymorphisms in the CYP2E1 gene among south Indian populations. Asian Pacific Journal of Cancer Prevention. 2013;**14**:179-182

[62] Malakar M, Devi KR, Phukan RK, Kaur T, Deka M, Puia L, et al. CYP2E1 genetic polymorphism with dietary, tobacco, alcohol habits, *H. pylori* infection status and susceptibility to stomach cancer in Mizoram, India. Asian Pacific Journal of Cancer Prevention. 2014;**15**:8815-8822

[63] Yu BW, Zhang LQ, Teng XL, Zhang Y, Zou LB, Ying HY. Association between the CYP1A1 polymorphisms and hepatocellular carcinoma: A meta-analysis. Genetics and Molecular Research. 2015;**14**:1076-1084

[64] Gropper SS, Smith JL, Groff JL. Advanced Nutrition and Human Metabolism. 5th ed. Belmont, CA: Wadsworth Publishing; 2008

[65] Plemenitas A, Kastelic M, Porcelli S, Serretti A, Makovec MR, Plesnicar BK, et al. Genetic variability in *CYP2E1* and catalase gene among currently and formerly alcohol-dependent male subjects. Alcohol and Alcoholism. 2015;**50**(2):140-145. DOI: 10.1093/alcalc/agu088

[66] Forsberg L, Lyrenas L, de Faire U, Morgenstern R. A common functional C-T substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels. Free Radical Biology and Medicine. 2001;**30**:500-505

[67] Hu X, Oroszi G, Chun J, Smith TL, Goldman D, Schuckit MA. An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. Alcoholism, Clinical and Experimental Research. 2005;**29**:8-16

[68] Koechling UM, Amit Z, Negrete JC. Family history of alcoholism and the mediation of alcohol intake by catalase: Further evidence for catalase as a marker of the propensity to ingest alcohol. Alcoholism, Clinical and Experimental Research. 1995;**19**:1096-1104