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REVIEWS

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ASSOCIATION OF *CYP2E1* GENE POLYMORPHISM WITH PREDISPOSITION TO CANCER DEVELOPMENT

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We summarize research results on association of cytochrome P450 2E1 (*CYP2E1*) genetic polymorphisms with the development of ecologically determined cancers. Cytochrome P450 monooxygenase enzyme system is involved in metabolic activation of procarcinogens, which is an important stage during normal cell transformation into a malignant one. Studies of association between *CYP2E1* gene polymorphisms and the risk of cancer development are of particular interest, since the enzyme participates in biotransformation of numerous procarcinogens. We place special emphasis on characterization of known *CYP2E1* polymorphisms and analysis of their role in pathogenesis of various cancer types. Results obtained provide evidence on association of *CYP2E1* genetic polymorphisms both with increased and decreased risk of development of malignant tumors. Ethnic and geographic peculiarities were also identified for frequencies of *CYP2E1* variants distribution.

Key Words: **cytochrome P450 2E1, gene polymorphism, genetic susceptibility.**

Due to increasing anthropogenic burdens — environmental pollution and rapid growth of cancer incidence — studies of "gene — environment" relationships are especially pressing and important. It is known, that malignant transformation of a cell is accompanied by DNA damage, appearance and accumulation of genomic mutations, in particular, deletions, insertions and point mutations. DNA damage is caused by organotropic carcinogens, which require metabolic activation to realize their carcinogenic effect.

Cytochrome P450 monooxygenase multi-enzyme system, which is mainly located in endoplasmic reticulum membranes, plays a key role in bioactivation of procarcinogens. Activated procarcinogens are involved in development of many cancer types. However, even in regions with high environmental pollution levels, malignant tumors develop only in a small portion of the population.

Therefore, it is supposed that certain genetic factors determine individual susceptibility to diseases. One of the most promising approaches to assessment of genetic and acquired human cancer susceptibility is a search for genetic markers to estimate probabilities of cancer development both for individuals and certain ethnic groups.

Investigation of association between cancer development risk and cytochrome P450 2E1 (CYP2E1) gene polymorphism is of significant interest, since this enzyme is involved in metabolism of aniline, vinyl chloride and urethane and participates in activation of N-nitrosodimethylamine, 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone and nicotine-dependent N-nitrosonornicotine [1–3]. All these compounds initiate malignancies of various localizations, including stomach, esophagus, liver, lung etc [4].

CYP2E1 catalytic activity was found to display individual differences, which can lead to increased risks of tumor development. Changes in enzymatic activity may be a consequence of genetic polymorphism or gene induction by xenobiotics. Indeed, a correlation was found between mRNA level, CYP2E1 catalytic activity and transcriptional activity of polymorphic gene variants. It is also demonstrated that CYP2E1 synthesis and catalytic activity levels are changed under exposure to environmental factors. This can result in the development of acquired susceptibility to diseases.

This review discusses the association of *CYP2E1* polymorphism with individual human susceptibility to malignancies.

Cytochrome P450 2E1 (CYP2E1) description

Human *CYP2E1* gene is located on the 10th chromosome, consists of 9 exones and 8 introns, contains a typical TATA-box and occupies 11413 b.p. of genomic DNA [5]. CYP2E1 is constituently expressed primarily in the liver [6]. CYP2E1 expression level is significantly lower in other organs and tissues, in particular, kidneys, pancreas, brain, lung, nasal and intestinal mucosa [7, 8].

Cytochrome P450 2E1 is a membrane-bound protein with molecular weight of ~ 57 kDa. It consists of 493 amino acid residues and is primarily associated with endoplasmic reticulum membranes [9]. CYP2E1 is the main enzyme component of microsomal ethanol oxidation system. It is involved in metabolism of more than 80 low-molecular hydrophobic toxicologically dangerous compounds and contributes to activation of many procarcinogens and several drugs to highly reactive metabolites [1, 8]. Specifically, CYP2E1 activates N-nitrosamines, contained in tobacco smoke and foodstuffs [1, 10], and several industrial [8] and endogenous carcinogens [4]. CYP2E1 possesses a unique ability to reduce molecular oxygen to highly reactive compounds — superoxide anion radical (O_2^-), single oxygen (O^1_2), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^-) even in the absence of substrate. Enhanced synthesis of active oxygen forms leads to intensified lipid and protein peroxidation, DNA damage and carcinogenesis [6]. Important endogenous CYP2E1 function consists in acetone transformation

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Abbreviations used: CYP2E1 – cytochrome P450 2E1; OR – odds ratio.

into gluconeogenetic precursors — acetole and hydroxyacetone [11].

CYP2E1 activity is mediated by various determinants — obesity, fasting, liver dysfunctions — and also by a number of environmental factors [2, 12, 13]. CYP2E1 expression is enhanced by different chemical compounds, in particular, acetone, ethanol, pyrazole and isoniazid [14]. For example, ethanol leads to significant (10–20 times) increase in CYP2E1 expression through higher mRNA translation rate and protein molecular stabilization [6]. CYP2E1 induction by isoniazid is also a result of activated mRNA translation, since it is fully blocked by cycloheximide and sodium fluoride [14]. On the other hand, compounds such as isothiocyanate, chlormethiazole and disulfiram suppress CYP2E1 activity [15]. Cytochrome P450 2E1 expression can be regulated on transcription, translation, mRNA stabilization and protein degradation levels [6]. Significant individual variability was found for *CYP2E1* gene expression level, protein and mRNA content [16, 17]. Increased enzyme catalytic activity is observed both *in vitro* on isolated microsomes (50 times) [18] and, to a lesser extent, *in vivo*, when chlorzoxazone — selective CYP2E1 substrate — is used [19].

Gene CYP2E1 polymorphism characteristics

Currently, more than 10 different polymorphic sites are identified, both in 5′-regulatory and in intron and transcribed *CYP2E1* gene regions. In this review, we use the nomenclature of polymorphic alleles as proposed in 2001 [20]. In 5′-flanking region in position from –2270 to –1672 b.p., a two-allele insertion was identified when using DNA restriction endonuclease XbaI. Allele containing 6 repeats with length of 42–60 b.p. is designated as *CYP2E1*1C*, and a rare allele with 8 repeats — as *CYP2E1*1D* [13, 21]. No differences were found *in vitro* in constituent expression for these two gene variants [21]. However, *CYP2E1*1D* polymorphism is supposedly associated with increased CYP2E1 metabolic activity in obese patients and chronic alcoholics. *CYP2E1*1C* frequency was 6.9 and 31% for Caucasians and Afro-Americans, correspondingly [13]. At the same time, *CYP2E1*1D* frequency in Chinese population was 23 times higher than that for Caucasians [21]. *CYP2E1* nucleotide sequence containing no mutations was designated as *CYP2E1*1A* [5].

CYP2E1 polymorphism was also identified in 5′-regulatory region with C→T replacement in position 1019 and RsaI restriction site loss (CYP2E1*5B) [22, 23]. Allele with RsaI site is defined as wild type and designated c1 and without this site — as variant or rare type and designated c2 [22]. Rare c2 allele frequency constitutes 24–30% for Asian populations [22, 24, 25], 2–3% for Caucasians [24, 26], 0.3–7% for Afro-Americans [24, 27, 28], 15% for Mexican Americans [27] and 18% for Taiwanese [29].

Variant c2 allele is expressed *in vitro* at higher rate compared to wild type, and homozygous c2/c2 genotype is associated with 10-times increase in *CYP2E1* gene transcription [23, 30, 31]. Data on association between certain allele type and mRNA and protein content are rather ambiguous. Some researchers attribute their higher level to variant gene [26, 30], while the others — to homozygous c1/c1 genotype [17, 32].

Increased expression of c2 allele *in vitro* may not reflect enzyme catalytic activity level *in vivo* [23, 30]. Thus, for patients carrying c2 allele base enzyme activity did not differ from similar parameters for individuals with c1/c1 genotype [19, 26]. However, evidence was obtained on increased catalytic activity (2 times) of the enzyme coded by variant c2 allele [26, 30]. Besides, a reverse relationship was found between high transcriptional activity of the rare c2 allele and low enzyme catalytic activity [32, 33]. Differences in enzyme activity appear to be determined not only by possession of *CYP2E1*5B* polymorphism. Functional significance of *CYP2E1*5B* polymorphism may be due to its localization in presumed binding sites for hepatic transcription factor — HNF-1 [23, 28, 30].

In Caucasians, *CYP2E1*5B* polymorphism is closely related to point mutation in position –1259 and to PstI restriction site (*CYP2E1*5A*) [22–24]. However, this replacement has significant impact neither on gene transcriptional activity nor on enzyme catalytic activity [23]. No association between two polymorphisms was identified for other ethnic groups. *CYP2E1*5A* frequency constituted 3, 15 and 24% for Caucasians, Afro-Americans and Japanese, respectively [24, 32].

Replacements of single nucleotides in gene regulatory region were also identified in positions –316 (A→G) (*CYP2E1*7C*); –297 (T→A) (*CYP2E1*7A*); –35 (G→T) (*CYP2E1*7B*). Out of these, only *CYP2E1*7B* polymorphism appears to be of functional importance and is associated with increased gene transcriptional activity [35]. Increased expression (1.8 and 2.5 times) was also demonstrated for variant gene containing two mutations –297 (T→A) and –35 (G→T), respectively, compared to wild type and a gene with one –297 (T→A) replacement only [35].

Several polymorphic sites were found in *CYP2E1* intron region. Two-allele polymorphism (CYP2E1*1B) in intron 7 –9896 (C→G) leads to TagI restriction site loss. Rare allele frequency ranged from 8 to 10% for Caucasians in North America [26, 36].

Replacement polymorphism T→A (*CYP2E1*6*) was identified in intron 6, position –7668 using DraI restrictase [34]. It has three genotypes — two homozygous designated CC and DD and one heterozygous — CD [37, 38]. Considering chlorzoxazone hydroxylation rate, CYP2E1*6 does not influence the enzyme expression and catalytic activity [34]. On the other hand, CYP2E1*6 is supposedly associated with altered CYP2E1 catalytic activity, but does not impact gene transcription [37]. Rare C allele frequency for Afro-Americans, Caucasians, Taiwanese and Japanese was 8, 11, 24 and 31%, correspondingly [17, 26, 38].

Mutations in gene coding region lead to corresponding amino acid replacements, which can result in protein structure modification and, finally, in the changes of its catalytic activity. Polymorphism –1168

(G→A) corresponding to amino acid replacement in position –76 (Arg→His) (*CYP2E1*2*) was found in nucleotide sequence of the second *CYP2E1* exon [11]. Polymorphic gene in expression system differs from the normal gene by lower enzyme synthesis (63%) and catalytic activity (64%) [11]. *CYP2E1*2* polymorphism was identified only in Chinese populations. *CYP2E1* second exon also contains a polymorphism with amino acid residue replacement in position –72 (Val→Leu), which occurs at low frequency among Japanese (2.6%) [39]. Point mutation in exon 4 (*CYP2E1*4*) results in nucleotide replacement G→A, amino acid residues –179 (Val→Ile) and can be identified by Tail restriction site in position –4804. *CYP2E1*4* frequency was 13%, and its characteristic feature is an absence of homozygous genotype for variant allele [35]. Two variant alleles were found in exon 8 in positions –10157 (C→T) [35] and –10059 (G→A) with a replacement –389 (Val→Ile) (*CYP2E1*3*) [11].

Thus, polymorphisms identified in gene coding region, except for *CYP2E1*2*, do not lead to changes in gene expression, enzyme synthesis and catalytic activity. Currently there is no convincing evidence on correlation between *CYP2E1* gene polymorphism and catalytic activity of cytochrome P450 2E1.

Association of CYP2E1 gene polymorphism with initiation and development of malignancies

This section discusses evidence on possible correlation between CYP2E1 polymorphism and development of environmentally determined cancers. According to epidemiological studies, 90% of cancers are associated with impact of environmental factors, including nitrosamines, which are acquired through tobacco smoke, vehicle exhaustions and foodstuffs [40–42].

Both inherited and acquired susceptibility play an important role in cancer initiation, which appear to be associated with changes in CYP2E1 activity. Under high intake of nitrosamines by humans, rate of variant gene expression rises substantially. This results in enhanced procarcinogens transformation into carcinogens, DNA damage and transformation of normal cells into malignant.

CYP2E1 polymorphism is supposedly associated with the risk of cancer development [4, 42] and correlates with individual and ethnic susceptibility to malignancies [43], i.e. availability of gene polymorphisms can be a genetic marker of cancer development probability.

Odds ratio (OR) is used to assess the association between genotype and susceptibility to cancer development [44]. OR represents probabilities of pathologic developments in individuals with certain genotypes.

Currently, the association between development of various cancers and *CYP2E1*6* and *CYP2E1*5B* polymorphisms is the best studied one.

Cytochrome P450 2E1 polymorphism can be an important link in multi-factor pathogenesis of esophageal cancer and a genetic marker in determination of individual susceptibility to this malignancy [25, 45, 46]. Indeed, the increased risk of the development of esophageal cancer in Chinese population is closely associated with c1/c1 genotype (*CYP2E1*5B*). Its frequency differs significantly for healthy donors, patients with esophageal cancer and with displasia and constitutes 44, 71.3 and 70.6%, correspondingly. For individuals carrying c1/c1 genotype, probability of the development of squamous cell carcinoma of esophagus increases 3.2 times [25]. Possession of c1/c1 genotype is one of the factors contributing to increased risk of esophageal cancer in Kazakh populations in China. c1/c1 genotype distribution frequency is substantially higher (77.9%) in patients with squamous cell carcinoma of esophagus compared to healthy subjects (24%) (OR = 11.3) [47].

At the same time, for other ethnic populations (Japanese and Taiwanese) no association was found between *CYP2E1* polymorphism and the risk of squamous cell carcinoma of esophagus, although OR parameter for rare alleles exhibited a trend towards increase, particularly for smokers [42, 48]. Distribution of homozygous c1/c1 genotype in these groups did not differ for patients with esophageal cancer (59.1%) and healthy subjects (61.7%) [42]. The reason for discrepancies in the results is most probably due to c1/c1 genotype distribution frequency in healthy subjects of different ethnic groups. Indeed, the frequency of this genotype in healthy subjects was 44% in Chinese population, from 64 [49] to 74% [32] — in Japanese and from 57 [33] to 62% [48] in Taiwanese.

Evidence on protective impact of *CYP2E1* polymorphic variant in endemic regions of China is particularly interesting. There, variant genotypes c1/c2 and c2/c2 were found in 17% of patients with epithelial hyperplasia of esophagus, in 20% of patients with esophageal cancer and in 55.6% of healthy subjects. Such a distribution appears to cause a significant (5 times) decrease in the risk of squamous cell carcinoma of esophagus in the individuals carrying the variant genotype [45]. Therefore, *CYP2E1* is presumably a genetically determined factor, which is involved in the early stages of esophageal carcinogenesis.

As for *CYP2E1*6* polymorphism, no association was found between an allele distribution frequency and risk of esophageal cancer [45]. At the same time, possession of heterozygous genotype is associated with an increased risk of esophageal cancer development in South African black population (OR = 5.9) [50].

Nasopharyngeal carcinoma occurs relatively often in certain ethnic populations, particularly, among Chinese, Thai, Vietnamese and Malai. Some environmental factors, especially active and passive smoking, contribute to increased risk of nasopharyngeal carcinoma [29, 51]. Besides, a role for organic solvents metabolized by CYP2E1 should be considered in nasopharyngeal carcinoma pathogenesis.

A pronounced association between *CYP2E1*5B* polymorphism and nasopharyngeal cancer risk was demonstrated. This type of cancer occurs in Taiwanese with c2/c2 genotype 7.7 times more often (OR = 2.6).

For patients heterozygous for variant gene, the risk of nasopharyngeal cancer was comparable to normal genotype [29, 51].

High frequency of homozygous c2/c2 genotype among Chinese and Thai in Thailand also determines higher risk of nasopharyngeal carcinoma in each of these ethnic groups (OR = 2.6) [52].

Statistically significant correlation was also established for CYP2E1 polymorphisms and hepatocellular carcinoma development in Taiwanese [53]. For example, c1/c1 genotype was found in 63.3% of healthy individuals and 83.3% of patients with hepatic carcinoma. The presence of c1/c1 genotype facilitates a significant increase in hepatic carcinoma risk, especially in smokers [53]. However, consumption of fresh fish and the meals rich in proteins can have protective effects [54].

On the other hand, higher risk of hepatocellular carcinoma in Spanish population is associated with rare c2 allele with frequency of 5.5% for patients with cancer and 2.5% in healthy subjects [55]. It should be noted that in case of alcoholic liver diseases both c2 allele frequency (up to 10.8%) and hepatocellular carcinoma risk increase [55, 56]. However, no association was found in Japanese [57], Korean [58] and British [59] populations between c2 allele and susceptibility to hepatocellular carcinoma. Perhaps, this is due to the absence of chronic alcohol abusers and patients with clinically confirmed alcoholic liver diseases in the sample. It should be noted that among Korean heavy drinkers variant genotype also occurs more frequently (OR = 3.0) [58].

Association between *CYP2E1* polymorphism, environmental factors and gastric cancer development is studied mostly in the regions with high frequency of occurrence of this type of cancer. In Chinese populations, c2 allele frequency in patients with gastric cancer and healthy individuals constituted 36.3 and 24.5%, correspondingly. In 6.6% of gastric cancer patients and 1.1% of healthy subjects, homozygous c2/c2 genotype was found. Although the results obtained were not statistically significant, an increased risk of gastric cancer (OR = 7.34) is associated both with c2 allele and impact of other factors [40]. The determinant factor for gastric cancer development in Taiwanese is also high c2/c2 genotype frequency. OR in this case was 2.9 [60]. Closer association between c2 allele frequency and gastric cancer was found in the case of exposure to additional factor — smoking [61, 62]. As for the homozygous c1/c1 genotype, its frequency did not differ for patients with gastric cancer (59.2%) and healthy individuals (61.7%) [42].

Therefore, variant c2 allele (*CYP2E1*5B*) leads to increased risk of gastric cancer, and combined impact of genetic and environmental factors may determine individual and group susceptibility to the malignancy. For example, the statistically significant differences were found in c2 allele frequency for two ethnic populations — Japanese (47.5%) and Brazilians (8%) [33].

Other studies indicated the lack of association between *CYP2E1*5B* polymorphism and the risk of gastric cancer in Japanese population (OR = 1.04) [57]. For example, no statistically significant differences were found for c2 allele distribution in Japanese patients with gastric adenocarcinoma (40.8%) as compared to healthy subjects (44.3%) [63]. No association was established between c1/c2 genotype and gastric cancer risk in South-Eastern Brazil populations [64], and no differences in *CYP2E1* genotype were identified depending on tumor differentiation and impact of other risk factors [63]. However, high risk of gastric cancer development was found for alcohol abusers [65]. Therefore, the existing evidence on association between *CYP2E1* polymorphism and gastric cancer susceptibility is controversial, and molecular mechanisms, which determine individual susceptibility, remain unclear.

In industrialized nations under conditions of growing exposure to negative environmental factors lung cancer is one of the most common malignancy types. An association of *CYP2E1* polymorphic variants with possibility of lung cancer development was first studied in Japanese population [37, 66]. The results indicated a substantial correlation between *CYP2E1*6* and lung cancer susceptibility; C allele frequency in patients with lung cancer is significantly lower than in healthy subjects (OR = 11.4) [66]. However, C allele occurrence in Japanese population is 3 times higher than in other ethnic groups. It can be assumed, that due to low C allele frequency in other ethnic populations, particularly, among Europeans and Afro-Americans [67], no differences in its frequency for lung cancer patients and healthy individuals were identified [67, 68].

On the other hand, a direct correlation was found between the increased risk of lung cancer and normal DD genotype (*CYP2E1*6*), which occurs in 78.1% of American Mexicans with lung cancer and in 69.9% of healthy individuals (OR = 2.4). Smoking in this case enhances lung cancer risk in males (OR = 3.4) [69].

Several studies identified the association between c1/c1 genotype (*CYP2E1*5B*) and increased lung cancer risk [27, 43, 70]. c1/c1 genotype was found in American Mexicans (86.7%) and Afro-Americans (89.1%) with lung cancer compared to 70.6 and 86.8% of healthy donors from the respective ethnic groups. It was found that c1/c1 genotype correlates with significant (14 times) increase in the risk of lung cancer in American Mexican populations, with 9.9-fold increased risk for former smokers compared to non-smokers and 15 times higher risk for males vs. female patients [27]. This means that, unlike in Afro-Americans, an absence of c2 allele in this ethnic group is observed together with increased probability of lung cancer development.

Association between c2 allele (*CYP2E1*5B*) and lower risk of lung adenocarcinoma was found for Chinese populations [70]. Variant c2 allele frequency in patients with lung adenocarcinoma was significantly lower than in healthy individuals. Thus, a rare c2 allele

is associated with the decreased risk of lung adenocarcinoma. Similar results were obtained for Chinese and Swedish populations, where c2 allele frequency was lower in patients with lung cancer [34, 43]. Heterozygous *CYP2E1* variant gene and its frequency are associated with lower (10 times) lung cancer risk as compared to c1/c1 genotype [71]. Distribution of c2/c2 genotype was higher in Japanese patients with small-cell lung cancer (9.4%) than in healthy individuals (4.1%) and in patients with lung adenocarcinoma (2.7%) [72, 73]. Since homozygous c2/c2 genotype was not found in patients with lung cancer in Caucasian and Afro-American populations, it can be assumed that c2 allele is not associated with higher risk of lung cancer in these ethnic groups [28]. Ethnic differences in rare c2 allele distribution were also identified. Thus, c2 frequency is significantly higher in Chinese (23%) compared to Swedish (5%) and Finnish (1%) populations [34, 67]. Rare c2 allele frequency also markedly differs in Japanese (27%), Afro-American (2%) and European (2%) populations [24]. Despite the absence of significant differences in c2 allele distribution among Afro-Americans and Caucasians, OR for lung cancer was 4.28 for Caucasians and 0.2 — for Afro-Americans [24]. Therefore, ethnic variability in frequency distribution of rare alleles can determine susceptibility to lung cancer.

Alleles *CYP2E1*5B* and *CYP2E1*6* occur less frequently in Chinese patients with lung cancer (0.2 and 0.22) compared to healthy subjects (0.25 and 0.26) and appear to be not associated with susceptibility to lung cancer development [43]. Thus, it can be concluded that normal genotype is associated with increased lung cancer risk, while c2 allele appears to have protective effect. It is of particular interest that *CYP2E1*5A* polymorphism is mostly associated with lung adenocarcinoma, i.e. with development of a certain cancer type [74]. Rare *CYP2E1*5A* allele frequency in patients with lung adenocarcinoma is 13.5%, which is 3.4 times higher than in healthy subjects [74].

On the other hand, several researchers failed to identify significant differences in variant c2 allele frequency and to establish the association between lung cancer development and *CYP2E1*5B* polymorphism [24, 28], even when the impact of other factors, in particular, consumption of alcohol and tobacco, was considered [67].

Association between *CYP2E1*1B, CYP2E1*1D* and *CYP2E1*2* polymorphisms and the risk of renal/urinary tract cancer in males of the same ethnic origin was not found for patients living in regions with varying environmental pollution levels [75, 76]. However, female patients exhibited an association between renal cancer susceptibility and heterozygous *CYP2E1*1B* and *CYP2E1*1D* genotypes. One possible explanation is the lower heterozygous genotype frequency in females, than in males [75].

As for the cancers of other localizations, a correlation was found between increased colorectal cancer risk and both *CYP2E1*5B* (OR = 1.91) [77, 78] and *CYP2E1*1D* [32] polymorphisms. It should be noted that the patients consuming roasted red meat [32] and salted meal [32, 78] are more (2–3 times) susceptible to colorectal cancer.

Significant risk of oral cavity cancer is associated not only with polymorphic c1/c2 and c2/c2 genotypes in Chinese population (OR = 4.7) [49], but also with normal c1/c1 genotype in Caucasians and Afro-Americans [79] and with variant CC genotype (*CYP2E1**6) [80]. In patients with laryngeal cancer, DD (*CYP2E1*6*) and c1/c1 (*CYP2E1*5B*) genotype frequency did not differ from that in healthy subjects [81]. Substantial increase in the risk of head and neck cancer was identified in German populations for smokers with variant genotype [82]. As for the patients with pancreatic cancer and respective healthy subjects, the results were not statistically significant, and clear evidence of association between *CYP2E1* polymorphism and increased pancreatic cancer susceptibility was not obtained [83].

Thus, multiple studies were undertaken to clarify molecular mechanisms of genetically determined individual cancer susceptibility. The results obtained emphasize an important role of *CYP2E1* polymorphism in forming the susceptibility to development of various malignancies.

Steady growth in cancer incidence is largely caused by increased anthropogenic pollution of the environment. Long-term intake of toxic and carcinogenic compounds contained in tobacco smoke, alcohol and some foodstuffs contributes to development of malignancies. Cytochrome P450-dependent monooxygenase microsomal multi-enzyme system plays a leading role in metabolism of exogenous and endogenous procarcinogens. To exercise a carcinogenic impact, procarcinogens must undergo an activation. Ethanol-dependent cytochrome P450 2E1 plays an important role in biotransformation of procarcinogens. CYP2E1 participates in metabolism of many low-molecular compounds, including N-nitrosamines, which initiate malignancies of various localizations. Cytochrome P450 2E1 is involved in ethanol microsomal oxidation with synthesis of acetaldehyde. It should be noted that cytochrome CYP2E1 activity is accompanied by generation of significant amount of active oxygen forms, which damage cell membranes and macromolecules and lead to formation of DNA-adducts.

Since CYP2E1 protein coding gene is polymorphic, it could be assumed that polymorphisms can, at least partially, explain the inherited individual and group susceptibility to development of malignancies.

Single nucleotide replacements, deletions or insertions in the gene result in synthesis of enzyme with substantial variability in catalytic activity and respective changes in the rate of endo- and xenobiotics metabolism. For example, it was demonstrated that *CYP2E1*5B* polymorphism is accompanied by a significant (10-fold) increase in enzymatic activity, which leads to growth in carcinogens content in human body and to initiation of malignancies. On the contrary, low *CYP2E1* expression and activity levels

appear to contribute to decreased risk of cancer development. Several studies indicate that CYP2E1 activity significantly (2 to 40 times) differs in individuals. This probably determines individual sensitivity to carcinogenic impact and susceptibility to development of tumors.

Given the aforementioned data, study of genetic prerequisites for tumor initiation is of significant interest. Despite the ambiguity and contradictions, the results obtained provide evidence on important role that *CYP2E1* polymorphism plays in the formation of susceptibility to development of malignancies.

It was shown that normal c1/c1 genotype carriers are to the larger extent prone to development risk of cancer of oral cavity [79, 80], larynx [80], esophagus [25, 45], liver [53], lung [27, 32] and pharynx [52] compared to variant c2/c2 genotype. However, opposite results were obtained on the absence of association between c1/c1 genotype and malignancies of liver [55], lung [28, 67] and stomach [42].

On the other hand, increased development risk of gastric [40, 60], nasopharyngeal [51, 52], hepatocellular [55], lung [72] and oral cavity [49] cancer was observed for variant allele carriers. It is supposed that *CYP2E1* c2/c2 genotype may be a determinant and a genetic marker for gastric cancer [60]. At the same time, no association was found between the variant genotype and the risk of hepatocellular carcinoma [57–59], gastric [33, 42, 57, 63, 64], esophageal [42, 48], oral [81] and lung [24, 28, 34] tumors.

The evidence on the protective effect of *CYP2E1* gene variant alleles and significant reduction of cancer risk is of particular interest. Such results were obtained for lung adenocarcinoma [27, 32, 34, 70, 71], hepatocellular carcinoma [53], esophageal [45] and gastric [33] cancer. It is demonstrated that in Japanese with variant c2/c2 genotype lung cancer risk decreases significantly. However, similar results were not obtained for European patients with lung adenocarcinoma [43, 67].

It should be emphasized that the probability to develop malignancy increases substantially for carriers of certain alleles under exposure to other risk factors, in particular, smoking and alcohol abuse. For example, it is shown that development risk of lung [27], gastric [40, 61], liver [53] and nasopharyngeal [51] cancer grows significantly (10 times) in smokers. Alcohol abusers are subject to higher risk of hepatocellular carcinoma [55, 58].

Unfortunately, the number of studies devoted to the association between polymorphic genotype frequency and cancer risk in Caucasians is limited due to low occurrence of variant alleles in these populations. Large samples are required to obtain statistically significant data.

Certain ethnic and geographic peculiarities were identified in gene variant frequencies and initiation probabilities for tumors of various localizations.

Among the possible reasons for discrepancies in results are different patient sampling criteria, and insufficient sample sizes. Impact of exogenous factors, particularly, smoking, was not always considered and assessed, although several studies clearly demonstrated increased cancer risk in smoking patients with polymorphisms. Besides, analysis of association between *CYP2E1* polymorphism and cancer development did not always consider the type and stage of malignant process. Utilization of varying statistical methods for estimation of data obtained also leads to the errors in interpretation of results.

Further accumulation of statistically significant evidence on association between *CYP2E1* polymorphism, susceptibility to cancer and impact of environmental factors will allow to assess both individual and populational risks for the development of malignancies of various genesis and to develop the new approaches toward cancer diagnostics and prevention.

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АССОЦИАЦИЯ ПОЛИМОРФИЗМА ГЕНА *CYP2E1* С ПРЕДРАСПОЛОЖЕННОСТЬЮ К РАЗВИТИЮ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ

В обзоре обобщены экспериментальные данные относительно ассоциации между полиморфизмом гена цитохрома Р450 2Е1 (*CYP2E1*) и развитием экологически обусловленных форм рака. Важным этапом трансформации нормальной клетки в злокачественную является метаболическая активация проканцерогенов, происходящая при участии монооксигеназной ферментной системы цитохрома Р450. Особое внимание уделено характеристике полиморфизма гена *CYP2E1,* изучению его ассоциации с риском развития онкологических заболеваний и анализу его роли в патогенезе различных форм рака. Данные литературы свидетельствуют об ассоциации полиморфных вариантов гена *CYP2E1* как с повышенным, так и со сниженным риском развития злокачественных опухолей определенной локализации. Выявлены также некоторые этнические и географические особенности частоты распределения вариантных типов гена *CYP2E1*.

Ключевые слова: **цитохром Р450 2Е1, полиморфизм гена, генетическая предрасположенность.**