Genetic Polymorphisms and Oral Cancer

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Abstract: Oral cancer, a disease associated with major morbidity and mortality, represents a significant worldwide health problem. It is clear that the major etiological factors for oral cancer are tobacco and alcohol exposure. It has been shown that metabolic activation is associated with cancer susceptibility. Various carcinogens and carcinogenic precursors, such as benzopyrene and nitrosamine, have been identified in tobacco smoke, and those are activated or detoxified by two types of metabolic enzymes, phase I and phase II. There are some polymorphisms for these enzyme genes, the functions of which are modified by the types of polymorphisms. On the other hand, there are some genes besides these enzyme genes related to cancer susceptibility. In this review, we discuss the relationships between polymorphisms concerned with oral cancer. Although there are many reports on the polymorphisms related to oral cancer, the results of these reports are controversial. Further studies are needed to evaluate the interactions between carcinogens and the genetic polymorphisms.

Key words: oral cancer, Cytochrome P450, N-acetyltransferases, glutathione S-transferase, TP53.

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Introduction

Oral cancer, a disease associated with major morbidity and mortality, represents a significant worldwide health problem. The prevalence of oral cancer is particularly high among men, the eighth most common cancer worldwide. Incidence rates for oral cancer vary in men from 1 to 10 cases per 100,000 inhabitants in many countries. However, the incidence rates of oral/pharyngeal cancers have been reported to a lesser extent in several countries and regions such as Australia, Japan, New Zealand and the USA.

Oral mucosa is exposed to tobacco, alcohol and many other carcinogens. Epidemiological studies consistently show a strong relationship between oral cancer and use of alcohol and tobacco [1]. Other minor contributing factors include nutrition, occupation, viral infection, and poor dental hygiene [2]. Various carcinogens and carcinogenic precursors such as benzopyrene and nitrosamine have been identified in tobacco smoke, and the role of tobacco smoke in the development of oral cancer has been established [3]. The relative risk of oral cancer from cohort studies is different depending on the country and race. The range of the relative risk for oral cancer in male cigarette smokers was from 2.9 in Japan to 13 in Britain [4, 5]. Alcohol is metabolized to acetaldehyde, which is a carcinogen, and intake of alcohol is also a risk factor of oral cancer. The relative risk is different depending on the volume of drinking. The relative risk of oral cancer from drinking has ranged from 1.75 to 6.1 [4]. The combined effects of alcohol and tobacco can be multiplicative for head and neck cancer risk [3].

There are two types of metabolic activation genes and enzymes (phase I and phase II) for chemical agents like benzopyrene and nitrosamine. Cytochrome P450s (CYP) are the phase I enzymes in the activation pathway. For example, CYP1A1, one of the forms of CYP, is considered to play an important role in the activation of polyaromatic hydrocarbon compounds (PAH) such as benzo(a)pyrene (BP) [6]. Furthermore, a similar association has been observed in the null genotype of a mu-class isozyme of glutathione S-transferases (GSTMI) that is classified as a phase II enzyme, which is involved in the detoxification of reactive metabolites of BP [7]. These results suggest that genetic variation in the metabolic activation of such chemical carcinogens may help to explain the difference between individuals in susceptibility to chemical carcinogenesis. At first, we will discuss the relationship between the polymorphisms of metabolic activation genes or cancer related genes and the susceptibility of oral cancer. After that, the relationship of other genes, Aldehyde dehydrogenase (ALDH2), Tumor Protein 53 (TP53), repair gene and CyclinD1 (CCN1), to oral cancer will be discussed.

1. Cytochrome P450

Cytochrome P450s (CYP) are the phase I enzymes in the activation pathway. More than 30 families of CYPs have been discovered in humans, and common CYP families (CYP1A1, CYP1A2, CYP2A6, CYP2C19, CYP2D6, and CYP2D6) have been well studied. CYP1A1, one of the well investigated forms of CYP, is considered to play an important role in the activation of polyaromatic hydrocarbon compounds (PAH) such as benzo(a)pyrene [3]. CYP1A1 metabolizes
benzo(a)pyrene in tobacco smoke to a major carcinogen, 7β, 8α-dihydroxy-9α, 10α-oxy-7, 8, 9, 10-tetrahydrobenzo(a)pyrene. There are two polymorphisms in \textit{CYP1A1}. The \textit{CYP1A1 Ile462Val} polymorphism is a result of A (\textit{CYP1A1*1A}) to G (\textit{CYP1A1*2C}) substitution in exon7, causing an amino acid change in the heme-binding region [8]. It has been reported that the \textit{Val/Val} genotype resulted in reduced catalytic enzyme activity. The other \textit{CYP1A1} polymorphism (\textit{MspI} polymorphism) is a T (\textit{CYP1A1*1A}) to C (\textit{CYP1A1*2A}) transition 1197 bp downstream of exon 7 [9].

It has also been reported that the \textit{MspI} polymorphism of \textit{CYP1A1} was associated with PAH-DNA adduct level [10] and the frequency of \textit{TP53} gene mutations [11]. These data suggest that a larger amount of reactive metabolites of carcinogens is produced in individuals with the susceptible genotype than in those with other genotypes. A number of reports suggested that the \textit{MspI} polymorphism of the \textit{CYP1A1} gene is associated with lung [11] and esophageal cancers [12].

Regarding the role of this polymorphism in oral cancer, Tanimoto \textit{et al.} [13] reported that the \textit{MspI} polymorphism of the \textit{CYP1A1} gene was a risk factor. A meta-analysis and pooled analysis showed a significant association with a nearly two fold increased risk between oral and pharyngeal cancer and the \textit{CYP1A1 MspI} homozygous variant [14].

Recently, another polymorphism of \textit{CYP1A1} gene, the isoleucine-valine (\textit{Ile-Val}) polymorphism, has been reported as a risk factor for tobacco related diseases such as lung and oral cancers [15, 16]. No difference was detected in the \textit{Ile-Val} polymorphism in exon 7 or the \textit{MspI} polymorphism of \textit{CYP1A1} between healthy controls and patients with malignant head and neck lesions [17]. However, a study in Japan found a correlation between the \textit{Val/Val} genotype and increased risk of squamous cell carcinoma of the head and neck [18]. These discrepancies may reflect ethnic differences in the patterns of \textit{CYP1A1} polymorphism. Concerning other polymorphisms of \textit{CYP}, it was reported that the \textit{CYP2E1 Rsal/PstI c1/c1} and c2/c2 genotypes were associated with a significantly increased oral cancer risk [19], but there are few reports about \textit{CYP2E1}. Additional studies will be needed for evaluation.

2. N-acetyltransferases

The major procarcinogens present in tobacco smoke are polycyclic aromatic hydrocarbon, aryl- and heterocyclic amines, and nitroso-compound. N-acetyltransferases (\textit{NAT}) is a phase II enzyme. \textit{NAT1} and \textit{NAT2} catalyze the N-, O-, or N, O-acetylation of the aryl- and heterocyclic amines. \textit{NAT1} is expressed in all tissues, and \textit{NAT2} is expressed mainly in the liver and in the bladder. Polymorphisms in the \textit{NAT1} and \textit{NAT2} genes are due to specific point mutations that result in a phenotypic variation. At least 15 \textit{NAT1} alleles have been identified in humans. The \textit{NAT1*4} allele was classified as the wild-type. \textit{NAT1*14} and *17 alleles reduced acetylation capacity [20], whereas the \textit{NAT1*11} allele is now agreed to have a higher acetylation capacity [21]. The prominent \textit{NAT1*10} allele contains two single-base mutations in the polyadenylation signal sequence, which probably results in elevated enzyme activity [22]. On the other hand, allelic variants of the \textit{NAT2} gene, which are determined by a pattern of polymorphisms, result in slow (SA), intermediate (IA) or rapid acetylator (RA) phenotypes and cause individual
differences in NAT2 metabolic capacity. The NAT2*4 allele (wild-type) encodes the RA phenotype, while other alleles (NAT2*5–7 and rare alleles) encode the SA or IA phenotype [23]. The slow acetylators can be distinguished from the fast acetylators at the DNA level on the basis of restriction enzyme sites or by measuring metabolic activity [24]. It has been shown from retrospective studies that there is an increased risk of bladder cancer among NAT2 slow acetylators and there may be an increased risk of colon cancer among fast acetylators [25]. There has been conflicting data on head and neck cancer. Fronhoffs et al. [26] reported that the distribution of the NAT1 (NAT1*3, *4, *10, *11, *14 and *17) genotype was not significantly different between head and neck cancer cases and controls. Olshan et al. [27] reported that the NAT1 polymorphism (NAT1*10/ NAT1*4 and NAT1*10/ NAT1*10) was associated with a nearly 5-fold increased risk of head and neck cancer among smokers (more than 40 packs /years). Henning et al. [28] found that the distinct genotype NAT2*4/*4 proved to be a rare but powerful host risk factor for larynx carcinoma. In contrast, Morita et al. [18] did not find an increased risk in fast acetylators but did demonstrate an increased risk for squamous cell carcinoma of the head and neck (excluding pharyngeal cancers) amongst slow and intermediate acetylators in the NAT2 polymorphism.

There are not many reports for oral cancer. Katoh et al. [29] reported that the NAT1*10 polymorphism was associated with the occurrence of oral squamous cell carcinoma in a Japanese population, independent from smoking behavior. Chen et al. [30] reported the absence of an overall association between the acetylator status of NAT2 and oral cancer.

3. Glutathione S-transferases

Glutathione S-transferases (GSTs) are a very important family of enzymes that catalyze the detoxification of a wide variety of active metabolites of tobacco carcinogens such as benzo(a) pyrene and other polycyclic aromatic hydrocarbons and monohalomethanes. Therefore, variations in the expression of GSTs due to genetic polymorphism probably modulate the processing of tobacco-derived carcinogens. Several polymorphisms of GSTs have been reported. Typical polymorphisms of GSTs are GSTM1, GSTT1, GSTP1 and GSTM3. GSTM1, GSTT1 and GSTP1 have been evaluated frequently. A number of different groups have shown that the GSTM1 null genotype is associated with an increased risk of lung cancer, bladder cancer, skin cancer, colon and mesothelium cancers [31–33]. Inheritance of the GSTT1 null genotype was also found to be associated with several types of carcinoma [34, 35].

The relationship between the risk of squamous cell carcinoma of the head and neck and GSTM1 and the GSTT1 null genotype has been assessed in several studies [34, 36]. These studies suggested that the null phenotype of either enzyme had a slightly increased risk of squamous cell carcinoma of the head and neck. In the meta-analysis, the summary odds ratios (ORs) for head and neck cancer were 1.23 for the GSTM1 null genotype and 1.17 for the GSTT1 null genotype [14]. For only oral cancer, Sreelekha et al. [37] showed that the null genotype of GSTM1 and GSTT1 was associated with an increased risk of oral cancer. Sato et al. [38] reported that the GSTM1 null genotype was one important factor that contributed to the
increased risk of oral cancer at low levels of cigarette exposure. For oral cancer of the floor of the mouth, Drummond SN et al. [39, 40] reported that the prevalence of the GSTM1 and GSTT1 null genotype was significantly higher for patients. In contrast, Geisler SA et al. [41] report that individuals with the GSTT1 functional genotype were twice as likely to die from any cause and were three times as likely to die from squamous cell carcinoma. On the other hand, it was suggested that the GSTT1 null genotype emerged as a protective factor against oral precancerous lesion and oral cancer [42]. A conclusion hasn’t been reached yet.

GSTP1 has variant alleles containing a point mutation at codon 105 and at codon114. These alleles indicate to increase or decrease enzyme activity depending on the substrate [43]. The wild genotype of codon 105 has been shown to increase the risk for laryngeal and esophageal cancer [18, 44], but the mutant genotype has been also reported to be associated with a high risk of bladder, testicular, prostate, and lung cancer [45, 46]. There were only a few reports on oral cancer and GSTP1. Park et al. [47] reported that the GSTP1 genotypes of codon 105 and 114 could be a risk factor for oral cancer, particularly among light smokers. Katoh et al. [48] also reported that the GSTP1 polymorphism at nucleotide 313 might be associated with susceptibility to oral squamous cell carcinoma in the Japanese population.

4. Aldehyde dehydrogenase

The incidence of various types of oral cancer (floor of mouth, tongue, and lower gingival) is significantly higher among alcoholics. It has been suggested that the direct carcinogenic effects of alcohol are likely to be responsible for the development of these types of oral cancer [49]. As far as the carcinogenic mechanism of alcohol-related cancer is concerned, Ristow et al. [50] reported that acetaldehyde might be a key component. There are other studies that suggested a direct mutagenic and carcinogenic effect of acetaldehyde [51, 52].

Aldehyde dehydrogenase (ALDH) is the major metabolic enzyme of acetaldehyde that is derived from alcohol in the body. Ethanol is oxidized to acetaldehyde and then to acetate. A single nucleotide polymorphism in the ALDH2 gene codes lysine (ALDH2*2) instead of glutamine (ALDH2*1) at residue 487. That polymorphism is characterized by a reduced ability to metabolize acetaldehyde. The mutant allele in the ALDH2 is prevalent in Asians, but has not been found in Caucasians or African-Americans [53]. Individuals with heterozygotes and homozygotes for the ALDH2*2 allele show respectively peak blood acetaldehyde concentrations after alcohol consumption 6 and 19 fold higher than those homozygous for the ALDH2*1 [54]. Individuals with homozygotes for the ALDH2*2 genotype were found to have a lower risk of liver cirrhosis or esophageal cancer [55], because the ALDH2*2 inhibits them from heavy drinking and the development of alcoholism by acetaldehydemia and alcohol flushing responses. Yokoyama et al.[56] reported that ALDH2 encoded by the gene ALDH2*1/*2 was a risk factor for esophageal and oropharyngolaryngeal cancer. Hashimoto T et al. [57] reported that persons with ALDH2*1/*2 had a significantly increased risk of squamous cell carcinoma of the head and neck, but available studies regarding the role of ALDH2 in oral cancer are limited. Katoh [58] reported that there was no significant difference between controls and patients with oral
cavity cancer in the ALDH2 polymorphism. In contrast, Nomura [59] reported that ALDH2 polymorphism was a risk factor for oral cancer. Asakage T et al. [60] also reported that the risk of hypopharyngeal cancer was significantly increased by ALDH2*1/2*2 in moderate-to-heavy drinkers, but oral cancer was not significantly affected by the ALDH2 genotype.

The metabolic reactions in alcohol consumption are also mediated by alcohol dehydrogenase (ADH). There are at least seven alcohol dehydrogenases (ADH1 to ADH7) present in humans. The ADH1 comprises ADH1A, ADH1B and ADH1C (formerly called ADH1, ADH2 and ADH3), which are very closely related to each other. Among these, the ADH1C gene displays functional polymorphisms that appear to have an impact on ethanol metabolism and susceptibility to alcoholism. ADH1C*2 is a low activity allele which reduces the rate of oxidation of ethanol to acetaldehyde by 2.5-fold, and that frequency varies from 0.12 to 0.39, depending on ethnicity. ADH1C*1, a fully functional allele, is considered as a protective factor in the risk of alcoholism [61]. However, ADH1C*1 has also been suggested as a risk factor in alcohol-related cancers. Rapid oxidation of ethanol would result in higher tissue levels of acetaldehyde, a putative carcinogen.

A study of oral cancer in Puerto Rico reported that the ADH1C*1/*1 genotype was a risk factor of oral cancer [62], but Schwartz et al. [63] and Solomon PR et al. [64] indicated that the ADH1C*2 genotype was a oral cancer risk. Other reports didn’t indicate that the ADH1C polymorphism was a risk factor of oral cancer [60]. Further studies will be needed to evaluate the relationship between ADH polymorphism and oral cancer risk.

5. TP53 tumor suppressor gene

The Tumor Protein 53 (TP53) is a representative tumor suppressor gene. The mutation of the TP53 gene can interfere with its DNA-binding properties and transcription function, and dis regulate cell cycle control and cell proliferation [65]. To date, it has been found that the codon 72 polymorphism on the 4th exon of the TP53 gene produces variant proteins with an arginine or proline. The frequency of the TP53 codon 72 polymorphism varies, depending on ethnicity. It has been reported that there is a significant decrease in the frequency of the Proline allele with increased latitude, ranging from 50% in African-Americans to 29% in Caucasians [66]. Japanese studies showed the frequency of the Proline allele ranging from 35% to 40% [67, 68].

The association of the TP53 codon 72 variant alleles with some cancers (e.g., lung cancer, cervical cancer) has been inconsistent. The Proline/Proline genotype was associated with an increased risk of lung cancer in Taiwanese and Japanese [68, 69] but not in Caucasian and African-American populations [66]. An increased risk of human papilloma virus (HPV)-related cervical cancer in individuals with homozygous arginine alleles at codon 72 of TP53 has been reported [70].

A positive association between the Proline allele and oral cancer has not been proven. Tandle et al. [71] reported a lack of association between the TP53 codon 72 polymorphism and oral cancer risk, as well as in a Brazilian and Southern Thai population. However, these studies did not use smoking to subclassify patients to analyze the relationship between the TP53
polymorphism and cancer risk. We analyzed the association between the TP53 genotypes and oral cancer risk in combination with smoking status. Our data indicated that the prevalence of oral cancer in both the Arginine/Proline genotype and the combination of Arginine/Proline and Proline/Proline genotypes in non-smokers was significantly higher than in controls [72]. Our results suggested that any Proline allele was associated with an increased risk of oral cancer in non-smokers.

6. DNA repair genes

DNA repair enzymes have been reported to play an important role in the carcinogenesis of several cancers. DNA repair enzymes are involved in repairing damaged DNA, and at least three pathways operate on specific types of DNA damage: 1) Base excision repair (BER), 2) Nucleotide excision repair (NER), and 3) mismatch repair (MMR). Enzymes in the BER include Xray repair cross complementing Protein1 (XRCC1) [73], and those involved in NER include Xeroderma Pigmentosum group C (XPC) and Xeroderma Pigmentosum group D (XPD) [74]. The XRCC1, one of the BER genes for oxidative damage, is a multi-domain protein that interacts with at least three other proteins (poly-ADP-ribose polymerase, DNA ligase III, and DNA polymerase β) to repair single-strand breaks in DNA[75]. The mechanistic basis for the present finding remains somewhat unclear. However, functional studies have suggested that the XRCC1 Arg399Gln allele, one of the three polymorphisms (codon 194, codon 280 and codon 399), is associated with an increased level of DNA damage, possibly due to reduced DNA repair function [76]. In a study that examined the relationship between the genetic polymorphisms of XRCC1 and risk for breast cancer [77], a significant association was observed between the 399Gln allele and breast cancer risk among white females. Other studies about the relationship between polymorphism at codon Arg399Gln and several cancer susceptibilities were held epidemiologically, but those results have given inconsistent results.

In relation to oral cancer, a lack of XRCC1 (codon194 T allele) was a significant risk factor for cancer of the oral cavity and pharynx, and lack of XRCC1 (codon399Arg allele) was also a risk factor for oral and pharyngeal cancer in smokers or drinkers [78, 79]. Betel quid chewers with the variant allele of XRCC1 (codon399Arg allele) also exhibited increased risk of oral cancer. However, there are some reports that the 399Gln gene could decrease the risk of oral cancer [27, 80]. The results about the polymorphism of XRCC1 and oral cancer are controversial.

The relationship between other repair genes (XRCC3 XPC XPD) polymorphisms and several cancer risks are also controversial, but there were no reports on oral cancer, so we couldn’t evaluate XRCC3 XPC XPD. We have to wait for the publication of new reports on those genes to investigate the interaction between those genes and oral cancer risk. It is difficult to do that, because oral cancer is rarer than lung and gastric cancer.

7. Cyclin D1

Normal cell cycle control ensures a resting period during the cell cycle, allowing DNA damage
<table>
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<tr>
<th>Gene and polymorphic site</th>
<th>Authors</th>
<th>Population</th>
<th>Number of Cases</th>
<th>Number of Controls</th>
<th>Result-1</th>
<th>OR (95% CI)</th>
<th>Result-2</th>
<th>OR (95% CI)</th>
<th>Result-3</th>
<th>OR (95% CI)</th>
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<td>100</td>
<td>100</td>
<td>Ile/Ile vs. Ile/Val</td>
<td>3.4 (1.8 - 6.4)</td>
<td>Ile/Ile vs. Val/Val</td>
<td>3.6 (1.4 - 9.5)</td>
<td>Ile/Ile vs. Ile/Val</td>
<td>3.5 (1.9 - 6.2)</td>
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<td>Ile/Ile vs. Val/Val</td>
<td>2.4 (0.9 - 6.4)</td>
<td>Ile/Ile vs. Ile/Val</td>
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<td>Taiwanese</td>
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<td>c1/c1 vs. c1/c2+c2/c2</td>
<td>4.7 (1.1 - 20.2)</td>
<td>Rapid vs. intermediate</td>
<td>1.1 (0.6 - 2.0)</td>
<td>Rapid vs. Slow</td>
<td>1.2 (0.7 - 2.2)</td>
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<td>3.7 (1.41 - 9.75)</td>
<td>NAT1*4/*4 vs. *10/*10</td>
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<td>Rapid vs. intermediate</td>
<td>1.1 (0.6 - 2.0)</td>
<td>Rapid vs. Slow</td>
<td>1.2 (0.7 - 2.2)</td>
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<td>60</td>
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<td>1/1 vs. 2/2</td>
<td>0.35 (0.57 - 2.17)</td>
<td>1/1 vs. 2 allele</td>
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<td>Indian</td>
<td>72</td>
<td>153</td>
<td>Pro/Pro vs. Pro/Arg vs. Arg/Arg</td>
<td>No association (0.3 &lt; P &lt; 0.5)</td>
<td>71</td>
<td></td>
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<td></td>
<td>Kuroda et al</td>
<td>Japanese</td>
<td>34</td>
<td>111</td>
<td>Arg/Arg vs. Pro/Arg in non-smoker</td>
<td>2.70 (1.07 - 6.82)</td>
<td>72</td>
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<td></td>
<td>Arg/Arg vs. Pro/Pro in non-smoker</td>
<td>2.48 (0.72 - 8.57)</td>
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<td></td>
<td>XRCC1</td>
<td>American</td>
<td>180</td>
<td>363</td>
<td>TT+CT vs. CC</td>
<td>2.46 (1.22 - 4.97)</td>
<td>78</td>
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<td></td>
<td>Sturgis et al</td>
<td>American</td>
<td>147</td>
<td>168</td>
<td>CC vs. CT</td>
<td>2.46 (1.41 - 4.29)</td>
<td>79</td>
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<td></td>
<td>Tao et al</td>
<td>Korean</td>
<td>430</td>
<td>695</td>
<td>Arg/Arg vs. Arg/Gln</td>
<td>0.97 (0.73 - 1.30)</td>
<td>80</td>
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<td></td>
<td>Hunag et al</td>
<td>American</td>
<td>430</td>
<td>695</td>
<td>Arg/Arg vs. Arg/Gln</td>
<td>0.97 (0.73 - 1.30)</td>
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<td></td>
<td>Huang et al</td>
<td>American</td>
<td>174</td>
<td>155</td>
<td>GO vs. AG</td>
<td>1.91 (1.05 - 3.48)</td>
<td>88</td>
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<td></td>
<td>Holley et al</td>
<td>German</td>
<td>174</td>
<td>155</td>
<td>AA vs. AG</td>
<td>2.22 (1.06 - 4.63)</td>
<td>89</td>
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<td></td>
<td>GG vs. AA</td>
<td>2.38 (1.16 - 4.87)</td>
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<td></td>
<td>AA vs. GG</td>
<td>3.53 (1.61 - 7.72)</td>
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</table>

#: wild (105 Ile=104 Ala) vs. variant (105 Val=114 Val); OR2.1 (95%CI 1.01-4.5)
in a cell to be repaired before the cells begin the process of growth, mitosis and division [81]. The transition through the G1 to the S phase of the cell cycle is regulated by cyclin-dependent kinases (CDKs) [81]. Cyclin D-1 (CCND1) is one of the major cyclins associated with cyclin-dependent kinases [82]. CCND1 is a key regulatory protein in this process, playing a critical role in the transition from the G1 to the S phase of the cell cycle. The activity of CCND1 reaches a maximum during the G1 phase, and is associated with CDK4 and CDK6 in the mid to late G1 phase. Alterations in CCND1 are thought to be involved in carcinogenesis because of activation of CCND1, and over-expression of CCND1 has been found in a variety of tumors, including those of the breast, head and neck, esophagus, larynx, and lung [83–85].

CCND1 exhibits a common A/G polymorphism (G870A). Zheng et al.[86] suggested that the A/A genotype of CCND1 polymorphism contributed to susceptibility to squamous cell carcinoma of the head and neck. In contrast, Matthias C et al. [87] reported that the CCND1 G/G genotype was associated with poorly differentiated tumors of the head and neck. There were only two reports about oral cancer. Huang, M et al.[88] reported significant associations between allele A and oral premalignant lesion (OPL). The CCND1 GG genotype is associated with increased susceptibility to oral squamous cell carcinoma with German patients [89].

Summary

The relation between genetic polymorphisms and cancer risk have not been evaluated sufficiently yet, because the results of studies on this issue have been controversial. Additional studies will be needed to reveal the interaction between carcinogens (chemicals in tobacco smoke or other chemicals) and genetic polymorphism. For example, our results about TP53 polymorphism indicated that genetic differences tend to be more important at exposure to none or low doses of a carcinogen (such as a low level of cigarette smoking). Wang et al. [69], also reported that genetic differences in cancer risk might be smaller at high loads of carcinogen. But for the GSTM1 polymorphism, a high dose of smoke exposure indicated a high cancer risk with some variants. Oral cavity organs are exposed to many carcinogens at high concentrations. Thus carcinogenic metabolic enzymes (GSTs, NAT etc.) will be more important than other enzymes (TP53, CCND1, XRCC1, etc.). We have to evaluate the effect of gene polymorphisms while considering that relationship.

References

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遺伝子多型と口腔がん

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要 旨： 高い疾病率や予後不良の点から口腔癌は世界的に重要な問題である。口腔癌の主な病因は喫煙や飲酒であり，化学物質の代謝活性は癌感受性に影響をおよぼしていることが示されている。喫草の煙にはベンゾピレンやニトロサミンなど多くの発がん物質や発がん前駆物質が含まれ，第1相および第2相酵素によって活性化または解毒される。これらの酵素遺伝子にはいくつかの遺伝子多型が存在し，これらの酵素の機能は遺伝子多型によって修飾される。一方，がん感受性に関与する遺伝子には，これらの酵素遺伝子以外にもいくつか存在する。我々はこの論説で口腔癌に関与する遺伝子多型の相互関係について紹介する。口腔癌に関与する遺伝子多型について多くの論文があるが，相反する結果も多く，今後，発癌物質および遺伝子多型との相互作用を評価するためには，さらなる研究が必要である。

キーワード： 口腔癌，シトクロームP450，N-アセチルトランスフェラーゼ，グルタチオンS-トランスフェラーゼ，TP53。

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