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Original Article

Association of EC-SOD, CYP1A1 gene polymorphisms, and smoking with oral cancer

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Abstract: We explored the correlation between smoking, polymorphisms of extracellular superoxide dismutase (EC-SOD) and cytochrome P450 (CYP) 1A1-Msp I and the prevalence of oral cancer. The genetic polymorphisms of EC SOD and CYP1A1-Msp I were detected by polymerase chain reaction (PCR) technique in peripheral blood leukocytes of 874 oral cancer patients and 874 non-cancer controls, and the correlations between smoking, genetic polymorphisms of the two metabolic enzymes and oral cancer were analyzed. The frequencies of EC-SOD (C/G) and CYP1A1-Msp I mutation homozygous genotype (m2/m2) were 37.87% and 63.62%, respectively, in the oral cancer patients, and 26.54% and 46.45%, respectively, in the healthy controls, both indicating significant differences (P<0.05). The risk of oral cancer was significantly higher in individuals with EC-SOD (C/G) than that in the controls (OR=2.68, 95% CI=1.46-5.17). The individuals carrying CYP1A1-Msp I (m2/m2) also had a higher risk of oral cancer (OR=2.35, 95% CI=1.63-4.92). The synergetic analysis of gene mutation indicated that the distribution frequency of EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) was 26.66% in the case group and 3.43% in the control group. The difference was statistically significant (P<0.05). The individuals carrying EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) had a higher risk of oral cancer (OR=5.46, 95% CI=2.73-8.94). The smoking rate in the case group was significantly higher than that in the control group (P<0.05), and statistic analysis indicated a synergetic interaction between smoking and EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) genotype polymorphisms, which increased the risk of oral cancer (OR=42.11, 95% CI=16.71-63.29). Smoking index (SI) higher than 400 and EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) genotype polymorphisms synergistically increased the risk of oral cancer (OR=246.32, 95% CI=176.23-386.14). EC-SOD (C/G) and CYP1A1-Msp I (m2/m2) were the risk factors for oral cancer. Smoking was also correlated with the susceptibility to oral cancer. EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) and smoking were working synergistically in elevating the incidence of oral cancer.

Keywords: Smoking, oral cancer, extracellular superoxide dismutase (EC-SOD), cytochrome P450 1A1-Msp I (CYP1A1-Msp I)

Introduction

Oral cancer is a common malignancy in the head and neck, with high morbidity and mortality. The five-year survival rate is only 41%-79.5% [1]. Recently, a number of studies prove that similar to other malignancies, the prevalence of oral cancer is the joint effort of many factors including environment and heredity [2, 3]. However, the exact pathogeny is not clear yet. Presently, smoking is considered as an important risk factor of oral cancer. Nitrosamine, polycyclic aromatic hydrocarbon and heterocyclic amines in cigarettes are known chemical carcinogens [4, 5]. The cancerization of the target cells caused by cancerogens largely depends on the activity of metabolic enzymes in the body. The gene of most metabolic enzymes is polymorphic, thereby resulting in the difference in tumor susceptibility among individuals.

The genesis of oral cancer is a complex process involving the interaction of host susceptibility and many etiological factors such as chemical carcinogenic factors, physical carcinogenic factors and biological carcinogenic factors. The exact pathogeny is not clear yet. An epidemiological investigation [6] shows an obvious relationship between smoking and the genesis of oral cancer. Cigarettes contain multiple cancerogens, such as benzopyrene, polycyclic aromat-

Table 1. Baseline data in the two groups

Characteristics		Oral cancer group (n, %)	Control group (n, %)	X^2/t values	*P* values
Sex	Male	562 (64.30)	548 (62.70)	0.417	0.26
	Female	312 (35.70)	326 (37.30)		
Age (years)		56.83 ± 6.93[a]	55.27 ± 7.31[a]	1.43[b]	0.25
Smoking	No	341 (39.01)	582 (66.59)	132.22	0.00
	Yes	533 (60.99)	292 (33.41)		
Smoking time (year)	≤15	121 (13.85)	185 (21.17)	124.17	0.00
	>15	412 (47.14)	107 (12.24)		
Smoking Quantity (n)	≤20	106 (12.13)	189 (21.62)	163.16	0.00
	>20	427 (48.86)	103 (11.79)		
Smoking index (SI)	≤400	119 (13.62)	187 (21.39)	110.85	0.00
	>400	414 (47.37)	105 (12.01)		
Location	Tongue	416 (47.60)	-		
	Buccal mucosa cancer	207 (23.68)	-		
	Gum cancer	133 (15.22)	-		
	Floor of mouth cancer	118 (13.50)	-		
Pathological type	Squamous cell carcinoma	795 (90.96)			
	Acinar cell carcinoma	79 (9.04)			

a: present as mean ± SD; b: t test.

ic hydrocarbon, heterocyclic amine and nitrosoamine, which can accept electron and form free radical. Moreover, the smoke of cigarettes contains multiple harmful free radicals, including carbon monoxide, nitric oxide, alkyl and alkoxy [7, 8]. Lots of free radicals enter the body upon smoking, act on and damage the target cells. They interfere with the redox potential of cells through damaging biomacromolecule, and subject nucleic acid and DNA of cells to attack. Then gene split and base modification occur, and oncogene is activated, finally leading to the cancerization of cells. In addition, inflammation affects the cancerized part of cells and the surrounding tissue. Lots of oxygen radicals O_2 and H_2O_2 active subst-ances, which are generated by respiratory burst, etc. in the phagocytosis of polynuclear neutrophils and other phagocytes, induce the formation of tumor [9].

As an antioxidant enzyme in the body, SOD plays a crucial role in the oxidation and antioxidation balance. SOD consists of CuZnSOD, MnSOD and EC-SOD. The former two types mainly exist in cytoplasm and nuclei of eukaryocyte, and can eliminate the superoxides in the cells. Existing in the extracellular fluid, EC-SOD can eliminate the hydrogen peroxide formed by superoxide anion, and protect cells against the oxidative damage caused by hydrogen peroxide [10]. A study [11] indicates that the polymorphisms of CuZnSOD and MnSOD can change the activity of corresponding enzymes and free radicals in the body, and are closely related to the susceptibility to tumors.

This paper investigated the relationship between smoking and extracellular superoxide dismutase (EC-SOD) and cytochrome P450 (CYP) 1A1 I gene polymorphisms, and explored the correlation between smoking, EC-SOD and CYP1A1 I gene polymorphisms and oral cancer.

Subjects and methods

Study subjects

874 oral cancer patients admitted by Department of Stomatology of our hospital between January 2010 and December 2015 were selected as the study subjects. All patients were diagnosed as having primary oral cancer by pathology. 874 healthy controls, without tumor or genetic disease in physical examination, were included in the control group. The information of study subjects, including demographic data, smoking history, occupational history and family history of tumor, etc. was investigated and collected. The analysis showed that the differences between the case

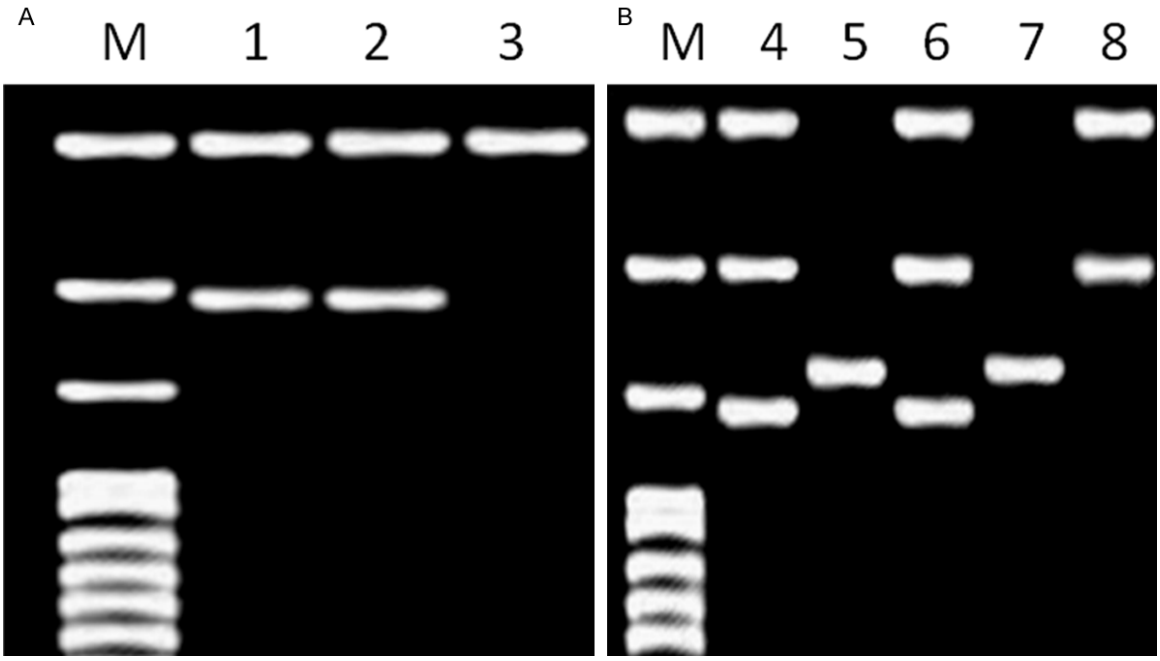

Figure 1. Genotyping results of EC-SOD (A) and CYP1A1-Msp I (B). M: marker; 1, 1, 2 C/G genotype; 3: C/C genotype; 4, 6 m1/m2 genotype; 5, 7: m1/m1 genotype; 8: m2/m2 genotype.

group and the control group were not statistically significant with respect to age, sex, nationality and native place (P>0.05). There was also no genetic connection. The smoking index (SI) was used to evaluate the smoking status: SI=cigarettes smoked per day × smoking years.

The study subjects were divided into non-smokers, SI≤400 and SI>400. See **Table 1**.

Experimental method

Reagents and equipments: QIAxmpDNA extraction kit (QIAgen, Germany); primers (synthesized by Sangon Biotech (Shanghai) Co., Ltd.); DNA ladder (Fermentas); Goldview (Beijing SBS Genetech Co., Ltd.); PCR amplifier (PE, America); The rest reagents were purchased from Promega, America.

Gene polymorphism analysis: Fasting peripheral venous blood was drawn. EDTA was used for anticoagulation. DNA was extracted from white blood cells by using DNA extraction kit.

Analysis on EC-SOD polymorphism: The primer sequences were 5'-GCAACCAGGCCAGCGTG-3' in cis-form and 5'-CCAGAGGAGAAGCTCAAAGGCAGA-3' in transform. PCR reaction system was carried out in a total volume of 50 μL, including 5 μL 10× Buffer, 4.0 μL dNTP, 0.25 μL TapDNA polymerase, 20 pmol of each primer, 100 ng template DNA and 3 dH_2O. The reaction requirements: initialization at 95°C for 5 min; denaturation at 94°C for 30 s, annealing at 64°C for 30 s, and extension at 72°C for 1 min for 30 cycles; and final elongation at 72°C for 10 min. The 5 μL PCR amplification product was taken. The 1.5% agarose gel electrophoresis was conducted under 100 V for 60 min. The 5 μL PCR amplification product underwent electrophoresis on a 1.5% agarose gel at 100 V for 60 min and was stained with Goldview. The amplification result was observed under the ultraviolet lamp. The enzyme digestion reaction was carried out in a total volume of 30 μL, including 5 μL amplification product, 11 μL restriction enzyme, 2 μL 10× PCR buffer solution and 12 μL distilled water. The system was mixed and incubated in a water-bath overnight at 37°C. 6 μL enzyme-digested product was subjected to 1.5% agarose gel electrophoresis for 60 min and Goldview staining. The result was observed under the ultraviolet lamp. The genotype was judged using 100 bp DNA ladder as the molecular weight standard. Two genotypes, namely EC-SOD(C/C) (111, 109 bp) and EC-SOD (C/G)

Table 2. Distribution of genotypes of EC-SOD and CYP1AI-Msp I polymorphisms

Gene	Genotype	Case (n, %)	Control (n, %)	OR	95% CI	X^2	P
EC-SOD	C/C	543 (62.13)	642 (73.46)	1.00	-	-	-
	C/G	331 (37.87)	232 (26.54)	2.68	1.46~5.17	25.68	0.00
CYP1A1-Msp I	non-m2/m2	318 (36.38)	468 (53.55)	1.00	-	-	-
	m2/m2	556 (63.62)	406 (46.45)	2.35	1.63~4.92	52.02	0.00

Table 3. Interaction between EC-SOD and CYPIAI-Msp I

Genotypes		Case (n, %)	Control (n, %)	OR	95% CI	X^2	P
EC-SOD	CYP1A1-Msp I						
C/C	non-m2/m2	213 (24.37)	369 (42.22)	1.00	-	-	-
C/C	m2/m2	352 (40.27)	338 (38.67)	1.76	0.76~3.82	2.64	0.34
C/G	non-m2/m2	76 (8.70)	137 (15.68)	1.22	0.58~2.47	1.82	0.47
C/G	m2/m2	233 (26.66)	30 (3.43)	5.46	2.73~8.94	22.17	0.00

Table 4. Relation between oral cancer and smoking

Items		Case (n, %)	Control (n, %)	OR	95% CI	X^2	P
Smoking	-	341 (39.01)	582 (66.59)	1.00	-		
	+	533 (60.99)	292 (33.41)	3.13	1.82~4.97	94.37	0.00
SI	≤400	119 (13.62)	187 (19.80)	1.00	-		
	>400	414 (47.37)	105 (13.61)	6.79	3.37~7.85	127.90	0.00

(220, 111, 109 bp), can be observed after digestion. The bands of 111 and 109 bp nearly coincided. The mutant homozygote (G/G) cannot be detected in both groups. See **Figure 1A**.

CYP1A1-Msp I polymorphism analysis: The primer sequences were 5'-CAGTGAAGAGGTGTAGCCGCT-3' in cis-form, and 5'-TAGGAGTCTTGTCTCATGCCT-3' in transform. The experimental method was the same as that described in 1.2.2.1. Three genotypes after digestion: The wild type (m1/m1) was 340 bp; the heterozygous type (m1/m2) was 340, 120, and 140 bp; the mutant type, namely, the homozygotic type (m2/m2) was 200, and 140 bp. See **Figure 1B**.

Statistical analysis

Excel form was used for data. SPSS18.0 software was adopted for statistic analysis of data. The x^2 test was used for the intergroup comparison of qualitative data. The *t* test was used for the intergroup comparison of quantitative data. The odds ratio (OR) and 95% confidence interval (CI) were used to show the relative risk. $P<0.05$ indicated significant difference.

Results

EC-SOD and CYP1A1-Msp I genotype distribution

The statistical analysis sho-wed that individuals carrying EC-SOD (C/G) accounted for 37.87% in the case group and 26.54% in the control group. The difference was statistically significant ($P<0.05$). The CYP1A1-Msp I mutation homozygous genotype (m2/m2) was 63.62% in the case group and 46.45% in the control group, indicating significant difference ($P<0.05$). See **Table 2**.

Synergy of EC-SOD and CYP1A1-Msp I genotypes on the susceptibility to oral cancer

The statistical analysis indicated that individuals carrying EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) accounted for 26.66% in the case group, but only 3.43% in the control group. The oral cancer morbidity of individuals carrying EC-SOD (G/C)/CYP1A1-Msp I (m2/m2) was 5.46 times of that among those carrying EC-SOD (C/C)/CYP1A1-Msp I (non-m2/m2). Synergy was found between 2 genotypes. See **Table 3**.

Correlation between smoking, SI and oral cancer

X^2 test was conducted for the number of smokers and non-smokers in the control group and case group. The results indicated that the prevalence of oral cancer was related to smoking,

Table 5. Interaction between EC-SOD/CYPIAI-Msp I and smoking

EC-SOD	CYP1A1-Msp I	Smoking	Case (n, %)	Control (n, %)	OR	95% CI	X^2	P
C/C	non-m2/m2	-	68 (7.78)	178 (20.37)	1.00	-	-	-
C/C	non-m2/m2	+	128 (14.66)	201 (23.00)	1.24	0.69~2.15	4.26	0.13
C/C	m2/m2	-	223 (25.51)	323 (36.96)	1.83	0.96~3.77	2.95	0.22
C/C	m2/m2	+	117 (13.39)	9 (1.03)	29.87	13.15~42.33	25.29	0.00
C/G	non-m2/m2	-	26 (2.97)	27 (3.09)	1.48	0.79~3.15	3.01	0.46
C/G	non-m2/m2	+	62 (7.09)	75 (8.58)	1.36	0.52|~3.87	3.07	0.11
C/G	m2/m2	-	24 (2.75)	54 (6.18)	0.31	0.29~1.40	5.99	0.06
C/G	m2/m2	+	226 (25.86)	7 (0.80)	42.11	16.71~63.29	76.81	0.00

Table 6. Interaction between EC-SOD/CYP1A1-Msp I genotype and SI

EC-SOD	CYP1A1-Msp I	SI	Case (n, %)	Control (n, %)	OR	95% CI	X^2	P
C/C	non-m2/m2	≤400	29 (3.31)	121 (13.84)	1.00	-	-	-
C/C	non-m2/m2	>400	106 (12.12)	50 (5.72)	14.37	7.93~16.92	9.13	0.02
C/C	m2/m2	≤400	34 (3.78)	8 (0.90)	47.54	25.85~67.25	16.84	0.00
C/C	m2/m2	>400	45 (5.15)	3 (0.34)	87.66	58.36~103.54	54.37	0.00
C/G	non-m2/m2	≤400	24 (2.75)	37 (4.23)	4.34	0.87~4.93	5.91	0.08
C/G	non-m2/m2	>400	33 (3.78)	47 (5.38)	4.23	0.96~5.42	7.62	0.08
C/G	m2/m2	≤400	32 (3.66)	21 (2.40)	23.18	17.23~34.61	116.47	0.00
C/G	m2/m2	>400	230 (26.31)	5 (0.57)	246.32	176.23~386.14	145.17	0.00

and that smokers were more susceptible to the oral cancer (OR=3.13, 95% CI=1.82-4.97, P<0.05).

Correlation between susceptibility to oral cancer and SI: Heavy smokers (SI>400) were more susceptible to oral cancer that light smokers (SI≤400) (OR=6.79, 95% CI=3.37-7.85, *P*<0.05). See **Table 4**.

Synergistic effect of EC-SOD/CYP1A1-Msp I genotypes and smoking on the susceptibility to oral cancer

The case group had significantly more individuals carrying EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) and more smokers than the control group. Smokers with EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) genotype accounted for 25.86% in the case group, but only 0.80% in the control group. The difference was statistically significant (*P*<0.05). See **Table 5**. The synergetic analysis on EC-SOD/CYP1A1-Msp I, SI and susceptibility to oral cancer indicated that the morbidity of individuals with EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) /SI>400 was 246.32 times of that among those with EC-SOD (C/C)/CYP1A1-Msp I (non-m2/m2) /SI≤400 (P<0.05). See **Table 6**.

Discussion

The present study indicated that EC-SOD (C/G) was related to the prevalence of oral cancer. The proportion of EC-SOD (C/G) genotype in oral cancer patients was significantly higher than that in the control group. The EC-SOD (C/G) carrier had a higher risk of oral cancer than the EC-SOD (C/C) carrier. These results are similar to those of previous report [12]. A study shows that the C-to-G variation at locus 637 of EC-SOD gene transforms the amino acid at position 213 from arginine into glycine, resulting in a decline in the affinity of EC-SOD enzyme and lecithin [13]. This mutation produces a fall in the antioxidant activity of EC-SOD, an increase of free radicals in the body and an increase of individual's susceptibility to oral cancer.

As one of the important phase I metabolic enzymes in the body, CYP1A1 can activate and detoxicate many procarcinogens in tobaccos. Through activation, procarcinogens without biological activity can be transformed into electrophilic compounds which further attack biomacromolecules within the cell, form into adduct with DNA or protein, inhibit tumor suppressor genes, activate oncogenes and result

in cancerization. Replacement of T6235C in the untranslated region at the 3' terminus of CYP1A1 gene can produce a Msp I digestion site, namely, Msp I polymorphism. There are 3 genotypes, namely, wild type (m1/m1), heterozygotic type (ml/m2) of 140 bp, and mutation homozygotic type (m2/m2). The mutant gene may influence the inductivity of CYP1A1 through the linkage with other gene polymorphisms in the regulatory region of this gene. Many studies [14, 15] have shown that Msp I site polymorphism is correlated with laryngeal cancer, breast cancer, stomach cancer and prostate cancer, etc. The present study also found that CYP1A1-Msp I (m2/m2) carrier had a significantly higher risk of oral cancer, which was consistent with the results of previous study [14]. A further study is needed to investigate the mechanism of action for the susceptibility to oral cancer by CYP1A1-Msp I (m2/m2) carrier. A foreign study [16] finds that the enzymatic activity of m2 genotype is higher than that of m1 genotype. Therefore, we conjecture that the reason why CYP1A1-Msp I (m2/m2) carrier is more susceptible to the oral cancer may be that high activity of CYP1A1 produces more active carcinogens [17].

The present study found that EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) had a significant synergistic effect on the incidence of oral cancer, and that the oral cancer morbidity of individuals carrying EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) was significantly higher than those carrying EC-SOD (C/C)/CYP1A1-Msp I (non-m2/m2). Moreover, smoking significantly increased the risk of oral cancer. Through the gene polymorphism and synergetic analysis with smoking, we found that EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) and smoking worked synergistically in increasing the risk of oral cancer prevalence. Heavy smokers (SI>400) carrying EC-SOD (C/G)/CYP1A1-Msp I (m2/m2) genotype had a much higher risk of oral cancer than light smokers (SI≤400) carrying EC-SOD (C/C)/CYP1A1-Msp I (non-m2/m2) genotype. The present study found that EC-SOD (C/G), CYP1A1-Msp I (m2/m2) and smoking were susceptible factors of oral cancer, and they worked synergistically in the incidence of oral cancer.

In summary, the genesis of oral cancer is a complex process involving the interaction of smoking and multiple genes. The present study suggests that the population carrying EC-SOD (C/G) and CYP1A1-Msp I (m2/m2) genes is the high-risk population of oral cancer, and attention shall be paid to such a population in the prevention and treatment of oral cancer. Detecting the susceptibility genes of oral cancer can predict the susceptibility to oral cancer, and corresponding control measures, such as quitting smoking and drinking, can be adopted to effectively prevent the oral cancer.

Disclosure of conflict of interest

None.

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