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Genetic polymorphisms in the Cytochrome P450 family and squamous cell carcinoma of the oral cavity, pharynx and larynx

Polimorfismos genéticos da família Citocromo P450 e carcinoma de células escamosas de cavidade oral, faringe e laringe

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A B S T R A C T

Objective: To analyze the genetic polymorphisms of the cytochrome P450 family and their relationship with squamous cell carcinoma of the oral cavity, pharynx and larynx. **Methods**: We present a narrative literature review, conducted in Pubmed, Lilacs and Cochrane Databases of articles published in the last five years correlating genetic polymorphisms of the cytochrome P450 family and cancer risk in different populations worldwide. **Results**: We initially found 65 articles and, after selection criteria, 20 case-control studies with various populations worldwide were eligible. The most studied polymorphisms were those of CYP2E1 and CYP1A1 subfamilies. There is little about the other subfamilies. The association found between polymorphisms and cancer risk amounted to a countless number of variables, amongst them: population, selection methods, racial factors and different modes of exposure to carcinogens, genotyping methods, and nomenclature of the polymorphisms. **Conclusion**: so far, there is no proven link between genetic polymorphisms of cytochrome P450 family and squamous cell carcinoma of the oral cavity, pharynx and larynx relationship.

Key words: Cytochrome P-450 enzyme system. Polymorphism, genetic. Head and neck neoplasms.

INTRODUCTION

Malignant neoplasms in general have been one of the most important public health problems in the world. Data from the World Health Organization (WHO) showed that in 2008 about 13% of all deaths worldwide were due to cancer, with 7.6 million deaths each year. For the year 2030 the annual estimate of cancer deaths is approximately 13.1 million people [1].

Upper aerodigestive tract cancers (UADTC), ie, oral cavity, pharynx, larynx and esophagus neoplasms, are responsible for an incidence of approximately 5.2% of cancer cases worldwide, such values being about 6.4% in Europe. Each year about 180,000 new cases are estimated, with around 100,000 deaths [2].

Cancers of the oral cavity and pharynx occupy the sixth position worldwide for men and women, showing large variations according to different regions of the planet. In India this is the most common cancer among men and third among women. In Europe and some Asian countries, it is highly incident. In Latin America and the Caribbean, it presents intermediate rates [3,4].

Particularly for the head and neck cancers, about 90% are squamous cell carcinomas (SCC) of the oral cavity, pharynx and larynx, these being among the ten most frequent worldwide [1,5,6].

Chewing tobacco and passive exposure to tobacco smoke components have been recognized as risk factors [3,7].

In Brazil, the incidence of neoplasms of the head and neck is high. Cancer of the oral cavity is among the five most prevalent types of cancer in the population, with about 13 new cases / 100,000 / year, the larynx one displaying the sixth highest incidence in males [8].

Cigarette smoking alone is the leading cause of cancer in the world and is considered by WHO a chronic and recurrent disease caused by nicotine dependence, being the leading cause of preventable death [9]. Smokers have about three and a half times more chance of cancer of the oral cavity and of the larynx [7]. Passive smokers who were exposed for more than 15 years at home or at work are almost twice as likely to have some type of cancer of the head and neck compared to unexposed individuals [9,10].

The consumption of alcohol has also been well accepted as an independent risk factor for head and neck cancers. When separately analyzing alcohol consumption, studies have shown an increased risk of cancer of alcoholics when compared to non-alcoholics [11].

In Brazil, there was a strong relationship between daily excessive drinking of cachaça, the Brazilian sugar cane rum, and and the risk of cancer of the oral cavity [12] In general, one can observe a direct relationship between dose

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and effect, according to the amount of intake, and cumulative consumption of alcohol [13]. Epidemiological studies of cancer, especially of case-control type, have shown that in tumors of oral and cavity oropharynx, around 75% of individuals make combined use of such agents, and in tumors of the hypopharynx and larynx that figure is around 60%. Regarding oral cavity and larynx lesions, the simultaneous use increases up to 15 times the risk of cancer [13].

In general, the vast majority of patients with UADTC are drinkers and / or smokers who have little education, in poor socioeconomic conditions, malnourished, with poor oral hygiene, thus forming a very clear profile of the population at risk for this kind of neoplasia. On the other hand, a small portion of patients with UADTC, about 10%, are individuals who never smoked or drank, nor had a significant exposure to these factors throughout their lives. This implies the possibility of some other factors, amongst which viral, such as HPV, and genetic [14].

Studies have shown that oropharyngeal carcinomas seem to have two different biological behaviors: one related to factors such as alcohol and tobacco, and other related to human papillomavirus [14]. Besides these, individual genetic characteristics may be the major factors in determining the effect of a substance abuser or agent responsible for a malignant neoplasm [15].

Regarding chronic exposure to substances such as alcohol and tobacco, it can be concluded that excretion mechanisms can affect the bioavailability and the degree of biochemical attack, and therefore a greater or lesser risk of cancer [15]. However, substances as nitrosamines found in tobacco smoke, called pre-carcinogens, must be metabolized to exert their deleterious effects. When there is metabolic activation of precarcinogens, the products formed are generally electrophilic agents capable of reacting with DNA and cause mutations [16].

Genetic variations responsible for the synthesis of enzymes involved in the metabolism of nicotine can significantly influence the behavior of smoking, metabolism of drugs in general, and also the activation of carcinogens found in tobacco smoke [17,18].

Thus, when referring to these genetic variations, including genetic polymorphisms, the consequence may be a change in the phenotypic characteristics of metabolism of nicotine and its derivatives, and especially the various types of carcinogens. In general, genetic polymorphisms are distributed in a very heterogeneous frequency in the world population. So, these genetic factors would b ecapable of increasing the risk of cancer in such patients, since they would cause the individual to be expose to more carcinogenic substances.

The first report of the association between genetic polymorphisms of CYP and cancer risk was an article published in 1984 about lung cancer and the polymorphism of the CYP2D6 gene [19].

Another very important epidemiological factor in this type of malignancy is the intake of alcoholic beverages. In its various presentations, the alcohol and its derivatives are metabolized to acetaldehyde by the alcohol dehydrogenases (ADH), and then to acetic acid by the acetaldehyde dehydrogenases (ALDH). Such conversions are performed mainly in the liver, but may also occur in the upper aerodigestive tract. There is evidence that polymorphisms in the genes ADH1B and ADH1C forms, plus ADH7 and ALDH2, are associated with UADTC [20,21].

The biotransformation of these xenobiotics, such as tobacco and alcohol, involve specific biochemical reactions, where each step counts with the participation of highly ordered enzymatic sequences. The production of these enzymes, in turn, is genetically determined through processes of translation and transcription [15]. An abnormality in the genes encoding the enzyme responsible for the production of these xenobiotic biotransformation can alter their bioavailability and excretion.

A major group of genes responsible for encoding these enzymes that aid in excretion of xenobiotics is the gene group "cytochrome P450" [15]. However, it seems that the process is extremely complex, since there are tens of polymorphisms of the cytochrome P450 family.

Certainly the most common variations between individuals are of the single nucleotide polymorphisms (SNPs), in which the difference found involves a single base in the DNA that, during the encoding process, may or may not give rise to an enzyme with increased, normal or decreased activity[22].

Racial factors have been important to detect the frequency of a particular polymorphism. Thus, some polymorphisms may vary greatly when compared between different populations [17,23,24].

A special nomenclature has been developed for the major cytochrome P450 system. Of the more than 700 families of CYP, about 110 are present in animals. According to "The Human Cytochrome P450 (CYP) Allele Nomenclature Database", nine families and 29 subfamilies were described till 2007 [25]. Currently, there are 18 families and 40 subfamilies described [26]. Numerous other allelic variants may exist in several subfamilies, totaling more than one hundred described polymorphisms.

There is a great variability of the methodology, results and conclusions in the literature on this subject. Thus, it is important to review the matter due to the great complexity of the study of genetics and its relationship to cancer.

Given the aforementioned, the authors aimed to analyze the genetic polymorphisms of the cytochrome P450 family and their relationship with squamous cell carcinoma of the oral cavity, pharynx and larynx.

METHODS

We sought articles published from March 2007 to March 2012 on genetic polymorphisms and head and neck cancers.

The survey was conducted in the following databases: PubMed, Lilacs and Cochrane. Furthermore, a search was made for all polymorphisms in the cytochrome P450 family in humans in the site http://www.cypalleles.ki.se/ in order to seek a different nomenclature for each member of the family and subfamily of cytochrome P450.

Tools like "MeSH Database" and "DeCS" were used for the choice of keywords, for the following: Pubmed Search: Cytochrome P-450 Enzyme System AND Genetic Polymorphism AND Head and Neck Neoplasms. Lilacs Search: cytochrome p450 enzyme system AND genetic polymorphism And cancers of the head and neck.

All bibliographic research was performed by two independent researchers. No manual search was conducted in the annals of Congresses, Societies' magazines or other scientific reports that were not indexed articles.

A new individual search was performed for each subfamily with a wide synonym base to obtain other papers on some kind of polymorphism that could not have been included in the initial search.

The selection criteria were: Case-control and cohort studies; Article containing squamous cell carcinoma of the oral cavity, pharynx and larynx; any article on genetic polymorphisms of the cytochrome P450 family. We did not include articles on: neoplamsms other than squamous cell carcinomas; other sites of disease not related to the main risk factors for cancer in question, such as carcinomas of the thyroid, salivary glands, lip, nasopharynx, and skin; carcinomas of the esophagus. We excluded: meta-analyzes; reviews; letters to the editor; comments in magazines; and articles related to response results.

RESULTS

We found 65 articles, which were submitted to three stages of selection: First step: 21 were excluded for not being case-control; Second step: 16 were excluded articles for dealing with other neoplasms; and Third stage: eight articles excluded for being unrelated to the purpose.

Thus, we selected 20 Case-Control articles on carcinoma of the oral cavity, pharynx and larynx, in which they presented some kind of polymorphism of the Cytochrome P450 family.

Of the 20 articles selected, the most studied subfamilies were CYP1A1 and CYP2E1, followed by CYP1B1 and CYP2A13. Other subfamilies such as CYP1A2, CYP2A6, CYP2C19, CYP3A4 and CYP26B1 were present in only one article (Table 1). Of the 20 articles, 16 were on the association between more than one polymorphism. For purposes of the study and individual analysis of the cytochrome P450 family, we sought the results only for data concerning polymorphisms of this family in isolation, without the association of more genetic factors.

We found the following results: CYP1A1: four national (Brazilian) articles, four Indian, one Pakistani, one Chinese and one from Indonesia. Five articles showed increased risk, four of them of the Indiana population, with 1,547 cases and 1,783 controls, whose polymorphisms were represented by different characters and symbols. The authors showed a variation in accordance with the risk polymorphism in question and its homo or heterozygous presentation (Table 2). We found nine articles without association with risk, four national, three Indian, one from China and one from Indonesia. All showed a higher frequency of polymorphisms in controls (Table 3); CYP2E1: we found six articles, three of them Brazilian, two Indian and one Chinese. Only two studies, one Indian and another Brazilian, showed increased risk after genotyping 403 cases and 395 controls (Table 2). There was no association of risk in four articles, with 1,321 genotyped cases and 1,450 controls, of Brazilian, Indian and Chinese populations (Table 3); CYP1A2: only one Brazilian paper ra was found, with 153 genotyped cases and 145 controls, where from the two polymorphisms analyzed, one was a risk factor and the other had no association (Tables 2 and 3); CYP1B1: three studies on this polymorphism were found in populations of the Czech Republic, India and China, with 550 genotyped cases and 550 controls. Only one form of polymorphism was a risk factor for cancer (Tables 2 and 3); CYP2A6: There was an Indian article with genotyping of 350 cases and the same

Table 1 - Distribution of selected articles according to the families and subfamilies of cytochrome P450.

Cytochrome P450 families	Subfamilies	Number of articles
CYP1	CYP1A1	11
	CYP1A2	1
	CYP1B1	3
CYP2	CYP2A6	1
	CYP2A13	2
	CYP2C19	1
	CYP2E1	6
CYP3	CYP3A4	1
CYP26	CYP26B1	1

number of controls, with an increased frequency of polymorphisms found in the controls compared with cases, resulting in a small decrease in risk. In a stratified analysis, the homozygous polymorphic form conferred a small protective effect, even to smokers (Tables 2 and 3); CYP2A13: two articles were found, one from the Czech Republic and another from India, with a total of 325 genotyped cases and 323 controls, where there was no association between polymorphism and cancer. However, a stratified analysis showed one polymorphic forms to be a risk factor for pharyngeal cancer, though not significant for tumors of the oral cavity and larynx (Tables 2 and 3); CYP2C19: in a single study in the Indian population, in which 300 cases were genotyped, as well as an equal number of controls, there was a significant increase in cancer risk in one of the polymorphisms. Considering another polymorphism locus, the frequency of the homozygous polymorphic genotype represented an increase in cancer risk, but without statistical significance (Tables 2 and 3); CYP3A4: one study in a Chinese population, with 278 cases and an equal number of controls, showed no significant difference between the frequency of polymorphisms of an allelic variant, both in its heterozygous polymorphic form and in the homozygous one (Tables 2 and 3); CYP26B1: one case-control study conducted among a Chinese population of Taiwan, with 247 cases and 338 controls, in which four polymorphism locuses were analyzed, only one being significant for cancer risk. In stratified analysis, this polymorphism, associated with the use of betel, showed a seventy-fold increase in cancer risk (Tables 2 and 3).

In summary, by analyzing the different frequencies of polymorphisms and cancer risk, we can observe that there was no association of risk in 20 articles, and an increased risk was found in 12 articles. If we consider the polymorphisms of CYP1A1, CYP2E1 and other polymorphisms, we observed no major differences in the risk of cancer (Table 4).

DISCUSSION

The enzymes of the cytochrome P450 family are primarily responsible for metabolizing carcinogens found in tobacco and alcohol. Over the past decades a number of case-control articles have been showing the frequency of polymorphisms correlated with different pathologies,

Table 2 - Results - Increased risk of cancer.

Authors	Polymorphisms	Year	Country
CYP1A1			
Sharma *et al.*	Homozygous T3801C polymorphism, pharyngeal and laryngeal cancer; OR=3.49; 95%CI: 1.34-9.05; p=0.01	2010	India
Tai *et al.*	Homozygous Ile/Val polymorphism – larynx / hypopharynxOR=2.39; 95%; CI: 1.11-5.16; p=0.02 Homozygous T3798C polymorphism OR=3.25; 95%CI: 1.76-6.03; p<0.001; heterozygous OR=1.56; 95%CI: 1.06-2.31; p=0.023	2010	China
Singh *et al.*	Heterozygous *2A – OR=1.66; 95%CI: 1.08-2.55; p=0.02Heterozygous *2C – OR=1.83; 95%CI: 1.17-2.85; p=0.0	2009	India
Sam *et al.*	Homozygous *2A – OR=3.55; 95%CI: 1.89-6.66; p=0.001Heterozygous *2A – OR= 1.72; 95%CI: 1.22-2.44; p=0.002	2008	India
Anatharaman *et al.*	Homozygous MspI – OR=1.34; 95%CI: 0.88-2.01Heterozygous MspI – OR=0.92; 95%CI: 0.72-1.67	2007	India
CYP2E1			
Ruwali *et al.*	*5B – OR=3.44; 95%CI: 1.45-8.14; p=0.008*6 – OR=1.76; 95% CI: 1.28-2.41 – p< 0.01	2009	India
Olivieri *et al.*	*5B - p=0.001	2009	Brazil
Other Polymorphisms			
Olivieri *et al.*	CYP1A2*1C – significant in pharyngeal tumors – p= 0.05CYP1A2*1D – homo and heterozygous – 11X increaseOR=11.14; 95%CI: 6.1-20.2	2009	Brazil
Sing *et al.*	Homozygous CYP1B1*2 – 2.29X increase, p<0.05Heterozygous CYP1B1*2 – 1.63X increase, p<0.036	2008	India
Sharma *et al.*	CYP2A13 – homozygous C578T polymorphisms – 3X, p=0.003	2010	India
Yadav *et al.*	CYP2C19*2 – heterozygous – OR= 1.67; 95%CI: 1.2-2.31; p=0.002 CYP2C19*2 – homozygous – OR= 2.42; 95%CI: 1.56-4.0; p=0.0001	2008	India
Chen *et al.*	CYP26B1 - OR=2.26; 95%CI: 1.35-3.8; p<0.05	2011	Taiwan

including cancers, besides studies of pharmacokinetics and pharmacodynamics of chemotherapy agents, with large result variation. We know that studying the mechanisms of carcinogenesis and anticarcinogenesis of the body are always complex. It is not yet possible to demonstrate them in their entirety, but it is assumed that genetic factors determine the behavior of a given tumor, either by transformation or activation of carcinogens, or by defense mechanisms through tumor suppressor genes.

The whole research was performed by two independent investigators with consensus meetings, with the concern to avoid any type of bias, such as selection, publication, time, language, and others. We did not exclude any language. It was not possible to access other databases, manual search or contact with others, which should be considered as a limiting factor of this study. None of the articles analyzed cited a sample calculation of the genotyped patients.

The entire search process was conducted through review of the genotyping-specific site of the cytochrome P450 family, its last update beinf on 2007 [26]. Currently there are a large number of phylogenetic sites available [27-31], with countless links to information and mapping of genes, their mutations and polymorphisms. Besides showing information on the human genome, such databases provide the exact position of the gene, its genetic polymorphisms, when they occur, and their frequency according to populations. Other sites, such as Omin [30] and Gene Bank[31], are also able to provide genetic sequences and reference. When analyzing this family, we can observe several tens of polymorphisms, known as allelic variants, which have been described and grouped into subfamilies. This by itself complicates any analysis of frequency data, clustering and performance of meta-analysis.

We found that the articles published were mostly from populations of Brazil, India, followed by populations

Table 3 - Results – No risk association.

Authors	Polimorfismos	Year	Country
CYP1A1			
Lourenço *et al.*	T6235C polymorphism – more frequent in controls – OR=1.2; 95% CI: 0.1-0.7; p=0.01 A4889G polymorphism – p>0.05	2011	Brazil
Cury *et al.*	MspI polymorphism– OR=1.01; 95%CI: 0.68-1.50; p=0.9522	2012	Brazil
Sharma *et al.*	T3205C, A2455G and C2453A polymorphisms	2010	India
Tai *et al.*	Heterozygous Ile/Val – OR=1.33; 95%CI: 0.93-1.92; p= 0.122	2010	China
Singh *et al.*	*4	2009	India
Amtha *et al.*	Ile/Val – OR=0.70; 95%CI: 0.39-1.25; p=0.226 for oral cavity	2009	Indonesia
Olivieri *et al.*	Heterozygous *2, more frequent in controls – p=0.003	2009	Brazil
Sam *et al.*	*2C	2008	India
Losi-Guembarouski et al	T3801C – OR=1.24; 95%CI: 0.67-2.31; p>0.05	2008	Brazil
CYP2E1			
Cury *et al.*	PstI – OR=0.48; 95%CI: 0.23-0.98; p=0.0449 – low riskDraI – OR=0.78; 95%CI: 0.46-1.32 – p<0.3545	2012	Brazil
Tai *et al.*	*5A and *5B - Homozygous polymorphism – p=0.938*5A and *5B - Heterozygous polymorphism – p=0.892	2010	China
Garcia *et al.*	*5B – p=0,237	2010	Brazil
Soya *et al.*	*1B; *5B e *6	2008	India
Other Polymorphisms			
Olivieri *et al.*	CYP1A2*1C – no association in the overall analysis	2009	Brazil
Singh *et al.*	CYP1B1*4 – p>0,2	2008	India
Soucek *et al.*	CYP1B1– Leu/Val – OR=0.49; 95%CI: 0.24-1.01; p=0.055CYP1B1 – Asn/Ser – p>0,05	2010	Czech Rep.
Tai *et al.*	CYP1B1*3, *5, *6 and *7 homozygous – p<0.903CYP1B1*3, *5, *6 and *7 heterozygous – p<0.865	2010	China
Ruwali *et al.*	CYP2A6 - *4C (deleted) – homo or heterozygous – MILD PROTECTOR EFFECT – p=0.02CYP2A6*1B – p>0.05	2009	India
Sharma *et al.*	CYP2A13 – PROTECTOR EFFECT – p=0.007	2010	India
Tai *et al.*	Heterozygous CYP3A4*1G – OR=1.17; 95%CI: 0.81-1.69; p=0.418 Homozygous CYP3A4*1G – OR=1.0; 95%CI: 0.52-1.92; p=0.998	2010	China

Table 4 - Polymorphisms of the Cytochrome P450 family and cancer risk.

Polymorphisms	Risk increase	No Association of Risk	Total
CYP1A1	5	9	14
CYP2E1	2	4	6
Other Polymorphisms	5	7	12
TOTAL	12	20	

of China, Taiwan, Pakistan and Czech Republic. We know that polymorphisms ofthis group are rare in Western populations. There was no article on a North American, African or even European population.

All studies alluded to risk according to the frequency of polymorphisms found in cases and controls. No article showed some sort of quantification of exposure to carcinogens. There were some meta-analytical studies [32-34] with polymorphisms of CYP2E1 and CYP1A1 subfamilies, where the authors gathered some information from one or two specific polymorphisms, leaving many others to be analyzed. In the three meta-analyzes compared with our review, the authors question the validity of their results due to the heterogeneity of data, the possibly inappropriate choice of polymorphisms, and the possibility of biases. In our review, the results are questionable because of the difficulty of comparing polymorphisms. This analysis was also hampered by the way the authors exposed the data, either by analyzing the single exchange of one nucleotide, or by analyzing the change of a codon, or by citing only restriction enzymes during the genotyping process, preventing comparisons between results.

From a genetic standpoint, to assign a specific biological effect to a genetic answer is quite complex. This is because a particular polymorphism may have no effect by being in an inactive area of the gene, not to be passed on. Moreover, these factors are always followed by other phenomena, such as gene-gene effects summation or termination of processes, phenomena of pleiotropy or epistasis, or environmental interference. Currently, we question whether the genotyping method employed by many researchers, whose results may suffer changes in large and different populations. In the identification and classification of these polymorphisms, we can also find inconsistencies. Specifically in the metabolism of carcinogens found in tobacco, many of them have, rather than their elimination, a paradoxical effect, with activation [35].

Since the variation of genetic polymorphisms is directly linked to people's ethnic and this sufferrs great variation, even in confined locations, to determine the frequency of a polymorphism is also difficult. To define race in certain countries is a difficult task in the face of great miscegenation. Perhaps these data can be compared in very close individuals, being incomparable between very different peoples [36].

The readings on this kind of article should always be viewed with caution, since all these reasons may be subject to erroneous conclusions. There is no consensus on the interindividual differences in the metabolism of carcinogenic substances and cancer etiology. The probable reason is that the chemically induced cancer is still a multifactorial process that involves multiple stages and events before a certain disease can manifest clinically.

To date, there is no proven relationship between genetic polymorphisms of the cytochrome P450 family and squamous cell carcinoma of the oral cavity, pharynx and larynx.

R E S U M O

Objetivo: *analisar os polimorfismos genéticos da família Citocromo P450 e sua relação com o carcinoma de células escamosas de cavidade oral, faringe e laringe.* ***Métodos:*** *por meio de uma Revisão Narrativa de literatura, realizada nas principais bases de dados* Pubmed, Lilacs, *e* Cochrane Database, *de artigos publicados nos últimos cinco anos, correlacionando polimorfismos genéticos da família citocromo P450 e risco de câncer nas diversas populações mundiais.* ***Resultados:*** *foram encontrados inicialmente 65 artigos, que, após critérios de seleção, tornaram elegíveis 20 artigos do tipo caso-controle em diversas populações mundiais. Os polimorfismos mais estudados foram os das subfamílias CYP1A1 e CYP2E1. Pouco existe sobre as demais subfamílias. A associação entre os polimorfismos encontrados e risco de câncer sofreu um incontável número de variáveis, entre elas, população estudada, métodos de seleção, fatores raciais e diferentes modos de exposição aos carcinógenos, métodos de genotipagem, e nomenclatura dos polimorfismos.* ***Conclusão:*** *até o momento, não existe relação comprovada entre os polimorfismos genéticos da família Citocromo P450 e o carcinoma de células escamosas de cavidade oral, faringe e laringe.*

Descritores: *Sistema enzimático do citocromo P-450. Polimorfismo genético; Neoplasias de cabeça e pescoço.*

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