Absence of history of oral cleft in first-degree relatives of patients with prostate cancer

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Abstract

Objective: To evaluate the occurrence of nonsyndromic cleft lip and/or palate (NSCL/P) in families of patients with prostate cancer (PC). **Study design:** We conducted a case-control study involving a total of 748 individuals, 280 of which had PC, and 468 were free-cancer healthy individuals. The patients answered a questionnaire with basic demographic information and family history of NSCL/P in first-degree relatives. The information collected was stored in a database and analyzed by using the statistical program SPSS® 24.0 *for Windows* (Chicago, IL, USA). In order to determine the association with NSCL/P, chi-square and Fisher's exact test and odds ratio (OR) with its 95% confidence interval (95% CI) for risk magnitude assessment. Values with $p<0.05$ were considered statistically significant.
Results: Of total patients with PC, 2 had a positive history of NSCL/P. In the control group, 7 patients reported family history of NSCL/P (1df chi-square, $p=0.34$; Fisher´s exact test, $p=0.49$). The average age of the cases diagnosed with PC was 71.35±7.70 years, and control group was 64.42±9.67 years.
Conclusion: Despite the limited population, the frequency of NSCL/P was not significantly increased in the first-degree relatives of patients with PC. Studies with larger samples and molecular analyses are needed to better understand the possible relationships in the etiology of cancer and NSCL/P.

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Introduction

Prostate cancer (PC) is one of the most frequent cancers in men, and it is estimated to affect 1,618,000 men, and led to 366,000 deaths globally in 2015 (1). An American estimate published in 2017 showed that prostate, lung and bronchus, and colorectal cancers account for 42% of all cases in men, with prostate cancer alone accounting for almost 1 in 5 new diagnoses. For women, the 3 most common cancers are breast, lung, and colorectum, which collectively represent one-half of all cases; breast cancer alone accounts for 30% all new cancer diagnoses in women (2). In Brazil, 68,220 new cases of PC are estimated for each year in 2018-2019. These values correspond to an estimated risk of 66.12 new cases for every 100 thousand men. PC is the most incident among men in all regions in Brazil (3).

Nonsyndromic cleft lip and/or cleft palate [(NSCL/P); OMIM #119530] is the most common craniofacial birth defect in humans with a global prevalence ranging from 1:500 to 1:2,500 live births (4). In Brazil, the prevalence varies from 0.36 to 1.54 per 1,000 live births (5,6). About 70% of the cases occur as a nonsyndromic form (NSCL/P), and the remaining 30% are associated with Mendelian disorders or chromosomal, teratogenic and sporadic conditions (7). Although there has been marked progress in identifying environmental and genetic risk factors associated with NSCL/P, its etiology in most of the cases remains unclear (4,8). Based on epidemiological features and embryologic timing, NSCL/P are traditionally divided in nonsyndromic cleft lip (NSCL), nonsyndromic cleft lip and palate (NSCLP) and nonsyndromic cleft palate (NSCP) (9).

It has been proposed that cancer and congenital malformations such as NSCL/P may occasionally have a common etiology. The underlying concept is that genes acting in normal development may also have an important role in malignancies (9). A study published in 2015 showed that having an oral cleft increases the risk for self-reported history of cancer in family members, and genetic variants in *DLX1* and *MMP3* are associated with oral cleft regardless of the history of cancer (10). Over the past years, epidemiological studies have assessed the relationship between cancer and NSCL/P in different populations [*Texas, USA* (11), *Southeast Asian* (12), *Denmark* (13), *Pittsburgh, USA* (14), *Latvia* (15), *India* (16), *The Netherlands* (17), *Danish* (18), *Turkey* (19), *Brazil* (20), *France* (21), *Brazil* (8,22), *Poland* (23), *Pakistan* (24), *Brazil* (25)], and the results are controversial.

The finding of an increased risk of NSCL/P in families with cancer case would strengthen the hypothesis that common genetic factors may play a role in both situations. Thus, the aim of this study was to evaluate the frequency of NSCL/P in first-degree families of patients with PC.

Materials and Methods

We conducted a case-control study. All patients with PC (case group; n=280) attended in a reference service in oncology, in Minas Gerais State, Brazil, from June 2016 to December 2017 were evaluated. The following inclusion criteria were applied: having a diagnosis of PC and to be undergoing treatment at the institution. The sampling was performed by convenience, and the groups were matched concerning age. The control group included 468 free-cancer healthy individuals randomly obtained at the general clinics and at the University Hospital. Study participants signed an informed consent and answered in person a structured questionnaire with basic demographic information that included the following data on self-reported for analysis: age, skin color, history of NSCL/P in first-degree relatives (mother, father, siblings and children) through self-identification by illustrative figures.

The information collected was stored in a database and analyzed by using the statistical program SPSS® version 24.0 (*Statistical Package for Social Sciences for Windows*, Inc., Chicago, IL,USA). A descriptive and comparative statistical analysis was initially carried out with baseline characteristics among groups such as age, skin color, and history of NSCL/P (first degree relatives). A binary logistic regression was used for statistical analysis of the color categorical variable. Mann-Whitney's test for unpaired samples was performed to compare the age averages between the groups. In order to determine the association with NSCL/P, chi-square and Fisher's exact test and odds ratio (OR) with its 95% confidence interval (95% CI) for risk magnitude assessment. Values with $p<0.05$ were considered statistically significant.

All subjects enrolled in this study lived in the same geographical area (Northern of the state of Minas Gerais, Brazil). Thus, controls group presented demographic ethnic and sociocultural characteristics similar to the PC group. Written informed consents were obtained, and the study was carried out with approval of the University Human Research Ethics Committee (# 436.750).

Results

The average age of the cases diagnosed with PC was 71.35±7.70 years, and control group was 64.42±9.67 years (p=0,000). The majority of the participants de

clared themselves to be brown or black, both in PC and in free-cancer healthy individuals groups (79.3%, 72.6%, respectively). Black subjects were 1.81 times more likely to have prostate cancer than white subjects, with a statistically significant difference (p=0.02; OR:1.81; CI:1.17-2.80). Nine out of 748 study participants had a positive history of NSCL/P. Among 280 patients with PC, 2 had a

identify approximately 4 or 5 cases of NSCL/P in relatives of patient with PC (280x16/1,000) and 7 or 8 cases among relatives of the controls (468x16/1,000). Thus, in this study NSCL/P frequency was not significantly increased in first-degree relatives of patients with PC.

Discussion

Cancer is a multifactorial disease in which both genetic and environmental factors play a significant role. Preventive plans for decreasing cancer incidence include both the removal of environmental agents known to be carcinogens and the

Table 1. Frequency of prostate cancer (PC) patients with positive and negative history of nonsyndromic cleft lip and/or palate (NSCL/P) in first-degree relatives

Family history of NSCL/P	PC Group n (%)	Control Group n (%)	OR	CI 95%	p-value
Yes	2 (0.7)	7 (1.5)			0.34[a]
			2.11	0.435-10.232	
No	278 (99.3)	461 (98.5)			0.49[b]

[a]Chi-square test; [b]Fisher's exact test

positive family history of NSCL/P. In the control group, 7 patient reported family history of NSCL/P (1df chi-square, p=0.34; Fisher´s exact test, p=0.49) (Table 1).

With this sample size, the frequency of NSCL/P as 1/1,000 live births and the average of the Brazilian family size of 16 individuals (8), we would expect to

identification of cancer susceptibility gene polymorphism or mutations (12). Cancer is a major public health problem in the world. It is currently the second leading cause of death, and approximately 14 million new cancer cases are reported worldwide (26). Prostate cancer is the fourth most common cancer in

both sexes combined and the second most common cancer in men. In 2012, estimates showed approximately 1.1 million new cases of PC, accounting for 15% of the cancers diagnosed in men (26). Regarding mortality, global estimates of the Globocan Project, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), pointed 307,000 deaths in 2012; and the overall mortality rate for the same year was 7.8/100,000, representing 6.6% of the total male cancer mortality (26).

In this research the frequency of NSCL/P was not significantly increased in first-degree relatives of patients with PC. Dietz *et al*. (2012) analyzed the risk of breast cancer in families with NSCL/P, but they were unable to confirm a general increase of breast cancer risk among female subjects in families with clefts (18). Martelli *et al*. (2014) analyzed the risk of NSCL/P in families of women with breast cancer, but they were unable to confirm a general increase in the risk of NSCL/P among families of women with breast cancer (8).

On the other hand, Menezes *et al*. (2009) showed a family history of cancer (colon, brain, leukemia, breast, prostate, skin, lung and liver) more often in relatives of NSCL/P compared to the control group (14). Taioli *et al*. (2010) evaluated the presence of NSCL/P in family members of cancer patients. Among cancer survivors with a family member with NSCL/P, there was an apparent

excess of testicular cancer and melanoma in comparison with the cancer survivors with no family history of NSCL/P (27). Jindal and Vieira (2012) showed a correlation between acute lymphoblastic leukemia and NSCL/P in a population from India. The occurrence of NSCL/P was more frequent in families with acute lymphoblastic leukemia than in families without the diagnosis of this pediatric cancer (16).

Possible mechanisms at the basis of an association between NSCL/P and cancer are shared genetic factors. The first study to characterize possible pleiotropic loci for NSCL/P and cancer using large genomic datasets was published in 2016. Suggestive evidence for a common genetic background was found for NSCL/P and follicular lymphoma at 6p21.33, and for NSCL/P and squamous cell carcinoma of the skin in 20q12 (28).

The hypothesized association between cancer and NSCL/P could be attributed to factors that have been suspected to be at the basis of these associations which are polymorphic variants in genes involved in cell-to-cell adhesion and cell motility (17,21). Study involving mutation analysis in PC cells pointed inactivating homozygous mutations in the *SYNJ2* and *CLPTM1* genes. Disruption of nonsense-mediated mRNA decay (NMD) pathway suggested that both genes carried nonsense mutations in LNCaP cells. The sequence analysis identifies homozygous deletions within mononucleotide repeats in the coding regions of both of these genes (29). Recently, we studied the relationship between breast and gastric cancer and NSCL/P. Our results suggest that polymorphic variants in *AXIN2* and *CDH1* may be associated with NSCL/P and reinforce the putative link between cancer and oral clefts (9). The finding of an increased risk of NSCL/P in families of cancer patients would strengthen the hypothesis that common genetic and epigenetic mechanisms are playing a role in both conditions.

Some limitations should be considered in the present study, including the use of self-reported information and the memory bias associated with the study design (control case), reason to choose the history of NSCL/P only in first degree relatives. The lack of ethnicity pairing may also be considered a potential limitation when taking into account the higher incidence of prostate cancer in black men worldwide. However, some studies consider the risk of prostate cancer to be similar among black and white men in Brazil (30).

Our results are in accordance with a systematic review with meta-analysis which has demonstrated a higher prevalence of prostate cancer in black men compared to Brazilian white or brown men (31). We believe that the complex ethnic mix in the Brazilian population, which includes the contribution of European, African and Native American ancestry, makes this kind of pairing difficult. A study on the genomic ancestry of individuals from different geographic regions of Brazil reported considerable variability in the ancestry of color categories in different regions, most of which are manifested in brown and black individuals. For individuals classified as black, they observed considerable but highly discrepant levels of European descents, ranging from 29.3% to 53.9%, depending on the region (32).

The reduced number of NSCL/P history among first-degree relatives in both groups did not allow a comparative analysis of the mean between them. Finally, the small size and type of sample involving individuals from hospitals may pose a risk of not representing the general population.

Conclusion

Our results conclude that the frequency of NSCL/P was not significantly increased in the first-degree relatives of patients with PC. Studies with larger samples and molecular analyses are needed to better understand the possible relationships in the etiology of cancer and NSCL/P.

Acknowledgments

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