Brazilian Dental Journal (2013) 24(3): 200-203
http://dx.doi.org/10.1590/0103-6440201302191
ISSN 0103-6440

Frequency of Cancer in First-Degree Relatives of Patients with Cleft Lip and/or Palate in the Brazilian Population

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Congenital malformations and cancer may share common etiological factors and the association between nonsyndromic cleft lip and/or palate (NSCL/P) and cancers has been observed in different studies. The objective of this study was to evaluate the frequency of cancer in relatives of patients with NSCL/P. This investigation was a cross-sectional, case-controlled study, evaluating 358 patients with NSCL/P treated at a Referral Center for craniofacial deformities (case group) and 358 patients without craniofacial alterations (control group). Information concerning the gender, age and family history of cancer in first-degree relatives for both groups was obtained. The frequency of cancer was 6.4% (n=46) in the studied population, with 18 subjects in the case group (5%) and 28 (7.8%) in control. In both groups, the most frequently reported cases were those of breast, colorectal, stomach, prostate and uterus cancers, but there was no association between the two groups. There was no association with a family history of cancer among the first-degree relatives (odds ratio=0.62; 95% IC: 0.34 to 1.15), neither when the analysis was made by type of cancer. In conclusion, both epidemiological and genetic studies have suggested common etiological factors for NSCL/P and cancer. However, in this population-based study, no association between cancer and NSCL/P could be confirmed.

Key Words: neoplasms, cleft lip, cleft palate, epidemiology, Brazil.

Introduction

Nonsyndromic cleft lip and/or palate (NSCL/P) (OMIM #119530) accounts for approximately 65% of all malformations of the craniofacial region (1,2). They present an approximate incidence of 1 case per 700 live births, varying according to geographic location, ethnics and socioeconomic status of the studied population (3). Its pathogenesis, although not fully understood, involves complex molecular events that occur during embryogenesis, with the participation of multiple genes and environmental factors (4,5).

Cancer is a multi-factorial disease in which both genetic and environmental factors play significant roles. Preventive plans for decreasing cancer incidence include both the removal of environmental agents known to be carcinogens and the identification of the cancer susceptibility gene polymorphism or mutations thereof (6).

Congenital malformations and cancer may share common etiological factors (7). Co-occurrences of malformations and cancers have been seen in children as the result of both genetic and environmental causes (8). In the last few years, epidemiological studies assessed the relationship between cancer and NSCL/P in different populations [Texas, USA, Steinwachs et al., (9); Pittsburgh, USA, Menezes et al., (1); Taioli et al., (10); Latvia, Vieira et al., (11)]. However, others have failed to find an association between NSCL/P and cancer (12). Thus, the objective of this study was to evaluate the frequency of cancer among relatives of patients with NSCL/P.

Material and Methods

This was a case-control cross-sectional study to evaluate the familial occurrence of cancer in first-degree relatives of patients with NSCL/P. The sampling was performed by convenience and the groups were matched concerning gender and age. The case group consisted of 358 patients with NSCL/P, all undergoing surgical rehabilitation and treated at the Reference Center for the Rehabilitation of Craniofacial Anomalies, Bauru, SP, Brazil. Patients with a history of other congenital anomalies or other genetic diseases were excluded from this group. The control group included 358 individuals seen at other clinics of the Center, without a personal or a family history of craniofacial anomalies or other congenital anomalies, and no history of consanguinity.

The clefts were categorized into 3 types, with the incisive foramen as reference (13): (a) cleft lip: includes complete or incomplete clefts pre foramen, uni- or bilateral; (b) cleft lip and palate: includes uni- or bilateral transforamen clefts and pre- or post foramen clefts and (c) cleft palate: includes all post foramen clefts, complete or incomplete. The patients were evaluated by professionals with a wide

experience of oral cleft symptoms.

Study participants signed an informed consent and answered a questionnaire that included the following data for analysis: age, gender, history of congenital anomalies and/or CL/P, history of consanguinity and cancer. The information collected was stored in a database and analyzed using the statistical program SPSS® version 18.0 (Statistical Package for Social Sciences for Windows, Inc., Chicago, IL, USA). Data were analyzed with descriptive statistics and binary logistic regression. The relative risk was only used for a family history of cancer to estimate odds ratios (OR) and a 95% confidence interval. To determine the association with cancers, chi-square and Fisher's Exact Test, as well as the descriptive statistics were used. It was considered an alpha of 0.05. The study was approved by the institutional Ethics Committee (Process #259/2010).

Results

Evaluating the distribution by gender and age, there was proportionality between the case and control groups,

Table 1. Distribution of patients with cleft lip and/or palate and controls by gender, age and associations with a family history of cancer in first-degree relatives

Variable	Case		Control		Total		x^2	OR	CI 95%		p
	n	%	n	%	n	%					
Gender											
Male	199	55.6	172	48.0	371	51.8	4.08[a]	-	-	-	0.052
Female	159	49.4	186	52.0	345	48.2					
Age (years)											
<20	253	70.7	249	69.6	502	70.1	6.52[a]	-	-	-	0.089
20 to 39	78	21.8	66	18.4	144	20.1					
40 to 59	26	7.3	37	10.3	63	8.8					
>59	1	0.3	6	1.7	7	1					
Family cancer history											
Yes	18	5.0	28	7.8	46	6.4	2.32[a]	0.62	0.34	1.15	0.127
No	340	95	330	92.2	670	93.6					
Breast											
Yes	3	0.8	6	1.7	9	1.3	1.01[a]	-	1.12	1.99	0.314
No	355	99.2	352	98.3	707	98.7					
Colorectal											
Yes	4	1.1	6	1.7	10	1.4	0.40[a]	-	0.18	2.36	0.524
No	354	98.9	352	98.3	706	98.6					
Stomach											
Yes	2	0.6	4	1.1	6	0.8	0.67[a]	-	0.90	2.73	0.412
No	356	99.4	354	98.9	710	99.2					
Prostate											
Yes	1	0.3	2	0.6	3	0.4	0.34[a]	-	0.04	5.52	0.563
No	357	99.7	356	99.4	713	99.6					
Uterus											
Yes	4	1.1	3	0.8	7	1	0.14[a]	-	0.30	6.02	0.704
No	354	98.9	355	99.2	709	99					
Total	358	100	358	100	716	100					

[a]Fisher's Exact test. OD: Odds ratio. CI: Confidence interval.

predominantly male (51.8% n=371), with 70.1% (n=502) subjects aged less than 20 years, in the studied population (Table 1). Considering the mixed nature of the Brazilian population, the ethnic distribution between cases and controls was not used for matching. The family history of CL/P in the case group was 43.9% (n=157). As to the type of cleft in the case group, 55% (n=197) were of the cleft lip and palate type; 25.1% (n=90) were of cleft lip type; 18.4% (n=66) were of cleft palate and only 1.4% (n=5) were uncommon clefts.

The frequency of cancer in first-degree relatives was only 6.4% (n=46) in the studied population, with 18 subjects in the case group (5.0%) and 28 (7.8%) in the control group. In both groups, the most frequently reported were colorectal 1.4% (n=10), breast 1.3% (n=9), uterus 1.0% (n=7), stomach 0.8% (n=6) and prostate 0.4% (n=3) cancers. For a family history of cancer in the first grade, there was no significant correlation (p=0.1; OR=0.60; 95% CI: 0.32 to 1.10), neither when the analysis was made by the type of cancer (Table 1).

Discussion

This study assessed the prevalence of cancer in family members of NSCL/P patients in the Brazilian population. The most frequently reported cancers by both groups were colorectal, breast, uterus and stomach. There were no gender differences. The frequency of cancer in first-degree relatives was 6.5% of the population studied, with 4.9% subjects in the case group and 8% in the control group, but there was no association.

In a retrospective study of NSCL/P, it was observed that 65.1% of the subjects were male and 34.8% female (14). In the results of this study, it was found that they were mostly males. In both studies, the sample was taken from a single Reference Center for Treatment and Rehabilitation of Craniofacial Anomalies, which justifies the comparison of results. Another study, evaluating Brazilian children with NSCL/P, showed prevalence of NSCL/P for males compared to females (15). In another study, the prevalence of NSCL/P among cancer survivors was higher in the case group when compared to the control group (6). The relationship between NSCL/P and cancer has been reported by several studies that identified specific genes involved in the pathogenesis of NSCL/P and that they could be part in the carcinogenesis of certain tumours. These genes serve as important determinants of risk for the occurrence of cancer (1,6). Gene modulators of fibroblast growth factor (FGF) have been associated with several cancers and it is well known that this gene participates in about 3% of cases of NSCL/P (16,17). Mutations in the inhibitory proteins (AXIN2) were also related to an increased susceptibility of colorectal cancer (18). At last, mutations in the epithelial adhesion molecule of cadherin were observed in two families, in which two or more members had hereditary diffuse gastric cancer and oral clefts (19). Mutations in the epithelial adhesion molecule, a cadherin, expressed in various types of epithelial cells, were also found in hereditary diffuse gastric cancer and the oral cleft (19). Thus, these findings suggested that common etiological mechanisms are involved in the genesis of NSCL/P and cancer (8,18,20).

Regarding most cancer-related types, it was observed in the case group an apparent excess of melanoma and testicular cancer among survivors of cancer with a CL/P family member, when compared with survivors with no family history of CL/P (6). In the present study, despite the greater frequency of colorectal cancers, breast and uterus in the case group, there was no association with a family history of cancer in first-degree relatives. Different cancers have been linked to NSCL/P and there was a higher risk of cancer in relatives with children born with oral clefts, especially for breast, primary tumors of the brain and lung cancers (21,22). Quite recently has been observed the association of oral cancer with oral clefts (23). However, this association was not confirmed in another study correlating the risk of breast cancer in families with NSCL/P (12).

In a study conducted in the USA, families with NSCL/P and controls with no history of cancer were evaluated. It also carried out molecular studies on genes in which mutations were known to be independently associated with cancer and craniofacial anomalies (10). The authors also found a high rate of transmission of the inhibitory protein of AXIS (AXIN2) in proband with NSCL/P. It may be concluded that families that present NSCL/P may have a greater probability of cancer, notably colon cancer, since this gene, when altered, leads to susceptibility of this type of malignancy (1,6). Population studies confirmed this association with breast, primary brain and lung cancers in individuals born with oral clefts (1,10,24). Recently was reported a significant association between NSCL/P and the hereditary diffuse gastric cancer syndrome. The authors highlight the importance of the historical aspects of NSCL/P to suspect occurrence of gastric malignancy (25).

The results of this study should by no means be considered conclusive and should be interpreted with caution because of the small sample size, but it deserves further investigation. Further studies should be conducted to better understand this possible correlation and the evaluation of a specific type of tumor may facilitate the understanding of the genes involved in the etiology of orofacial clefting.

In conclusion, this is the first study to be conducted for this purpose in a Brazilian population and the results do not confirm the association between NSCL/P and

cancer. This preliminary finding should be confirmed by further epidemiological studies on large cohorts. Both epidemiological and genetic studies suggested common etiological factors for NSCL/P and cancer. However, the results of this study showed no association between NSCL/P and cancer.

Resumo

Malformações congênitas e o câncer podem compartilhar fatores etiológicos comuns e a associação entre fissura labial e/ou palatina não sindrômica (FL/PNS) com o câncer tem sido observada em diferentes estudos. O objetivo foi avaliar a frequência de câncer em parentes de pacientes com FL/PNS. Conduziu-se um estudo transversal, do tipo caso-controle, avaliando 358 pacientes com FL/PNS, assistidos em um centro de referência para tratamento de deformidades craniofaciais (grupo caso) e 358 pacientes sem alterações congênitas (grupo controle). Foram obtidas informações a respeito de gênero, idade e histórico familiar de câncer em parentes de primeiro grau para ambos os grupos. A frequência de câncer na população estudada foi de 6,4% (n=46), com 18 históricos no grupo caso (5%) e 28 (7,8%) no grupo controle. Em ambos os grupos, os principais cânceres relatados foram de mama, colorretal, estômago, próstata e útero, mas não houve associação quando comparados os dois grupos. Também não houve associação de histórico familiar de câncer em parentes de primeiro grau (*odds ratio*=0,62; 95% IC: 0,34 a 1,15), nem quando a análise foi feita pelo tipo de câncer. Estudos epidemiológicos e genéticos têm sugerido fatores etiológicos comuns entre FL/PNS e câncer. Contudo, na população do presente estudo, não se verificou a associação entre câncer e FL/PNS.

Acknowledgments

This work was supported by grants from The Minas Gerais State Research Foundation (FAPEMIG), Brazil, and from The National Council for Scientific and Technological Development (CNPq), Brazil (HMJ and MSOS).

References

1. Menezes R, Marazita ML, McHenry TG, Vieira AR. AXIS inhibition protein 2, orofacial clefts and a family history of cancer. J Am Dent Assoc 2009;140:80-84.
2. Paranaíba LM, Miranda RT, Ribeiro LA, Barros LM, Martelli Júnior H. Frequency of congenital craniofacial malformations in a Brazilian Reference Center. Rev Bras Epidemiol 2011;14:151-160.
3. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. Lancet 2009;374:1773-1785.
4. Jugessur A, Farlie PG, Kilpatrick N. The genetics of isolated orofacial clefts: from genotypes to subphenotypes. Oral Dis 2009;15:437-453.
5. Bufalino A, Paranaíba LMR, Aquino SN, Martelli-Junior H, Swerts MSO, Colleta RD. Maternal polymorphisms in folic acid metabolic genes are associated with nonsyndromic cleft lip and/or palate in the Brazilian population. Birth Defects Res A Clin Mol Teratol 2010;88:775-780.
6. Zhu JL, Basso O, Hasle H, Winther JF, Olsen JH, Olsen J. Do parents of children with congenital malformations have a higher cancer risk? A nationwide study in Denmark. Br J Cancer 2002;87:524-528.
7. Friedman J. Genetics and epidemiology, congenital anomalies and cancer. Am J Hum Genetic 1997;60:469-473.
8. Narod SA, Hawkins MM, Robertson CM, Stiller CA. Congenital anomalies and childhood cancer in Great Britain. Am J Hum Genet 1997;60:474-485.
9. Steinwachs E, Amos C, Johnston D, Mulliken J, Hecht J. Non syndromic cleft lip and palate is not associated with cancer or other birth defects. Am J Hum Genet 2000;90:17-24.
10. Taioli E, Ragin C, Robertson L, Linkov F, Thurman NE, Vieira AR. Cleft lip and palate in family members of cancer survivors. Cancer Invest 2010;28:958-962.
11. Vieira AR, Khaliq S, Lace B. Risk of cancer in relatives of children born with isolated cleft lip and palate. Am J Med Genet 2012;158A:1503-1504.
12. Dietz A, Pedersen DA, Jacobsen R, Wehby GL, Murray JC, Christensen K. Risk of breast cancer in families with cleft lip and palate. Ann Epidemiol 2011;22:37-42.
13. Spina V, Psillakis JM, Lapa FS, Ferreira MC. Classification of cleft lip and cleft palate. Suggested changes. Rev Hosp Clin Fac Med São Paulo 1972;27:5-6.
14. Paranaíba LMR, Almeida H, Barros LM, Martelli DRB, Orsi-Júnior JD, Martelli Júnior H. Current surgical techniques for cleft lip-palate in Minas Gerais, Brazil. Braz J Otorhinolaryngol 2009;75:839-843.
15. Martelli-Junior H, Porto LCVP, Barbosa DRB, Bonan PRF, Freitas AB, Coletta RD. Prevalence of nonsyndromic oral clefts in a reference hospital in Minas Gerais State between 2000-2005. Braz Oral Res 2007;21:314-317.
16. Jung JH, Shin KIF, Park JG. Mutations in fibroblast growth factor receptor 2 and fibroblast growth factor receptor 3 genes associated with human gastric and colorectal cancers. Cancer Res 2001;61:3541-3543.
17. Riley BM, Mansilla MA, Ma J, Daack-Hirsch S, Maher BS, Raffensperger LM. Impaired FGF signalling contributes to cleft lip and palate. Proc Natl Acad Sci U S A 2007;104:4512-4517.
18. Lammi L, Arte S, Somer M, Järvinen H, Lahermo P, Thesleff I. Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. Am J Hum Genet 2004;74:1043-1050.
19. Frebourg T, Oliveira C, Hochain P, Karam R, Manouvrier S, Graziadio C. Cleft lip/palate and CDHI/E-cadherin mutations in families with hereditary diffuse gastric cancer. J Med Genet 2006;43:138-142.
20. Windham GC, Bjerkedal T, Langmark F. A population-based study of cancer incidence in twins and in children with congenital malformations or low birth weight, Norway, 1967-1980. Am J Epidemiol 1985;121:49-56.
21. Nishi M, Miyake H, Takeda T, Hatae Y. Congenital malformations and childhood cancer. Med Pediatr Oncol 2000;34:250-254.
22. Bille C, Winther JF, Bautz A, Murray JC. Cancer Risk in Persons with Oral Cleft - A Population-based Study of 8,093 Cases. Am J Epidemiol 2005;161:1047-1052.
23. Andrade Filho PA, Letra A, Cramer A, Prasad JL, Garlet GP, Vieira AR. Insights from studies with oral clefts suggest associations between WNT-pathway genes and risk of oral cancer. J Dent Res 2011;90:740-746.
24. Mili F, Khoury MJ, Flanders WD, Greenberg RS. Risk of childhood cancer for infants with birth defects, part I: a record-linkage study, Atlanta, Georgia, 1968-1988. Am J Epidemiol 1993;137:629-638.
25. Benusiglio PR, Caron O, Consolino E, Duvillard P, Coulet F, Blayau M, et al.. Cleft lip, cleft palate, hereditary diffuse gastric cancer and germline mutations in CDH1. Int J Cancer 2013;132:2470.

Received April 8, 2013
Accepted May 17, 2013