

Risk of leukemia in first degree relatives of patients with nonsyndromic cleft lip and palate

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Abstract: The aim of this study was to determine the frequency of leukemia in parents of patients with nonsyndromic cleft lip and/or cleft palate (NSCL/P). This case-control study evaluated first-degree family members of 358 patients with NSCL/P and 1,432 subjects without craniofacial alterations or syndromes. Statistical analysis was carried out using Fisher's test. From the 358 subjects with NSCL/P, 3 first-degree parents had history of leukemia, while 2 out of 1,432 subjects from the unaffected group had a family history of leukemia. The frequency of positive family history of leukemia was not significantly increased in first-degree relatives of patients with NSCL/P.

Keywords: Leukemia; Cleft Lip; Cleft Palate; Epidemiology; Neoplasms.

Introduction

Cancer and birth defects may share factors that influence risk, being of genetic and/or environmental origin.¹ Furthermore, a malformation may involve physiological changes or changes in lifestyle that might in turn affect cancer risk.² 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,³ depending on ancestry, geographic residential location, maternal age and prenatal exposures, and socioeconomic status.⁴

In recent years, epidemiological evidence has shown the association of cancer with NSCL/P in several populational studies.^{5,6,7,8} It has been proposed that cancer and congenital malformations such as NSCL/P may occasionally have a common etiology. The underlying concept is that the same genes can act in normal and also malignant development.^{1,7} The association between NSCL/P and leukemia remains unclear and there are no studies evaluating this association in Brazil.

The aim of the current study was to determine the frequency of leukemia in parents of subjects with NSCL/P in a Brazilian population.

Methodology

After proper local and Center for Rehabilitation of Craniofacial Anomalies, Minas Gerais State, Brazil, Institutional Review Board approval, we conducted a case-control study which was approved by the Ethics Committee on Institutional Research #259/2009, for the

time period of 2010-2012, evaluating 358 patients with NSCL/P, seen at a referral center for the treatment of craniofacial deformities, and 1,432 patients without craniofacial alterations or any syndrome (control group), identified randomly from the General Clinics of the Dental School at the *Universidade de Alfenas*, Minas Gerais State, Brazil. We obtained information concerning the gender, age and family history of leukemia in first-degree relatives (mother, father and siblings) for both groups. No participants declined to respond to the questionnaire. The t-test assessed whether the means of age for the two groups were statistically different from each other. Statistical analyses were also carried out using Fisher's exact test (expected frequency values fell below 5) and the odds ratio (OR) with its 95% confidence interval (95%CI) to estimate the magnitude of the risk. Values with $p < 0.05$ were considered statistically significant.

Results

The average age of the cases diagnosed with NSCL/P was 13.57 years. The average age of the control group was 14.22 years. There was no difference of age distribution between affected and unaffected women ($p = 0.55$). From the 358 subjects with NSCL/P, 3 first-degree relatives had a positive family history of leukemia, while 2 of the 1,432 subjects from the unaffected group had a positive family history of leukemia (Table 1). The Fisher exact test showed $p = 0.057$ and OR = 6.04 (95%CI = 0.69 - 72.49). Thus, in the present study the frequency of leukemia was not significantly increased in the first-degree relatives of patients with NSCL/P.

Discussion

In the present study the frequency of positive family history of leukemia was not significantly increased in first-degree relatives of patients with NSCL/P. Similarly, the risk of breast cancer in families with patients affected by NSCL/P was not increased.⁹

On the other hand, a study 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. Recently, we evaluated the risk of NSCL/P in relatives of women with breast cancer in the Brazilian population and found no association between the two conditions.^{5,10}

Another study¹¹ showed that 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. These preliminary results suggest a common etiologic background for cancer and NSCL/P.

A recent study assessed the frequency of NSCL/P in families of children diagnosed with leukemia. The results of this study provide suggestive evidence that families with children diagnosed with leukemia report a family history of NSCL/P more often than families without cases of pediatric cancer.⁷

The association between cancer and NSCL/P could be attributable to both genetic factors and/or familial environmental factors that are both teratogenic and carcinogenic.⁹ Another possibility could be that having a cleft leads to social marginalization and changes in lifestyle that may be predisposed to an individual and their family to cancer (*i.e.* smoking, high alcohol use, etc.).¹²

Conclusion

To investigate the relationship between malformations and malignancies is important, as it is speculated that they might have common causes. In the present study the frequency of a positive family history of leukemia was not significantly increased in first-degree relatives of patients with NSCL/P. The main limitation of our study was the sample size. Studies with larger samples and molecular analyses are needed for a better understanding between NSCL/P and leukemia.

Table 1. Risk of leukemia in first-degree relatives of patients with nonsyndromic cleft lip and palate (NSCL/P)

Groups	N° of subjects	Positive history of leukemia	OR (95%CI)/p value
Control	1,432	2	Reference
NSCL/P	358	3	6.04 (0.69-72.49)/0.057

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