



## Non-syndromic oral clefts and risk of cancer: a systematic review

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### Abstract

**Objective:** To discuss the risk of cancer among relatives of individuals with cleft lip and palate (CL/P), as well as the risk of CL/P among relatives of individuals with cancer, since studies currently published have suggested an increased risk of cancer among relatives of individuals with clefts.

**Methods:** A systematic literature review was carried out in accordance with the Cochrane Collaboration Group protocol, including literature search strategy, selection of papers through the inclusion and exclusion criteria, data extraction and quality assessment. PubMed, Scopus and ISI - Web of Science databases were systematically searched using the following search strings: "cleft lip and palate" AND "cancer," "oral clefts" AND "cancer" and "orofacial clefts" AND "cancer."

**Results:** From 653 studies accessed, eight comprised the final sample: six investigating CL/P index cases and their family history of cancer and two investigating individuals with cancer and their family history for CL/P. The sample sizes were not homogeneous. Oral clefts, the type of cancer and the degree of kinship family were not categorized in all studies. Leukemia, breast cancer and colon cancer were the most cited types, even as first- and second-degree relatives.

**Conclusion:** An increased risk of cancer among relatives of individuals with clefts could not be entirely confirmed. However, studies with this specific purpose suggest that first- and second-degree relatives of individuals with cleft have some types of cancer more often than unexposed families, highlighting that future studies should expand their samples to investigate possible common molecular mechanisms that allow relating oral clefts and cancer.

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### Introduction

Orofacial malformations are the most common form of congenital anomalies in the world [1]. Among the orofacial alterations, the most prevalent is the cleft lip with or without cleft palate (CL/P) [2-5], which may occur more commonly in an isolated and non-syndromic form as a specific phenotype or, more rarely, composing several associations or syndromes [6,7]. Embryologically, clefts result from primary fusion defects of the craniofacial processes that form the primary and secondary palate in the first intrauterine trimester [8].

The incidence of CL/P varies according to geographical location, racial and ethnic

groups, environmental exposures, and socioeconomic status, affecting approximately 1/700 live births with wide variability across geographic origin. Generally, Asian and Amerindian populations have the highest reported birth prevalence rates, often as high as 1/500, European-derived populations have intermediate prevalence rates at about 1/1000, and African-derived populations have the lowest prevalence rates at about 1/2500 [5,9,10].

According to Vieira (2008) [7], the last decade was crucial to elucidate issues concerning the etiology of CL/P when compared to other defects observed at birth. As this is a multifactorial trait, environmental risk factors such as smoking, alcohol, parental age,

medications, birth order, interpregnancy interval, and folic acid deficiency are listed as modifiers, and risk factor identification is the first step to better understanding and to prevent such craniofacial changes [7,11,12].

However, current knowledge about the causes of CL/P points particularly towards genetic risk factors, and the study of the pathogenesis of CL/P has provided ample opportunities to identify candidate genes for this disorder and even link them to the occurrence of cancer in relatives of individuals born with CL/P, or even in these individuals themselves when at an adult age, supporting the hypothesis that common genetic factors may be present in both conditions [13]. Although other genes that have



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not been explored yet can be involved in the both conditions, three genes are suspected to underlie such associations: FGF - fibroblast signaling pathway, CDH1 - epithelial cadherin and AXIN2 - AXIS inhibition protein 2 [14]. Colorectal and breast cancer are the most associated with mutations of these genes [2]. Thus, given the growing number of studies published currently suggesting a common etiology for CL/P and cancer and increased risk of cancer among relatives of cleft individuals [2,5,13-18], the current study aimed to discuss the issue through a systematic literature review in order to provide additional evidence of these genetic risks, which will aid in the development of strategies that target more aggressive screening programs and preventive chemical treatments.

## Methods

The present review was carried out in accordance with the Cochrane Collaboration Group protocol for systematic reviews [19], including a literature search strategy, selection of papers through the inclusion and exclusion criteria, data extraction, and quality assessment. Meta-analysis was not possible since selected studies did not observe the same variables, methods, participants, and outcomes, which prevented comparisons.

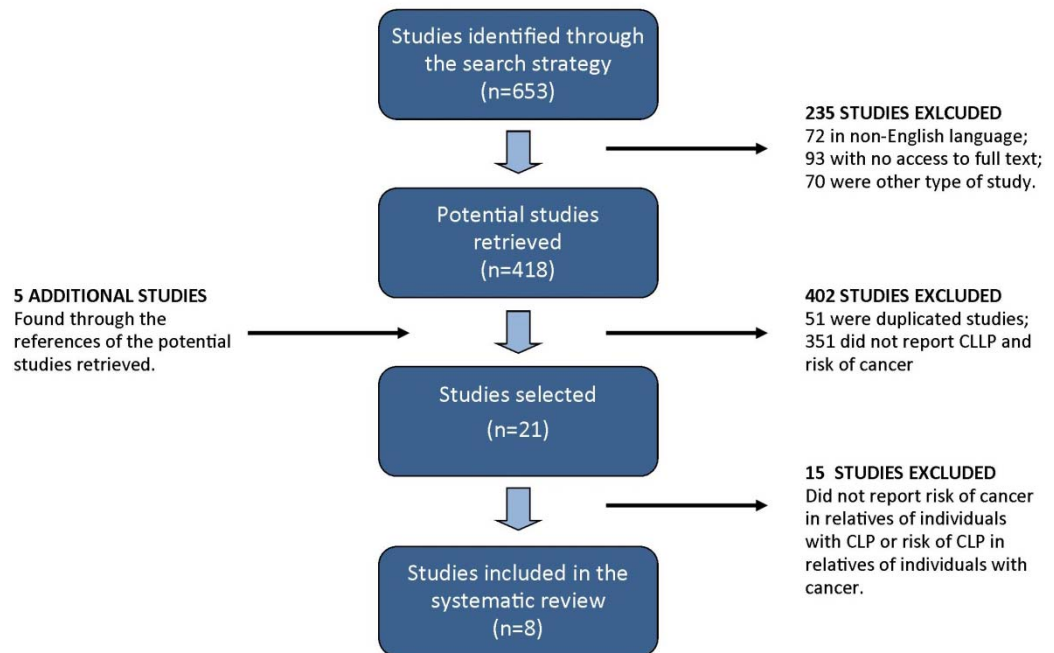
### Literature search strategy

Our review was performed in February 2013 in order to obtain literature regarding cleft lip and/or palate and family history of cancer. PubMed, Scopus, and ISI - Web of Science databases were systematically searched using two basic approaches: the search strings "cleft lip and palate" AND "cancer," "oral clefts" AND "cancer," and "orofacial clefts" AND "cancer" for studies published up to that time.

### Selection of papers through the inclusion and exclusion criteria

The selection of papers is diagrammatically explained in Figure 1. Of the 653 studies originally found through the literature search strategy, 235 studies were excluded (in non-English language, with no full text available, and non-cross-sectional, prevalence, cohort, or case-control design), remaining with 418 papers. Additional studies were found through the references of the potential studies retrieved. Then, all studies involving oral clefts (associated or not with craniofacial syndromes or any anomalies) and cancer were selected. Afterwards, only studies presenting information regarding

**Figure 1:** Flowchart of the studies included and excluded



risk of cancer in relatives of individuals born with non-syndromic oral clefts were included in the present study, as well as articles regarding the frequency of non-syndromic oral clefts among relatives of individuals diagnosed with cancer.

The following specific inclusion criteria were used to identify relevant articles: (1) Index cases with non-syndromic cleft lip and/or palate, whose relatives were investigated for any type of cancer; (2) Index cases with any type of cancer, whose relatives were investigated for non-syndromic cleft lip and/or palate; (3) Index cases compared to healthy controls for risk assessment; (4) The degree of relationship between index cases and investigated family members is investigated in the study. All studies that included individuals with cleft lip and/or palate associated with other abnormalities, having syndromic causes or regarding Mendelian traits were excluded. Thus, eight studies were selected. (Figure 1)

### Data extraction

Title and abstract screening was performed by two reviewers (DAVP and HMJ) who worked independently to identify potentially relevant papers for which full text publications were retrieved. If, however, there was any discrepancy of opinion, the reviewers reexamined the paper together and arrived at a joint final decision. A standardized form was used to extract information, such as author and year of publication of the paper, origin of participants, study design,

sample size, type of oral clefts, type of cancer, degree of kinship of family members and the association between non-syndromic oral clefts and cancer.

### Quality assessment

STROBE methodology (Strengthening the Reporting of Observational Studies in Epidemiology) [20], considered the guideline for an appropriate assessment of observational studies, was used to perform the quality assessment of the studies selected. The specific STROBE items considered were inclusion and exclusion criteria, assessment of exposure and outcome, statistical methods, confounders, bias, and report limitation.

### Results

The initial database search identified 653 citations published between 1980 and 2013. After screening, 235 studies were excluded (72 in non-English language, 93 with no full text available, and 70 which type of study was other than those listed in the methodology), remaining with 418 papers.

A second screening was performed on the remaining papers and other studies were excluded, this time for the following reasons: 51 articles in duplicity (found in more than one of the databases) and 351 articles that did not report non-syndromic cleft lip and/or palate and risk of cancer. In addition, five papers listed in the references of the selected ones were included, resulting in 21 papers for the final screening.

**Table 1:** Main characteristics of the eight selected papers.

First author, year [reference]	Country of study	Study design	Exposure	Sample size (case/population)	Cleft Classification	Type of cancer	Statistical test	Kinship with index cases	Outcome
Jindal, 2012	India	Case-control	Individuals diagnosed with cancer	142 (85/57)	CL/P	Leukemia	X2 and Fischer exact	First-degree	Increased risk
Taioli, 2010	United States	Case-control	Cancer survivors	338 (168/170)	All	Unspecified	Logistic regression	First/second-degree	Increased risk
Yildirim, 2012	Turkey	Case-control	Cleft individuals	319 (158/161)	All	Unspecified	Logistic regression	First-degree	Increased risk
Menezes, 2009	United States	Case-control	Cleft individuals	168 (75/93)	Unspecified	Unspecified	X2 and Fischer exact	Not reported	Increased risk
Zhu, 2002	Denmark	Case-control	Cleft individuals	41206 (45/41161)	Unspecified	Unspecified	Odds Ratio	First Degree	Increased risk
Vieira, 2012	Latvia	Cross-sectional	Cleft individuals	89	Unspecified	Unspecified	Risk Ratio	First/second/third-degree	Increased risk
Dietz, 2012	Denmark	Retrospective cohort	Cleft individuals	1809	All	Breast Cancer	Cox regression	First-degree	No association when all non-syndromic CL/P were analyzed together
Steinwachs, 2000	United States	Cross-sectional	Cleft individuals	196	CL/P and CL	Unspecified	Odds Ratio	First/second-degree	No increased risk

The full text of these papers was read and 13 were there after excluded for not reporting risk of cancer in relatives of individuals with non-syndromic cleft lip and/or palate, as well as for not reporting the frequency of non-syndromic cleft lip and/or palate in relatives of individuals diagnosed with cancer. Thus, eight papers were selected for the systematic review.

The characteristics of the eight selected papers are presented in Table 1. Three used a case-control design, two used a cross-sectional/prevalence design and one was a retrospective cohort study. Those reporting frequency of non-syndromic cleft lip and/or palate in relatives of individuals diagnosed with cancer also used a case-control design.

The sample sizes and the population investigated varied considerably amongst the studies, not being homogeneous. From those investigating risk of cancer in relatives of individuals with non-syndromic cleft lip and/or palate, two were conducted in the United States, two in Denmark, one in Turkey, and one in Latvia. Regarding those reporting frequency of non-syndromic cleft lip and/or palate in relatives of individuals diagnosed with cancer, one was conducted in the United States and one in India (Table 1).

Most of studies investigated all types of oral clefts. Type of cancer and the degree were not categorized in all studies of kinship in the family. Despite this, leukemia, testicular cancer, melanoma, colon-rectal cancer, lymphoma, and breast cancer were the most cited types of cancer (Table 2) in both first- and second-degree relatives (Table 1).

The relationship between oral clefts and cancer within the studies was tested using chi-square and Fisher's Exact tests [14, 18], Logistic regression [2, 17], Odds ratio [15, 21], Risk ratio [13], and Cox regression [5] (Table 1).

All eight studies were submitted to quality assessment using STROBE guidelines. Inclusion and exclusion criteria were described in all of them (Table 3). The outcomes of two studies provide suggestive evidence that families with individuals diagnosed with some types of cancer report family history of cleft lip and/or palate more frequently than families without cases

**Table 2:** Most cited types of cancer among relatives of cleft individuals and cancer index cases.

First author, year [reference]	Most commonly found types of cancer	Types of cancer with increased risk at index cases relatives
Jindal, 2012	Leukemia*	Leukemia
Taioli, 2010	Breast, colon-rectal, melanoma, testicular	Testicular, melanoma, colon-rectal
Yildirim, 2012	Unspecified	Unspecified
Menezes, 2009	Unspecified	Unspecified
Zhu, 2002	Breast, melanoma of skin, testis, cervix uteri, brain and nervous system	Lymphoma, Leukemia
Vieira, 2012	Unspecified	Unspecified
Dietz, 2012	Breast*	Breast
Steinwachs, 2000	Breast, lung, leukemia, colon, uterine.	None found

\*The study specifically searched for this type of cancer only.

**Table 3:** Inclusion and exclusion criteria among the eight selected papers.

First author, year [reference]	Inclusion Criteria	Exclusion Criteria
Jindal, 2012	All subjects were children being cared for at the General Hospital of Chandigarh, India. Cases were identified from the Pediatric Leukemia Clinic and controls were identified randomly from the Allergy/Immunology clinic.	Children with lymphoma were excluded from the case group and the ones with positive history for cancer, from the control group.
Taioli, 2010	Case group was composed of patients who were treated for cancer in the past, who were considered in remission for at least six months, and who were scheduled for an appointment for a routine checkup. Control group was composed by healthy people from the general population who were 18 years of age or older.	Not reported.
Yildirim, 2012	All subjects were patients at the Department of Pedodontics clinic, Istanbul University, Turkey. Case group was composed of individuals born with any type of CL/P and controls were individuals unrelated to them. Case group members' first-degree relatives were evaluated, also.	Case and control siblings were excluded.
Menezes, 2009	All subjects were from white ancestry families from Pittsburgh. Cases were recruited from a registry maintained by the Cleft-Craniofacial Center, Children's Hospital of Pittsburgh of UPMC.	Not reported.
Zhu, 2002	Subjects were identified from the Denmark's Central Population Registry by their kinship with patients diagnosed with cancer and registered at the Cancer Registry. They also ought to have been born between 1977 and 1995 in Denmark to mothers with a Danish citizenship.	Patients whose parents had other children before 1977, who were diagnosed with patent ductus arteriosus, undescended testis and hip dislocation.
Vieira, 2012	Subjects were picked from the Riga Cleft Lip and Palate Centre Registry from the time period of 1980-2009.	Not reported.
Dietz, 2012	Subjects were individuals with non-syndromic CL/P registered at the Danish Facial Cleft Register.	Individuals born after 1975 were excluded.
Steinwachs, 2000	Subjects ought to have been diagnosed with cleft lip with or without cleft palate and have no known syndromal cause for the cleft.	Not reported.

of cancer [2,18]. From studies investigating cancer in relatives of individuals with oral clefts, only two suggest that the first- and second-degree relatives of the individuals with clefts are not at an increased risk for cancer [5,21]. All studies defined the exposure variables (Table 1). Although all studies had described potential bias/limitations, only three properly reported identification of bias/limitations (Table 1). Although all studies had described potential bias/limitations, only three properly reported identification of bias/limitations (Table 4).

## DISCUSSION

This systematic review assessed available studies suggesting a common etiology for non-syndromic oral clefts and cancer and increased risk of cancer among relatives of cleft individuals, as well as increased risk of non-syndromic oral clefts among relatives of individuals diagnosed with cancer, thereby providing additional evidence of these genetic risks, which could aid in the development of strategies that target more ag-

gressive screening programs and preventive chemical treatments.

Our original intention was to integrate the results of included studies through a meta-analysis, however, given the differences in variables, methods, participants and outcomes among the studies, the most suitable and responsible was to address the issue through a systematic review.

We demonstrated that there is a large amount of literature distinguishing non-syndromic cleft lip and palate from those cases of clefts associated with other abnormalities, syndromes, or Mendelian traits. Our findings also demonstrated that the studies published agree that non-syndromic oral clefts are one of the most common human malformations, with an average prevalence of 1 per 700 or 1,000 live births [2,4,5,7,16,17,21-26], as well as that its incidence varies according to gender: 2:1 being the ratio of males to females for cleft lip and palate and 1:2 the approximate ratio of male to female for isolated cleft palate [1,10,16, 26,27].

Other common information between the studies is the fact that unilateral clefts are more common than bilateral clefts, and of the unilateral cases of non-syndromic cleft lip and palate, left-sided cleft lips occur more frequently than right-sided cleft lips [4,5,21,23,28,29]. Many studies have also demonstrated that genetic factors may play a role in the cause of non-syndromic oral clefts in addition to certain environmental and/or stochastic factors, meaning that this malformation is a multifactorial trait [2,21,22,26,30,31]. Similarly, studies have shown that cleft lip, with or without cleft palate, is entirely different from isolated cleft palate in both embryological and pathogenetic standpoints [32,33].

Likewise, many of the studies report relationships between non-syndromic oral clefts and cancer or childhood cancer [14,18,25,34-41]. Nonetheless, the studies that presented information regarding risk of cancer in relatives of individuals born with non-syndromic oral clefts or regarding the frequency of non-syndromic oral clefts



among relatives of individuals diagnosed with cancer, besides being scarce, vary greatly in their characteristics and designs, precluding a meta-analysis of the results found.

In the current systematic review, both studies assessing the prevalence of CL/P in family members of cancer patients had a case-control design and suggest that this malformation is more frequent in families of cancer survivors in comparison with families of a population-based sample of controls. In the study of Taioli et al. (2010) [2], the results were not statistically significant and the authors relate it to the sample size of the study and to the rarity of CL/P occurrence. In the second study, relating CL/P and childhood cancer, none of the children from the unaffected group had a positive family history of cleft lip and palate, while five children with leukemia had a positive history of oral clefts [18].

In these studies, the population investigated, or their parents or guardians, answered standardized questionnaires with demographic information about the respondents and their family history of CL/P. It was a consensus between the authors that information on number of second-degree relatives is lacking for both, which could explain

their findings for the first-degree relatives, since the more distant the relative is, less information is known about him.

In the study investigating adult individuals who survived cancer, the most frequent types of cancer were melanoma, testicular, breast, colon-rectal, and lymphoma. The authors state, however, that one limitation of the study was to include cancer survivors instead of newly diagnosed cancer patients, which could exclude highly fatal cancers [2].

Despite the different characteristics of the populations investigated in the studies of Taioli et al. (2010) and Jindal and Vieira (2012) [2,18], both suggest that shared genetic factors may explain an association between oral clefts and cancer. Thus, investigating the relationship between malformations and malignancies becomes important as it is speculated that they might have common causes. Endorsing that possibility, Chalothorn et al. (2008) and Küchler et al. (2013) [42,43] have previously proposed an association between tooth agenesis and cancer. In some cases, tooth agenesis and oral cleft may share the same genetic background.

This review also accessed studies [5,13-15,17,21] regarding risk of cancer in relatives of individuals born with non-

syndromic oral clefts. From the six studies found, three also had a case-control design and more cancer cases were reported among relatives of cleft individuals than by controls [14,15,17]. The most prevalent types of cancer have not been plainly identified in all studies, which was a limitation of the studies declared by the authors. However, in those which it was possible, a clear predominance of colon cancer and leukemia cases was noticed, as well as some reports of breast cancer, lymphoma and brain cancer [14,15]. The most affected relatives were specified only in the study of Zhu et al. (2002) [15], which exclusively investigated parents. A further limitation that was found is the fact that the specific data regarding the age of onset of cancer was not accessed, which makes it impossible to determine if family members of individuals with cleft developed cancer at earlier ages than the general population.

A higher prevalence of cancer in family members of individuals born with CL/P was presented in a cross-sectional study with a Latvian population, too [13]. The risk was calculated by dividing the prevalence of cancer in the target group by the prevalence of cancer in that population. It was demonstrated that this risk is three times higher in

Table 4: Potential bias/limitations and the author's efforts to identify them among the eight selected papers.

First author, year [reference]	Bias/limitations	Identification of bias/limitations
Jindal, 2012	Information concerning illnesses on relatives more distant than the first-degree may not be so reliable.	Not reported.
Taioli, 2010	Since it researched cancer survivors and not patients diagnosed with cancer <i>per se</i> , the most fatal forms of cancer tend to have their association with CL/P not reported accurately. Also, an association between the type of cancer and CL/P becomes impossible to be made in this case because of characteristic survivorships in each type.	Not reported.
Yildirim, 2012	As information regarding specific types of cancers was not available for all individuals, an analysis by cancer types could not be done. Also, the specific data regarding the age of onset of cancer was not accessed, which made it impossible to determine if family members of cleft individuals developed cancer at earlier ages than the general population.	Not reported.
Menezes, 2009	The cancer types reported may not all have been related to the same causes. Also, as there was no access to data that specified the age of cancer development in those individuals' family members, it was no possible to determine if family members of cleft individuals developed cancer at earlier ages than the general population.	Proposes new research with increased sample size to replicate findings and test the association between genetic variants and specific types of cancer.
Zhu, 2002	There may have been some confusion from the teratogenic effects of cancer treatment in parents who had cancer previous to the child's birth. The outcome of previous births also could induce some bias as well as maternal age at birth and sex of the child. Lastly, the lack of data on stillbirths may have biased results if fetal mortality differs between parents who will develop cancer and parents who won't.	It only used parents whose cancer diagnostic came up after the birth of their indexed children. Also, the children analyzed were only firstborns and the age of the mother at birth and the child's sex were reported.
Vieira, 2012	The population studied was composed mostly by individuals in their first years of life, and because of that, the prevalence of pediatric or earlier onset types of cancer was relatively increased when compared with the other types. The same is true for their relatives, as they are most likely also relatively young.	Not reported.
Dietz, 2012	A left and right truncation in this study was observed, as no information can be gotten neither previous nor post the period studied.	Not reported.
Steinwachs, 2000	There is known lack of accuracy in information provided by patient reports about their family members.	Proposes new and larger studies with sufficient power to study only first-degree relatives.

first- and second-degree relatives and decreases to 1.5 times in third-degree relatives. Similar to most available studies with the same proposal, the types of cancer were not consistently reported and, because of that, this study did not discriminate by cancer types.

As well as in the studies addressing prevalence of CL/P in family members of cancer patients, findings from four [13-15,17] of six studies regarding risk of cancer in relatives of individuals born with non-syndromic oral clefts provide additional support for a common etiology between CL/P and cancer, suggesting that these families have a higher genetic load for CL/P, which also impacts their cancer risk.

On the other hand, two other studies regarding risk of cancer in relatives of individuals with clefts could not conclude the same [5,21]. The first one, performed by Steinwachs et al., (2000) [21] was emphatic in denying an increased risk for cancer in the first- and second-degree relatives of individual affected with non-syndromic CL/P. The population investigated was composed of Caucasians, Hispanics, African Americans, and Asian individuals. The cancer data were analyzed in aggregate by type of cancer, by degree of relation to the index case, and by ethnicity. As a result, neither first-degree relatives nor second-degree relatives of the index cases had a significantly increased risk for cancer. No particular ethnic group demonstrated an excessively increased risk for cancer. Not even the most commonly reported cancers (lymphoproliferative cancers, female cancers, and lung cancer) were increased as a whole or in first-degree relatives only.

In the same way, in a recent retrospective cohort study [5] testing whether mothers and sisters of individuals born with CL/P have an increased risk for breast cancer, the authors were not able to confirm a general increase in this risk for breast cancer among the study population. However, some associations were revealed when cleft subtype was analyzed, and having a child with isolated cleft palate was associated with an increased risk of breast cancer for the mother, which may be biologically plausible due to the evidence that the different cleft types have different genetic origins [44,45].

Thus, the hypothesis that parental cancer and congenital malformations in offspring may be correlated could not be entirely confirmed by the present systematic review. Despite it being known that possible mechanisms at the basis of an association between CL/P and cancer are shared genetic factors, once polymorphisms in genes involved in cell-cell adhesion and cellmotility

are associated with both cancer and CL/P [16,18], studies in this direction are very scarce and of those existing and most investigated all subtypes of oral clefts, which sets a limitation to find out such correlation.

There is agreement among almost every reviewed author [2, 14,17,18] that the investigated populations in their studies need to be expanded in order to avoid any random findings in multiple testing or the potential impact of Type I error. It is also in agreement that future studies should explore the possibility that there is a preferential occurrence of specific types of cancer in families with individuals born with CL/P and test the hypothesis that common genetic and epigenetic mechanisms are playing a role in both conditions [14,17]. Through this information, future studies may be better able to identify the causes of non-syndromic orofacial clefts and ultimately to predict its occurrence and to facilitate genetic counseling of affected families [21]. Another issue raised by Dietz et al. (2012) is the fact that having a cleft leads to social marginalization and changes in lifestyle could predispose not only the individual, but also their family for cancer, which seems plausible from a standpoint of relationship between stress and cancer, as discussed in the literature.

**Conflict of interest:** There are no conflicts of interest to report.

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