Published in final edited form as:
Am J Epidemiol. 2005 June 1; 161(11): 1047–1055. doi:10.1093/aje/kwi132.

Cancer Risk in Persons with Oral Cleft—A Population-based Study of 8,093 Cases

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Abstract

The authors conducted a nationwide study of the occurrence of cancer among 8,093 Danish oral cleft cases born in 1936 through 1998 and followed in the Danish Cancer Registry from 1968 through 1998, a total of 175,863 person-years, to assess a possible association between cancer and oral clefts. Observed and expected numbers of cancers among oral cleft cases were summarized as the overall and as 52 site-specific standardized incidence ratios. The expected overall number of all cancers was 131, but 140 incident cancers were found, corresponding to a standardized incidence ratio of 1.07 (95% confidence interval (CI): 0.90, 1.26). Analyses of the 52 sites for all oral cleft cases and analyses stratified for three cleft subgroups and the two sexes revealed only a few significant associations: an increased occurrence of breast cancer among females born with cleft lip and/or cleft palate (standardized incidence ratio (SIR) = 1.52, 95% CI: 1.05, 2.14), primary brain cancer among females born with cleft palate (SIR = 3.11, 95% CI: 1.14, 6.78), and primary lung cancer among males born with both cleft lip and cleft palate (SIR = 2.49, 95% CI: 1.00, 5.14). The results do not provide evidence for an increased overall cancer risk for individuals born with oral clefts.

Keywords

abnormalities; cleft lip; cleft palate; cohort studies; follow-up studies; neoplasms

Cancer and congenital malformations may occasionally have a common etiology (1–3). The etiology can be environmental, as observed with maternal phenytoin treatment's resulting in fetal hydantoin syndrome and neuroblastoma in the offspring (4,5), and it can be genetic. A well-studied example where genes explain the concurrence of congenital anomalies and cancer is trisomy 21 that results in Down's syndrome. Population-based studies of the occurrence of leukemia among cases with Down's syndrome (6) and of Down's syndrome among leukemia patients (2) have found increased concurrences. The single-gene disorder basal cell nevus syndrome, which is caused by mutations in the patched gene, includes both congenital malformations (rib anomalies, clefts) and cancers (basal cell carcinoma, medulloblastoma) (7). Concurrences of cancer and congenital malformations have been found in population-

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based studies of both cases with major malformations (8–10) and cases with cancer (11). Increased concurrences of minor malformations or mild errors of morphogenesis and cancers have been found in clinical series of cases with cancer (12,13), suggesting a common etiology. Most studies have, however, been small, and the populations-based studies often rely on incomplete reporting systems, such as death certificates and birth-defect registries. In addition, population-based studies often include multiple comparisons between a number of congenital malformations and a number of cancers, thus introducing a substantial risk of false positive results.

One of the most common congenital malformations, oral clefting, was recently associated with cancer (especially leukemia) among the parents in a Danish population-based case-control study (14). Although mainly positive associations of oral clefts with cancers have been published, the results are conflicting (15–20). A publication bias of spurious associations resulting from multiple comparisons may explain the positive findings. Large population-based studies with high ascertainment of both oral clefts and neoplasms are needed to corroborate the previously suggested associations.

Health care in Denmark is free of charge, and there are well-established nationwide population and health registers. These registers include the Danish Cancer Registry covering the period 1943 through 1998 and the Danish Facial Cleft Register comprising all children born with oral clefts in Denmark in the period 1936 through 2001. Consequently, Denmark offers an ideal setting for large population-based studies of cancer occurrence among people with oral clefts. The aim of this study is to assess the overall cancer occurrence and the occurrence of site-specific cancers among individuals with oral cleft and to compare these with the occurrence in the general population to evaluate whether oral clefts and cancer are associated.

MATERIALS AND METHODS

To assess the risk of cancer among individuals with oral clefts, we conducted a register-based cohort study with data from the Danish Civil Registration System, the Danish Facial Cleft Register, and the Danish Cancer Registry.

The Danish Civil Registration System

The Danish Civil Registration System was established in 1968 and registers all persons residing in Denmark on April 1, 1968, or later with a unique 10-digit personal identification number. This number includes birth date (six digits) and a serial number (four digits) that keeps information about sex and century. Furthermore, it has a built-in check code disclosing invalid numbers and ensuring a highly reliable identification of cases. The register contains the full name and information on birthplace and vital status (alive, dead, or emigrated), as well as the date of death or emigration. The personal identification number of persons born before April 1, 1968, and alive on April 2, 1968, can in most cases be traced in the registry on the basis of name plus date and place of birth. This registration system is the key to the public health care system as well as national statistics.

The Danish Facial Cleft Register

The Danish Facial Cleft Register has previously been described in detail (21). It was recently updated to include also the 1988–2001 cohorts and now covers the birth cohorts from 1936 to 2001 (22). Capture-recapture methods have indicated that nearly all (99 percent) liveborn oral cleft cases in Denmark without associated malformations have been ascertained (except submucous cleft palate, which often remains asymptomatic) (21). Owing to the incomplete ascertainment of defects in stillbirths, only livebirths have been included. The register now includes 9,483 liveborn individuals with oral clefts, of which 8,623 (91 percent) are registered

by a personal identification number. Clefts are grouped into cleft lip, cleft lip with cleft palate, and cleft palate only, as embryologic and recurrence risk data suggest that these groups have different underlying mechanisms (23). The cleft palate-only group comprises cases with clefts in the hard and/or soft palate and submucous cleft. Isolated bifid uvula is not considered a cleft palate.

Regarding associated anomalies, a case with an associated malformation or malformation syndrome is registered in the cleft register if the presence of such a malformation is documented in any of the sources of the register. Eighty-two percent of the cases born before 1987 were, as reported earlier (24), described in infancy by one man—Poul Fogh-Andersen—at the time of the operation, and all medical records of cases born in the period 1988 through 2001 were scrutinized by one of us (C. B.) to enhance information about associated anomalies. Malformations such as neural tube defects, as well as monogenic traits, syndromes, and sequences, were designated as major anomalies. Defects such as congenital dislocation of the hip or postaxial poly-dactyly were considered minor malformations. Oral cleft cases with less than three minor associated malformations were defined as “nonsyndromic” (n = 7,435), and oral cleft cases with major or with three or more minor associated malformations were defined as “syndromic” (n = 658).

The Danish Cancer Registry

The Danish Cancer Registry is population based and includes all cancers diagnosed by clinicians or pathologists (either in biopsy or at autopsy) after January 1, 1943. Any changes of the initial diagnosis are forwarded to the registry. Linkage with the National Patient Registry and the Danish Registry of Causes of Death provides additional data on unreported cancer cases (25). Details of individual cancer cases are available according to a modification of the *International Classification of Diseases*, Seventh Revision, for all years. A core data set is kept for each individual, including personal identification number, date of birth, sex, date of cancer diagnosis, method of verification, date of death, and cause of death.

Linkage and information retrieval

The study group included 8,093 oral cleft cases born in Denmark in the period 1936 through 1998 and alive on April 1, 1968. The study group was divided into 2,342 cleft lip cases, 3,035 cleft lip with cleft palate cases, and 2,716 cleft palate cases.

A follow-up of all cleft cases was made using the Civil Registration System where vital status is registered. Use of the personal identification number as the link between the registers implies that the study population under review was alive on April 1, 1968. Therefore, the follow-up period is April 1, 1968, through December 31, 1998. The personal identification number was used to make a linkage with the Danish Cancer Registry to identify the onset of primary cancers at 52 specific sites.

Statistics

For each of the 52 sites, the total number of cancers was recorded, including multiple cancers per individual. Original codes assigned by the Danish Cancer Registry were used so that a direct comparison with rates from the registry could be made. Incidence rates by sex and by 5-year age and calendar-year groups for each cancer were applied to the appropriate person-years under observation to obtain the number of cancers expected had these patients experienced the same rates that prevailed in the general Danish population. We used statistical methods based on the assumption that the observed number of cancer cases in any specific category will follow a Poisson distribution. Standardized incidence ratios taken as the observed-to-expected individual cancers served as a measure of the relative risk. The standardized incidence ratio was calculated with the use of the exact Poisson probabilities when

the observed number of cases was small; otherwise, an accurate asymptotic approximation was used. A significance test and 95 percent confidence interval for the standardized incidence ratio were estimated.

We stratified the analysis into the three subtypes of cleft, into sex, and into a priori status as nonsyndromic and syndromic oral cleft cases. The numbers of syndromic oral cleft cases with cancer (n = 5) were, however, too small for making informative site-specific analyses.

RESULTS

A total of 8,093 oral cleft cases were followed from 1 day to 30 years and 9 months, a total of 175,863 person-years. At the start of follow-up in 1968, the cases were between 0 years and 32 years, corresponding to the birth cohorts 1936–1968. Table 1 shows the birth year, cleft type, and syndromic/nonsyndromic cases distributed over men and women. The sex distribution for each subtype of cleft is in accordance with known distributions. Females are usually overrepresented in the cleft palate group compared with males, while males constitute the majority of the cleft lip and cleft lip with cleft palate groups.

In table 2, the distribution of contributing person-years according to age and sex is shown. It can be seen that the majority of person-years are among younger cases. Only 4 percent of the person-years are among cases aged 50 years or more.

The observed and expected numbers of overall and specific cancer types for all oral cleft cases are shown in table 3. Because of their predominantly benign outcome, nonmelanoma skin cancers are often underreported and were therefore excluded from the analyses of overall cancer occurrence. The expected overall number of primary cancers was 131 and 140 cancers occurred, corresponding to a standardized incidence ratio of 1.07 (95 percent confidence interval (CI): 0.90, 1.26). Stratification into nonsyndromic and syndromic cleft subjects revealed a standardized incidence ratio of 1.05 (95 percent CI: 0.88, 1.25) and 1.71 (95 percent CI: 0.55, 3.98), respectively (data not shown).

Table 3 shows observed and expected cancers among all oral clefts when analyzed as a single group (not divided into cleft lip, cleft lip with cleft palate, and cleft palate or into syndromic and nonsyndromic clefts). Of the 52 cancer sites analyzed, only sites with three or more observed cancers are shown. The only statistically significant deviation in cancer risk was found for breast cancer. Among all oral cleft cases, the observed number of breast cancers was 33, where 22 were expected, corresponding to a standardized incidence ratio of 1.52 (95 percent CI: 1.05, 2.14). All observed breast cancer cases were females with a nonsyndromic oral cleft.

Since breast cancer in males is very rare, only female occurrences were considered when stratifying into subtype of cleft. The stratification revealed an increased but not statistically significant standardized incidence ratio for all three subtypes of clefts as shown in table 4.

Analyses with stratification by cleft type were done for all specific cancer sites (data not shown). The only specific cancer sites with a significantly increased occurrence in subtypes of oral clefts were primary brain cancer in females with cleft palate and primary lung cancer in males with cleft lip with cleft palate.

Brain cancer was registered for eight cases with cleft palate (two males and six females). As shown in table 5, only two brain cancers were expected among females with cleft palate, resulting in a standardized incidence ratio of 3.11 (95 percent CI: 1.14, 6.78). An increased occurrence was not seen for males or for cleft lip or cleft lip with cleft palate cases. No syndromic cleft cases were registered with a brain cancer.

Results from analyses of lung cancer among males with oral cleft are shown in table 6. Seven males with both cleft lip and cleft palate were registered with lung cancer where only three were expected. A similar high risk was not seen for any other subtype of oral cleft. The occurrence of lung cancer among females did not differ from the expected, and no syndromic cleft cases were registered with lung cancer (data not shown).

Table 7 shows the standardized incidence ratio for cancer sites other than lung cancer convincingly related to tobacco smoking. These sites include the larynx, oral cavity, tongue, pharynx, esophagus, pancreas, renal parenchyma, renal pelvis, and bladder (26). Data are stratified for sex and cleft type. None of the estimated standardized incidence ratios was statistically significant. Neither was the standardized incidence ratio statistically significant when analyzing oral cleft as one group (not stratifying into cleft type) (standardized incidence ratio (SIR) = 1.11, 95 percent CI: 0.64, 1.81).

All analyses were stratified for sex. The observed overall number of cancers among males was 66, and 66 were expected (SIR = 1.00, 95 percent CI: 0.78, 1.28). Among females, 74 were observed and 65 were expected (SIR = 1.13, 95 percent CI: 0.89, 1.42). Except for the above-mentioned lung, brain, and breast cancers, sex- and site-specific cancer occurrence was not significantly different from the expected (results not shown).

DISCUSSION

Analyses of the occurrence of cancer among 8,093 oral cleft cases followed for 175,863 person-years revealed no association between cancer risks in general and oral clefts. The Danish Facial Cleft Register has a very high case ascertainment (24), and furthermore the Danish Cancer Registry is believed to have an almost complete ascertainment of cancers other than skin cancers (25,27). However, in the Facial Cleft Register, only 90 percent of the individuals were registered with a personal identification number (enabling a linkage between the two registers) at the time of analyses. Selection bias would imply that oral cleft cases without a personal identification number were more likely to have cancer than cases with a personal identification number. This is unlikely, as the main reasons for failing to locate the personal identification number in the registry were common last names and emigrations before the establishment of the Civil Registration System in 1968.

Separate analyses of nonsyndromic and syndromic oral cleft cases are preferable since the etiologies of these two groups are presumably different (28). In our study group, 8.1 percent of the cases were syndromic, which is a low percentage compared with some studies, indicating that associated anomalies are probably underreported in our sources. We cannot dismiss the possibility that we still have a mixture of cases with and without associated anomalies in the nonsyndromic study population. However, since Fogh-Andersen, one of the leading experts within this field, described the majority of the oral cleft cases in 1942, we may assume that all severe malformations have been identified, leaving only the possibility for subjects with milder associated anomalies to be mixed into the nonsyndromic group. Our data showed a higher association of syndromic than of nonsyndromic oral cleft with cancer. This was, however, based on only five syndromic oral cleft cases and was not statistically significant. A moderate mixture of syndromic oral clefts in the study population is therefore not likely to bias the results considerably.

We assumed that there is no difference in risk factors for oral clefts with no minor associated anomalies and oral clefts with one or two minor associated malformations. Including cases with minor associated anomalies in the nonsyndromic cleft group might bias the results if the etiology is different for clefts with or without minor associated anomalies. Excluding cases with minor associated anomalies, however, might bias the study as the group would represent

a healthier group than the population in general. For these biases to be of any concern, the associated anomalies have to be related to cancer occurrence, which is unlikely with the findings described here.

The facts that most cancers occur at higher ages and that a relatively high contribution of person-years occurred at the lower ages in the present study imply that only a minimum of the cancers to occur has already occurred. A lag in time could be incorporated by studying only persons of a certain age, but this would have resulted in a loss of information on childhood cancers where most concurrences with congenital malformations have been found. A future follow-up will include more person-years among older persons and provide increased power to detect cancers normally occurring at higher ages.

Our data demonstrate an association between oral clefts and three site-specific cancers. When analyzing 52 specific cancer sites separately and stratifying the analyses further for each site on sex, cleft type, and syndromic/nonsyndromic cases, we made numerous comparisons. The risk of false-positive results is substantial, and the few statistically significant associations found in the present study could be an effect of the multiple comparisons. Other explanations are discussed in more detail for each of the three positive associations separately.

Analysis of oral cleft as one group (not stratifying into subtypes of oral cleft) revealed an increased occurrence of breast cancers among females. With stratification for cleft type (cleft lip, cleft lip with cleft palate, and cleft palate), the tendency remained in all subgroups, although it was statistically insignificant. Breast cancer is associated with environmental risk factors such as nulliparity, late age at first birth, and a long period between menarche and menopause (29). We believe that a possible association between breast cancer and oral cleft could, at least partly, be explained by these factors. Fewer individuals with oral cleft have children, and when they do have children they have them later in life (30). In Norwegians, the postponing of motherhood is minimal for female oral cleft cases and seen only for cleft palate cases (31). Our data showed, however, a mean maternal age at first birth of 25.8 years for all Danish livebirths compared with 27.3 years for cleft cases in the period 1974 through 1998. A study with data from the Danish Cancer Registry has shown that the postponing of motherhood for 5 years increases the risk of breast cancer by 9 percent (32). Alternatively, the increased occurrence of breast cancer could be due to other confounders such as smoking, which is more frequent among cleft cases (33), or could be a random finding in the multiple testing.

The term “brain cancer” refers to a mixed group of neoplasms originating from intracranial tissues. The etiology is largely an enigma. Apart from an association with certain inherited syndromes such as the Li-Fraumeni syndrome in 1–2 percent of the cases, only high doses of ionizing radiation are a known risk factor (34,35). Current theories suggest that brain cancer develops as a consequence of accumulated genetic alterations that destroy normal regulatory mechanisms in the cell (36). Infections and immune factors have also been suggested to play a role in the etiology (36,37). Intracranial lipoma has been associated with cleft lip, and cutaneous polyps in the Pai syndrome (38) and papilloma of the choroid plexes have been described in the Aicardi syndrome together with cleft lip with cleft palate (39). In our study, brain cancer was found only in cases with nonsyndromic oral clefts, and the occurrence was increased only for females with cleft palate. The large population-based study by Narod et al. (11) investigated congenital malformations among 20,304 children with cancer. The authors described a higher frequency of oral cleft among children with brain tumor, neuroblastoma, and retinoblastoma than among children with leukemia. The study included no data on occurrence of oral cleft. Even with a relatively low total prevalence of 1.5 oral cleft cases per 1,000 livebirths, about 30 oral cleft cases were to be expected among the 20,304 children. Only 17 oral cleft cases were identified, suggesting that ascertainment bias is present.

The present finding of an increased occurrence of brain cancer among female cleft palate cases and the recent finding of increased mortality due to epilepsy among Danish female cleft palate cases (40) together indicate that intracerebral morbidity and cleft palate may have a common etiology, but this still remains to be established.

The most important risk factor for lung cancer is smoking. A higher substance abuse and an impaired level of wellbeing have been found for cases with oral clefts (33,41,42). Whether this can account for the increased occurrence of primary lung cancer among males with cleft lip with cleft palate is uncertain. The trend was positive but nevertheless not statistically significant for either cleft lip or cleft palate or for females. An increased occurrence of cancer types other than lung cancer convincingly related to tobacco smoke (26) would support a tobacco confounding factor. This was, however, not found.

Associations of particular congenital malformations with specific cancers and associations of congenital malformations with cancer in general have been studied in clinical series of individuals with either cancer (12,43,44) or congenital malformations (45,46) and also in population-based studies (2,8,11,47). The most consistent result has been an association of leukemia with Down's syndrome (6,10,17), but numerous other associations have been found (47). A common etiology could be due to genetic or non-genetic factors or an interaction between both. Homeobox-containing genes have been suggested as the molecular link between congenital malformations and cancer (48,49). Here, some cancers arise as a result of fusion events between transcription factors and growth factors, leading to unregulated cell growth. Germ-line point mutations in the same genes result in clefting syndromes (50,51). Since many chemical carcinogens are known teratogens, environmental factors might also be responsible for concurrences of cancer and congenital malformations (52).

Zhu et al. (14) found an increased cancer risk, especially of lymphomas and leukemia, among parents of oral cleft cases, and reports of increased concurrences of oral clefts and cancer have been published from other population-based studies (17,18). Associations of oral clefts and specific cancers, the basal cell nevus syndrome (7) and retinoblastoma (53,54), have also been found in clinical series. A pedigree study revealed an autosomal dominant hereditary pattern of Wilms tumor and cleft in a unique family (20). Clefting is furthermore well described in the ectrodactyly-ectodermal dysplasia-clefting syndrome caused by mutations in the *P63* gene, a family member of *P53* in which mutations are the causes of multiple forms of cancers (55). Additionally, it has recently been shown that, while germ-line mutations in the *PTPN11* gene result in the Noonan syndrome, somatic mutations in the same gene are leukemogenic (56–58). A few studies that are negative for the association of clefts with cancer have also been reported. Blot et al. (16) studied 11,500 children with cancer and found no indication of an association between clefts and cancer. Likewise, Steinwachs et al. (15) did not find an increased frequency of cancer in the index cases or in the first-degree or second-degree relatives of 196 nonsyndromic oral cleft cases.

An association between cancer and oral cleft is expected if 1) genetic factors of etiologic importance for clefts are involved in causing one or more common cancers, 2) environmental factors act both as carcinogens and teratogens, or joint genetic and environmental triggers are acting in concert, or 3) the malformation leads to societal marginalization and thus to changes in lifestyle of importance to cancer risk (smoking, high alcohol intake, late childbirth, and so on).

Since we have no data on any of the possible putative mechanisms, we cannot rule out that a positive link postulated by one mechanism is hidden by a similar negative association by another mechanism (if, e.g., cleft patients have better lifestyles or less environmental

exposure). Lifestyle factors for Danish patients with clefts are not known, but the high occurrence of lung cancer does not indicate negative confounding by smoking.

Our study did not confirm any of the previously suggested associations between clefts and cancer risk, and we did not find an increased overall cancer occurrence among the oral cleft cases compared with what is seen in the general population. Although our follow-up period of cleft cases is uniquely long, it is still a limitation of our study that the oldest person included is only 62 years of age. Most cancers occur at older ages, and a future extension of the follow-up period might provide increased statistical power and show an increase of cancer occurrence at some cancer sites.

Abbreviations

CI	confidence interval
SIR	standardized incidence ratio.

Acknowledgments

The Center for the Prevention of Congenital Malformations is made possible by a grant from the Egmont Foundation. The Danish Facial Cleft Database has received support from the National Institute of Dental Research (grant R01 DE 11948), the Egmont Foundation, and (in connection with this project) Boernecancerfonden.

The authors acknowledge the two National Institutes of Defects of Speech, the University Hospital of Copenhagen, Statistics Denmark, the Egmont Foundation, the National Institute of Dental Research, and the Faculty of Health, University of Southern Denmark. The authors also thank Dr. Jørgen H. Olsen, Institute of Cancer Epidemiology, Copenhagen, Denmark, for useful comments on the draft version of this work.

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TABLE 1

Danish cleft cases born in 1936 through 1998 and followed in the Danish Cancer Registry during 1968 through 1998 for a total of 175,863 years

	Men		Women		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
Total	4,851	100	3,242	100	8,093	100
Birth year						
1936–1939	157	3.2	111	3.4	268	3.3
1940–1949	624	12.9	437	13.5	1,061	13.1
1950–1959	705	14.5	467	14.4	1,172	14.5
1960–1969	942	19.4	585	18.0	1,527	18.9
1970–1979	898	18.5	573	17.7	1,471	18.2
1980–1989	748	15.4	512	15.8	1,260	15.6
1990–1998	777	16.0	557	17.2	1,334	16.5
Diagnosis						
Cleft lip	1,506	31.0	836	25.8	2,342	28.9
Cleft lip + cleft palate	2,101	43.3	934	28.8	3,035	37.5
Cleft palate	1,244	25.6	1,472	45.4	2,716	33.6
Nonsyndromic	4,502	92.8	2,933	90.5	7,435	91.9
Syndromic	349	7.2	309	9.5	658	8.1

TABLE 2

Contributing person-years according to age and sex of Danish cleft cases born in 1936 through 1998 and followed in the Danish Cancer Registry during 1968 through 1998

Age (years)	Men (person-years)	Women (person-years)	Total (person-years)
0–9	25,632	16,743	42,375
10–19	25,529	16,234	41,764
20–29	23,974	15,307	39,282
30–39	17,761	11,844	29,605
40–49	9,769	6,870	16,639
50–59	3,460	2,520	5,981
60–69	127	86	213
Total	106,256	69,607	175,863

TABLE 3

Standardized incidence ratio of cancer occurrence in 8,093 Danish patients with oral clefts during follow-up from 1943 to 1998*

ICD-7† codes	Observed (no.)	Expected (no.)	Standardized incidence ratio	95% confidence interval
140–205 (all minus other skin cancers)‡	140	131.00	1.07	0.90, 1.26
150–159 (digestive organs and peritoneum)	14	15.50	0.90	0.49, 1.52
153 (colon, including rectosigmoid)	6	5.40	1.11	0.41, 2.42
160–164 (respiratory system)	14	11.55	1.21	0.66, 2.03
161 (larynx)	3	1.28	2.34	0.47, 6.85
162.0–162.1 (lung primary, tracheae)	11	9.42	1.17	0.58, 2.09
162.x (non-small cell lung cancer)	10	7.67	1.30	0.62, 2.40
170 (breast)	33	21.64	1.52§	1.05, 2.14
171–176 (female genital organs)	10	12.85	0.78	0.37, 1.43
171 (cervix uteri)	6	6.99	0.86	0.31, 1.87
175 (ovary, fallopian tube, broad ligaments)	4	3.48	1.15	0.31, 2.94
177–179 (male genital organs)	12	11.59	1.04	0.53, 1.81
178 (testis)	10	10.38	0.96	0.46, 1.77
180–181 (urinary system)	10	7.53	1.33	0.64, 2.44
181 (bladder including papilloma)	8	4.38	1.83	0.79, 3.60
192–197 (other specified sites)	17	17.59	0.97	0.56, 1.55
193 (brain and nervous system)	12	12.30	0.98	0.50, 1.70
200–205 (lymphatic and hematopoietic tissue)	19	16.57	1.15	0.69, 1.79
200, 202 (non-Hodgkin's lymphoma)	3	5.51	0.54	0.11, 1.59
201 (Hodgkin's disease)	6	3.60	1.67	0.61, 3.63
204 (leukemia)	9	6.59	1.36	0.62, 2.59
204.1 (acute myelogenous leukemia)	3	1.83	1.64	0.33, 4.80

*A total of 52 sites were studied, but only sites with three or more observed cases are shown. Nonmelanoma skin cancers are excluded because of underreporting.

†ICD-7, *International Classification of Diseases*, Seventh Revision.

‡ICD-7 (modified version) code 191.

§Statistically significant standardized incidence ratio.

TABLE 4

Standardized incidence ratio of breast cancer in 2,933 Danish females with nonsyndromic oral cleft during follow-up from 1943 through 1998*

Breast cancer (females)†	Observed (no.)	Expected (no.)	Standardized incidence ratio	95% Confidence interval
Cleft lip only	8	5.69	1.41	0.61, 2.77
Cleft lip + cleft palate	11	6.48	1.70	0.85, 3.04
Cleft palate only	14	9.02	1.55	0.85, 2.60

*Data are stratified into subtypes of nonsyndromic oral cleft.

†No male with oral cleft had breast cancer, and none of the syndromic cleft cases had breast cancer.

TABLE 5

Standardized incidence ratio of primary brain cancer in 2,933 Danish females with nonsyndromic oral cleft during follow-up from 1943 through 1998*

Primary brain cancer†	Observed (no.)	Expected (no.)	Standardized incidence ratio	95% Confidence interval
Cleft lip only	1	1.25	0.80	0.01, 4.45
Cleft lip + cleft palate	0	1.34	0.00	0.00, 2.75
Cleft palate only	6	1.93	3.11‡	1.14, 6.78

*Data are stratified into subtypes of nonsyndromic oral cleft.

†None of the syndromic cleft cases had primary brain cancer or cancer of the trachea.

‡Statistically significant standardized incidence ratio.

TABLE 6

Standardized incidence ratio of primary lung cancer in 4,502 Danish males with nonsyndromic oral cleft during follow-up from 1943 through 1998*

Primary lung cancer†	Observed (no.)	Expected (no.)	Standardized Incidence ratio	95% Confidence interval
Cleft lip only	1	1.98	0.51	0.01, 2.82
Cleft lip + cleft palate	7	2.81	2.49‡	1.00, 5.14
Cleft palate only	2	0.96	2.09	0.23, 7.53

*Data are stratified into subtypes of nonsyndromic oral cleft.

†None of the syndromic cleft cases had primary lung cancer or cancer of the trachea.

‡Statistically significant standardized incidence ratio.

TABLE 7

Standardized incidence ratio of cancer sites other than lung cancer convincingly related to tobacco smoke* among Danish nonsyndromic oral cleft cases followed from 1943 through 1998

	Observed (no.)	Expected (no.)	Standardized incidence ratio	95% confidence interval
Cleft lip only				
Total	7	4.66	1.50	0.60, 3.09
Men	6	3.82	1.57	0.57, 3.42
Women	1	0.85	1.18	0.02, 6.58
Cleft lip + cleft palate				
Total	5	6.30	0.79	0.26, 1.85
Men	4	5.28	0.76	0.20, 1.94
Women	1	1.02	0.98	0.01, 5.45
Cleft palate only				
Total	4	3.42	1.17	0.31, 3.00
Men	2	1.97	1.02	0.11, 3.67
Women	2	1.45	1.38	0.15, 4.97
Total	16	14.38	1.11	0.64, 1.81

* Cancer sites other than lung cancer convincingly related to tobacco smoke include the larynx, oral cavity, tongue, pharynx, esophagus, pancreas, renal parenchyma, renal pelvis, and bladder.