

ABSENCE OF AN ENVIRONMENTAL EFFECT ON THE RECURRENCE OF FACIAL-CLEFT DEFECTS

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Abstract *Background.* The rate of recurrence of a broad range of birth defects may decrease among women who change residence after the birth of their first infant. The aim of the present study was to determine the effect of changing residence on the recurrence of congenital facial-cleft defects.

Methods. We identified 4189 women who had had infants with facial-cleft defects by linking a data base comprising the records of children with facial clefts born between 1952 and 1987 with the Central Person Registry in Denmark. Among the 4189 mothers, 1902 each had additional children after the first child with a facial-cleft defect. A total of 2692 younger siblings were identified. We compared the proportion of infants with facial-cleft defects among the younger siblings between mothers who had changed municipalities or sexual partners and those who had not.

Results. Changing the municipality of residence did not decrease the frequency with which facial-cleft defects recurred in younger siblings. Among the 907 infants of mothers who changed municipalities but not partners, 29 (3.2 percent) had facial-cleft defects, as compared with 48 (3.4 percent) of 1425 infants of mothers who changed neither municipality nor partner (relative risk, 0.9; 95 percent confidence interval, 0.6 to 1.5). However, a change of partner reduced the recurrence risk significantly. Among 236 infants of mothers who changed partners, 1 (0.4 percent) had a facial-cleft defect, as compared with 77 (3.3 percent) of 2350 infants of mothers who did not change partners (relative risk, 0.1; 95 percent confidence interval, 0.02 to 0.9).

Conclusions. Recurrence of facial-cleft defects is not linked to the residence of the mother, but having a different partner reduced a woman's risk of having a second child with this defect. (*N Engl J Med* 1995;333:161-4.)

THE search for genetic factors that influence the occurrence of birth defects has been more successful than the search for environmental factors, particularly with regard to malformation syndromes. Specific DNA deletions associated with specific malformation syndromes have been identified, and a number of positive genetic-linkage and genetic-association studies have been published in recent years.¹⁻⁴ More indirect methods, such as segregation analyses and twin studies, also indicate that genetic factors have a major role in the pathogenesis of some of the major birth defects.⁵⁻⁷

Since thalidomide was recognized as a potent teratogen, substantial effort has been directed toward identifying environmental factors that play a part in causing birth defects. Except for the recognition that folic acid protects against neural-tube defects,⁸ such efforts have been disappointing. A number of risk factors have been identified for some birth defects — for example, smoking,⁹ alcohol,¹⁰ and various drugs¹¹ — but the associations are usually weak.

Last year in the *Journal*, Lie et al.¹² reported a reduction in the risk of the same birth defect's occurring in two siblings born to women in Norway who moved from one municipality to another between the two births; there was no significant reduction in risk among women who changed sexual partners. The study considered 24 groups of birth defects, including 2 groups of facial-cleft defects. The finding was particularly unexpected

in a country such as Norway, which has homogeneous social conditions and high environmental standards. This study may have been vulnerable to detection bias in the routine malformation-registration system, because more than half of the birth defects considered belong to categories of malformations whose recognition may be difficult.¹³ The aim of the present study was to estimate the effect of a change in partner or residence on the recurrence of cleft lip, with or without cleft palate, and isolated cleft palate, which are among the most common birth defects that are well defined and easily diagnosed.

METHODS

We obtained the data for this study from the Danish Central Person Registry and from a data base on all children with facial-cleft defects born in Denmark between 1936 and 1987. The Danish Central Person Registry, which was established in 1968, registers all persons residing in Denmark on April 1, 1968, or later with a unique 10-digit identification number. The identification number of any person born before April 1, 1968, can be traced in the registry through his or her name and the date and place of birth. The registry includes the identification numbers of the mothers of virtually all infants with facial-cleft defects born after 1960. For infants born before 1952, the mother's identification number is available for less than 10 percent, and the proportion increases from 43 percent in the 1952 cohort to 96 percent in the 1959 cohort. The father is identified slightly less often, peaking at a 99 percent level in the 1970s. For births before January 1, 1978, the registry contains data only on the place of birth and not the home address. Both the place of birth and the home address (when it is given) are identified as to parish; the approximately 2200 parishes can be pooled to form 276 municipalities, which is still a fairly extensive division of a country of 44,000 km² and 5 million inhabitants. The registry does not contain information on the biologic parents of adopted children, but in the Danish birth cohorts considered (1952 to 1987), only about 1.2 percent of children born in Denmark were adopted, according to official statistics.

The Danish facial-cleft data base has previously been described in detail.^{14,15} In brief, the identification of cases has been based on data from two sources. The first, the Deaconess Hospital and University Hospital of Copenhagen, has been responsible for all surgical treatment of facial-cleft defects in Denmark since the 1930s. Throughout this period, lip operations have been performed on infants at about

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two months of age and palate operations at about two years of age. The surgical files contain information on major associated malformations or syndromes known at the time of surgery. The second source of data, the National Institute for Defects of Speech, coordinates multidisciplinary treatment for children with facial-cleft defects. Since 1954, midwives in Denmark have been obliged to report any newborn with a cleft lip or cleft palate to the institute. Facial cleft defects recognized later in a child's life (e.g., submucous cleft palate diagnosed after the development of speech difficulties) are also reported to the institute. Reported cases dating back to 1939 are registered, and information about major associated malformations is included. Both of these sources of data contain the names and dates of birth of the children with facial-cleft defects and, in nearly all cases, their places of birth. Other sources have been used, including a national registry of congenital malformations, a national death registry, and local registers, and capture-recapture methods have indicated that nearly all cases (99 percent) of liveborn infants with facial-cleft defects without associated anomalies have been identified, except for cases of submucous cleft palate, which often remains asymptomatic or nearly asymptomatic.^{14,15}

The facial-cleft data base includes information about 7290 liveborn infants, of whom 89 percent have unique identification numbers, 6 percent died before the introduction of identification numbers in 1968, and 5 percent could not be identified further than by name and date of birth. For the period from 1952 to 1987, 92 percent of the children in the facial-cleft data base have identification numbers.

The Danish facial-cleft data base and the Central Person Registry were linked by identification numbers in the following manner. The identification numbers of children with facial-cleft defects who were born between 1952 and 1987 were obtained through the facial-cleft data base. The parental identification numbers as well as the places of birth were obtained for these children from the Central Person Registry. The identification number of a mother was used to obtain from the Central Person Registry the identification numbers of children born after her first infant with a facial-cleft defect. Through the identification numbers of these younger siblings, the fathers and the places of birth could be identified in the Central Person Registry. Finally, these children were linked, by their identification numbers, to the facial-cleft data base to identify affected younger siblings. Only siblings born in Denmark between 1952 and 1987 were included, without reference to birth order. All multiple births were excluded.

Only infants with facial-cleft defects and no associated major or minor defects were considered in the study. Major defects included anomalies such as neural-tube defects, monogenic traits (Van der Woude's syndrome), and other disorders (trisomy and Pierre Robin's syndrome). Anomalies such as polydactyly and clubfoot were considered minor defects. Minimal anomalies such as nevi and undescended testes were not considered to be associated defects.

The risk of recurrence was estimated as the proportion of younger siblings with facial-cleft defects stratified according to the mothers' change of municipality and change of partner. Since a change of partner and a change of municipality are not independent events, a Mantel-Haenszel test was used to assess the effect of a change of municipality after stratification according to whether there was a change of partner, and vice versa.

RESULTS

We obtained information about 4189 mothers, each of whom had at least one infant with a facial-cleft defect born between 1952 and 1987. This total included 4108 mothers each with one infant having a facial-cleft defect, 74 mothers each with two infants having a facial-cleft defect, and 3 mothers each with three infants having this defect. The first affected infant was not necessarily the mother's first-born child. Four mothers who each had one infant with a cleft lip and one infant with an isolated cleft palate were not considered to have two infants with the same birth defect, because these two birth defects are etiologically distinct.¹⁶ Among the 4189 mothers, 1902 had additional children after

Table 1. Effect of Changes in Municipality or Sexual Partner on the Risk of Facial-Cleft Defects in Younger Infants of 1902 Mothers Who Had Already Had Infants with Such Defects.

PARTNER/MUNICIPALITY*	NO. OF YOUNGER SIBLINGS	NO. OF YOUNGER SIBLINGS WITH FACIAL-CLEFT DEFECTS (%)
Same/same	1425	48 (3.4)
Same/different	907	29 (3.2)
Different/same	97	0
Different/different	138	1 (0.7)
One or both unknown	125	2 (1.6)
Total	2692	80 (3.0)

*Municipality is the actual place of birth before January 1, 1978, and the mother's home address from that date on.

the first infant with a facial-cleft defect. A total of 2692 such younger siblings were identified (the infants with facial-cleft defects and their siblings were all born in the period 1952 to 1987) (Table 1). On the basis of the Danish facial-cleft data base, the prevalence of facial clefts at birth was estimated to be 0.2 percent during the period 1952 to 1987 (unpublished data).

The risk of recurrence of facial-cleft defects among younger siblings did not depend on whether the mothers moved to a new municipality (Table 1). Among the 907 infants of mothers who changed municipalities but not sexual partners, 29 (3.2 percent) had facial-cleft defects, as compared with 48 (3.4 percent) of 1425 infants of mothers who changed neither municipality nor partner (relative risk, 0.9; 95 percent confidence interval, 0.6 to 1.5). Change of partner and change of municipality are not independent events, but stratifying the results according to whether there was a change of partner did not alter the relative risk (0.9; 95 percent confidence interval, 0.6 to 1.5). A change of partner reduced the risk of recurrence. Among the 236 infants of mothers who changed partners, 1 (0.4 percent) had a facial-cleft defect, as compared with 77 (3.3 percent) of 2350 infants of mothers who did not change partners (relative risk, 0.1; 95 percent confidence interval, 0.02 to 0.9). When the effect of a change of partner was stratified according to whether there was a change of municipality, the results were similar (relative risk, 0.1; 95 percent confidence interval, 0.02 to 0.7). The results of analyses of subgroups based on the type of defect — cleft lip with or without cleft palate and isolated cleft palate — were similar, but the numbers of affected infants were small.

The results were similar if the analysis was restricted to the period after 1977 or if only the mothers' first and second pregnancies were considered (the latter analysis included 1290 mothers). An analysis identical in approach to that of the Norwegian study¹² (restricted to first and second pregnancies in the period after 1977 and using residence at the municipality level) had similar results, but the numbers were small. Among 29 infants of mothers who changed municipalities but not partners, 1 (3.4 percent) had a facial-cleft defect, as

compared with 3 (2.1 percent) of 143 infants of mothers who changed neither municipality nor partner (relative risk, 1.7; 95 percent confidence interval, 0.2 to 16.7). Among the 19 siblings of affected infants with different fathers, none had facial-cleft defects.

DISCUSSION

Our study focused on two well-defined birth defects — cleft lip with or without cleft palate and isolated cleft palate — although there probably is etiologic heterogeneity even within these categories. If an adverse outcome of pregnancy (such as the presence of a facial-cleft defect) decreases the probability of another pregnancy, the risk of recurrence will be underestimated if older siblings are included in the analysis,¹⁷ because families having an affected infant might be less likely to have more children. Therefore, we considered recurrence among younger siblings only. Since parental age is not related to the occurrence of facial-cleft defects, the analysis included all younger siblings.¹⁸ Separate analyses were performed that were restricted in various ways (considering only the first and second child or only the period after 1977). The restriction of the time period minimized the number of siblings who could not be linked to parents in the Central Person Registry and eliminated the possibility that there would be only a hospital address at birth for a child instead of a home address. The results of the main and the restricted analyses were similar.

Recurrence rates were probably somewhat underestimated in this study because of the missing identification numbers in the Danish facial-cleft data base. However, because only 8 percent of the cases in the data base of infants born between 1952 and 1987 were missing identification numbers and because the identification of cases of facial cleft by capture-recapture methods has been estimated to be nearly complete,¹⁴ it seems likely that the fraction of facial-cleft cases that were not identified in this study was considerably smaller than the estimated 20 percent not identified in the Norwegian study.¹² The estimates of the risk of recurrence of facial-cleft defects in the two studies were, however, very similar (3.6 percent in the Norwegian study and 3.0 percent in this study). Despite the probable underreporting of facial-cleft defects in the Norwegian study, it is likely that the recurrence of birth defects was reported accurately, since the mothers were undoubtedly aware of the possibility of a similar defect in their second children and therefore the likelihood of registration of the defect would be greater.

Both our study and the Norwegian study provide evidence that a change of sexual partner reduces the risk of recurrence of birth defects, a finding that emphasizes the importance of genetic factors in the causation of birth defects. The intriguing finding that a mother's change of residence between pregnancies protects against the recurrence of birth defects could not, however, be corroborated for facial-cleft defects in Denmark. The effect of change of a mother's municipality in the Norwegian study was due as much to changes in

the reference groups as to changes in the index-case group. Among couples who had healthy first children, the risk of having second children with birth defects was 47 percent higher for those who changed residences between the two births than for those who did not,¹² possibly because of a detection bias induced by movement from rural to urban areas with an associated increase in the availability of diagnostic expertise and facilities. Similarly, when a woman had had one infant with a birth defect, she and those providing her health care were undoubtedly aware of the possibility of a similar defect in the second child. If the second child did not in fact have the defect in question, he or she was more likely to be classified correctly in a specialized setting, whereas the high a priori probability of the defect might cause a false positive diagnosis in a healthy second child in a hospital with poorer diagnostic facilities. Such a detection bias would lead to lower recurrence rates among women who moved from rural to urban areas than among those who did not.

The study by Lie et al.¹² was based on a routine registration system (using birth certificates). Danish studies have shown that only about 75 percent of the birth certificates of children with facial-cleft defects contain any reference to the defect, although this defect is among the most easily diagnosed.¹⁹ Differences in the frequency of a defect determined by such systems could therefore reflect differences in rates of diagnosis and registration among hospitals more than true differences in the frequency of the defect.

The use of a Danish population reference group was not feasible in the present study, but a reanalysis of the Norwegian data¹² with a reference group similar to the one we used showed results similar to those obtained with the use of a population reference group. The present study did not include all the types of birth defects considered in the Norwegian study, but the facial-cleft defect is a good candidate for a defect caused by a gene-environment interaction. Our results show that the recurrence of facial-cleft defects is not linked to the residence of the mother but that having a different partner reduces a woman's risk of having a second infant with the same defect.

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