Maternal Passive Smoking and Risk of Cleft Lip With or Without Cleft Palate

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Background: Maternal smoking has been consistently associated with increased risk of cleft lip with or without cleft palate (CL/P). Few studies have explored the possible effect of passive smoking. We examined the association between maternal passive smoking and the risk of CL/P among nonsmoking women in China.

Methods: Subjects included 88 infants with CL/P and 651 infants with no major external birth defects. Data were collected by trained health workers through face-to-face interviews.

Results: The odds ratio (OR) for CL/P associated with maternal passive smoking was 1.8 (95% confidence interval = 1.1–2.8). After adjustment for maternal occupation, periconceptional flu or fever, and infant sex, the risk was 2.0 (1.2–3.4). The adjusted ORs for exposure levels of 1–6 times per week and more than 6 times per week (at least 1 cigarette each time) were 1.6 (0.9–2.9) and 2.8 (1.5–5.2), respectively.

Conclusion: Maternal passive smoking during pregnancy was associated with an increased risk for CL/P in offspring.

Orofacial clefts, particularly cleft lip with or without cleft palate (CL/P) are among the most common congenital malformations worldwide.[1] Many studies have suggested a positive association between maternal smoking and the risk of CL/P.[2] Few studies, however, have investigated the effect of passive smoking on risk of CL/P. In China, about two-thirds of Chinese adult men are regular smokers, whereas few Chinese women smoke; therefore women's passive smoking is widespread.[3] We examined the association between maternal passive smoking and the risk of CL/P in a Chinese population with high prevalence of orofacial clefts (about 3/1000).[4]

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METHODS

Data came from a population-based case-control study of external malformations in 4 counties (Pingding, Xiyang, Taigu, Zezhou) of Shanxi Province in China, which has been described elsewhere.[5] Briefly, cases were live born or stillborn infants with major external birth defects identified by an active surveillance system. Controls were infants without identified malformations, matched to cases by county, sex, maternal ethnic group, and approximate date of conception. Exposure information was collected by trained health workers through face-to-face interviews within 1 week after delivery. The study was approved by the Institutional Review Board of Peking University Health Science Center.

For this analysis, we used data collected between January 2003 and December 2006. The cases were liveborn or stillborn infants assigned in the surveillance system an ICD-9 diagnosis of 749.1 (cleft lip) or 749.2 (cleft lip and palate). All cases were reviewed by 3 pediatricians at Peking University Health Science Center. Passive smoking was defined as exposure to smoking on average at least once per week and at least 1 cigarette each time, from other people at home or in public places, from 1 month before to 2 months after pregnancy. For women who reported passive smoking, we also investigated the frequency of the passive smoking. To increase the power of this study, all controls, including controls for other external malformations as well as controls for CL/P, were compared with CL/P cases. We excluded infants of women who reported active smoking during the periconceptional period. Risks were estimated by the odds ratio (OR) and its 95% confidence interval (95% CI). Multivariable logistic regression was used to estimate the adjusted OR. Potential confounders adjusted for in the analysis included the matching variables (infant sex, season of conception, resident county), plus maternal age, education, occupation, gravidity, parity, history of birth defect in a previous pregnancy, flu or fever in early pregnancy, and periconceptional folic acid use. Maternal occupation, periconceptional flu or fever and infant sex were included in the final model. Data analysis was carried out using SPSS 11.5 (SPSS, Chicago, IL).

RESULTS

We collected questionnaires for 89 CL/P cases and 680 controls. Participation was about 70% for cases and 90% for controls. We excluded 1 case and 23 controls whose mother

reported active smoking during the periconceptional period or did not report smoking status. We further excluded 2 infants because of missing data on maternal passive smoking, and 4 infants whose mother was not Han ethnicity, the largest ethnic group in China. This left 88 cases and 651 controls in the final analysis. Nine cases (10%) had other major external malformations.

Case mothers were less likely to be farmers and more likely to have had a periconceptional flu or fever than control mothers. Infants with CL/P were more often boys compared with control infants. The distribution of other characteristics was similar for the 2 groups (Table 1). The OR of CL/P with maternal passive smoking was 1.8 (95% CI = 1.1–2.8). After adjustment for maternal occupation, periconceptional flu or fever and infant sex, the OR was 2.0 (1.2–3.4). There was a positive dose-response relationship between exposure frequency and the risk of CL/P: adjusted ORs were 1.6 and 2.8 for exposure frequencies of 1–6 times per week and more than 6 times per week, respectively ($P_{\text{for trend}} = 0.0012$, Table 2). The adjusted ORs were slightly higher among boys (2.3 [1.2–4.5]) than among girls (1.7 [0.8–3.9]). Neither the exclusion of the 9 CL/P cases with other malformations or exclusion of subjects with missing covariates in multivariable analyses changed the results substantially (not shown).

TABLE 1. Demographic and Obstetric Characteristics According to Case or Control Study Groups in Shanxi Province, China, 2003–2006

Characteristics	Cases (n = 88) No.[a] (%)[b]	Controls (n = 651) No.[a] (%)[b]
Season of conception		
Spring	19 (22)	148 (23)
Summer	20 (23)	159 (25)
Autumn	22 (25)	151 (24)
Winter	26 (30)	181 (28)
Resident county		
Pingding	19 (22)	188 (29)
Xiyang	11 (13)	73 (11)
Taigu	26 (30)	122 (19)
Zezhou	32 (36)	268 (41)
Maternal age (years)		
<25	43 (49)	273 (42)
25–29	31 (36)	202 (31)
30–34	9 (10)	143 (22)
≥35	4 (5)	28 (4)
Maternal occupation		
Farmer	53 (60)	467 (72)
Other	35 (40)	184 (28)
Education		
Primary school or lower	12 (14)	45 (7)
Junior high school	60 (70)	520 (80)
High school	11 (13)	65 (10)
College or higher	3 (4)	18 (3)
Gravidity		
1	55 (63)	346 (53)
2	26 (30)	220 (34)
≥3	7 (8)	85 (13)
Parity		
Primiparas	84 (99)	604 (95)
Multiparas	1 (1)	29 (5)
History of birth defect-affected pregnancy		
No	83 (94)	635 (98)
Yes	5 (6)	15 (2)
Maternal flu or fever in early pregnancy		
No	54 (68)	572 (91)
Yes	26 (33)	56 (9)
Periconceptional folic acid use		
No	82 (94)	590 (96)
Yes	5 (6)	26 (4)
Infant sex		
Male	54 (61)	313 (49)
Female	34 (39)	331 (51)

[a]Values for some characteristics may not be equal to total numbers of case or control groups because of missing values.
[b]Values for some characteristics may not be equal to 100 because of rounding.

DISCUSSION

Our study suggests that maternal passive smoking during periconceptional period may increase risk of CL/P in offspring. The risk appeared to rise with more frequent exposure. Few previous studies have explored the effect of passive smoking on CL/P, although the link between active maternal smoking and CL/P has been well established.[2] Shaw et al[6] found nonsmoking women who reported exposure to smokers in their home at a close distance (within 6 feet) were at increased risk for isolated CL/P (adjusted OR = 2.0 [95% CI = 1.2–3.4]). Little et al[7] suggested a weak effect of passive smoking in nonsmokers. The adjusted OR for the highest tertile of hours of passive smoking, compared with no exposure, was 1.5 (95% CI = 0.7–3.2) for CL/P. Lie et al[8] observed a 1.6-fold increased risk of isolated CL/P associated with passive smoking (adjusted OR = 1.6 [95% CI = 1.0–2.5]). A recent nested case-control study[9] observed an increase in risk of CL/P (OR = 3.3 [95% CI = 0.9–12]) for women with levels of cotinine that indicate exposure to passive smoking. However, based on a larger case-control study, Honein et al[10] did not find an association between exposure to any passive smoking at home or work and the risk of CL/P (OR = 1.2 [95% CI = 0.7–1.8]) among nonsmoking mothers. The discrepancy of these results may result from different definitions of passive smoking, the different ethnic/racial groups, or other factors.

We found the risk of CL/P associated with maternal passive smoking tended to be higher for boys than for girls. This is similar to Romitti et al's report,[11] which suggested a greater effect of active smoking in boys. However, Little et al[7] found that the CL/P risk with smoking was greater in girls, and Honein et al[10] suggested the effects of maternal smoking on CL/P were similar for boys and girls.

TABLE 2. Maternal Passive Smoking During Periconceptional Period and Risk for CL/P in Shanxi Province, China, 2003–2006

	Cases (n = 88) No. (%)	Controls (n = 651) No. (%)	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
No passive smoking	29 (33)	303 (47)	1.0	1.0
Any passive smoking[b]	59 (67)	348 (54)	1.8 (1.1–2.8)	2.0 (1.2–3.4)
1–6 times/week	31 (35)	234 (36)	1.4 (0.8–2.4)	1.6 (0.9–2.9)
>6 times/week[c]	28 (32)	114 (18)	2.6 (1.5–4.5)	2.8 (1.5–5.2)

[a]Adjusted for maternal occupation, periconceptional flu or fever and infant sex.
[b]Exposure to smoking on average at least once per week and at least one cigarette each time from other people at home or at other public places, from one month before to 2 mo after pregnancy.
[c]Test for trend $P = 0.0012$ for comparison of no passive smoking, 1–6 times/week, and >6 times/week between the case group and the control group.

Several limitations should be considered in interpreting our results. Although the study was population-based, differential participation between cases and controls (70% vs. 90%) may have created selection bias. Recall bias is the main concern in a case-control study. In our study, women were interviewed within the first week after delivery, and local women would have little knowledge about a possible association between passive smoking and CL/P. These factors should have reduced the problem of recall bias. The prevalence of passive smoking (54%) among control mothers is similar to that reported in the Chinese National Study.[7] For the associated cases, other malformations were limited to only external defects, and therefore we could not identify syndromes or sequences.

Our study has several strengths. The study was conducted in a high clefts prevalence area, which increased the likelihood of identifying important risk factors. The high prevalence of men's smoking and low prevalence of women's smoking in the study population, combined with the restriction to nonsmoking mothers, allowed us to examine the effect of maternal passive smoking unconfounded by maternal active smoking.

Women's passive smoking is an important public health problem in China owing to the high proportion of male smokers and poor awareness of smoking damage. Our results, together with evidence of the association of CL/P with maternal active smoking, suggest that passive smoking could be an important contribution to CL/P risk in China.

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