

Parental smoking and risk of childhood cancer: hospital-based case-control study in Shiraz

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تدخين الوالدين واختطار سرطان الطفولة: دراسة حالات مُشَهَّدة بالشواهد المرتكزة على المستشفى في شيراز
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الخلاصة: تهدف هذه الدراسة للحالات المُشَهَّدة التي أُجريت في مدينة شيراز إلى تحديد العلاقة بين تدخين الوالدين وبين سرطان الطفولة. وقد أُجريت استبيان لثمان وتسعين أمًّا لأطفال تم تشخيص إصابتهم بالسرطان حديثاً قبل بلوغهم سن الرابعة عشرة، ولمئة طفل من الشواهد المتوافقين معهم في العمر والجنس. ولم يترابط تدخين الأمهات (قبل وأثناء الحمل وبعد الولادة)، ولا عدد السجائر التي تدخنها الأمهات بزيادة اختطار إصابة أطفالهن بالسرطان، إلا أن تعرّض الأمهات القسريّ للتدخين السلبي أثناء الحمل قد زاد من اختطار إصابة أطفالهن بالسرطان (OR = 3.6, 5.0 - 1.3). كما ترابط تدخين الآباء قبل الحمل (OR = 1.8, 6.0 - 1.4; IC/95). وأثناء الحمل (OR = 3.0, 5.0 - 1.4; IC/95). ترابطاً يُعتدُّ به إحصائياً بزيادة اختطار السرطان، وقد ازداد الترابط مع شدة التدخين. ولم تشاهد علاقة بين زيادة اختطار الإصابة بسرطان الطفولة وبين تدخين الآباء بعد ولادة الطفل.

ABSTRACT This case-control study in Shiraz aimed to determine the relationship between parental smoking and childhood cancer. A questionnaire was completed by the mothers of 98 children newly diagnosed with cancer before the age of 14 years and 100 age- and sex-matched controls. Maternal smoking (prior to and during pregnancy and after the birth), and the numbers of maternal cigarettes smoked were not associated with an increased risk of childhood cancer. However, maternal exposure to passive smoke during pregnancy increased the risk of cancer childhood (OR = 3.6, 95% CI: 1.3-5.0). Father's smoking prior to (OR = 1.8, 95% CI: 1.4-6.0) and during pregnancy (OR = 3.0, 95% CI: 1.4-5.0) was significantly associated with an increased risk of cancer and this increased with heavy smoking. There were no relationship between an enhanced risk of childhood cancer and father's smoking after the child's birth.

Tabagisme des parents et risque de cancer chez l'enfant : une étude cas-témoins en milieu hospitalier à Chiraz

RÉSUMÉ La présente étude cas-témoins, conduite à Chiraz, visait à déterminer la relation entre le tabagisme parental et le cancer chez l'enfant. Un questionnaire a été rempli par les mères de 98 enfants chez lesquels un diagnostic de cancer avait été posé récemment et avant l'âge de 14 ans et par 100 témoins appariés selon l'âge et le sexe. Le tabagisme maternel (avant, pendant et après la grossesse), et le nombre de cigarettes fumées par la mère n'étaient pas associés à un risque accru de cancer chez l'enfant. Toutefois, l'exposition de la mère au tabagisme passif pendant la grossesse augmentait le risque de cancer chez l'enfant (O.R. = 3,6 ; IC à 95 % : 1,3-5,0). Le tabagisme paternel avant la grossesse de la mère (O.R. = 1,8 ; IC à 95 % : 1,4-6,0) et pendant (O.R. = 3,0 ; IC à 95 % : 1,4-5,0) était significativement associé à un risque accru de cancer, et ce risque était même supérieur en présence d'un tabagisme paternel important. Aucun lien n'a été retrouvé entre un risque accru de cancer chez l'enfant et le tabagisme paternel après la naissance.

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Introduction

The evidence for a link between parental smoking during pregnancy and childhood cancer is controversial. Several types of childhood cancer have been researched in relation to parental smoking including kidney cancer, eye tumours, Ewing's sarcoma, lung cancer and endocrine tumours. However, the results are too varied to permit a conclusion [1].

Genetic changes that occur in certain childhood haematopoietic cancers may originate *in utero* [2]. A case-control study reported a non-significant increasing trend for risk of childhood leukaemia associated with paternal pre-conception smoking and a significantly decreasing trend for maternal smoking during pregnancy [3]. In contrast, a large case-control study did not detect evidence of the relationship between childhood leukaemia and paternal or maternal smoking before or during pregnancy [4]. Smoking also appears to lead to oxidative damage and aneuploidy of the sperm [5], supporting a finding that the rate of childhood cancer is higher in those whose fathers smoke more than 10 cigarettes per day [6]. Some studies [7,8] but not others [9,10] have shown a positive association between paternal smoking and brain tumours in children. A research study also indicated that regular exposure of the mother to the father's cigarette smoke during pregnancy was associated with an increased risk of astroglial tumours in the children [11]. Preston-Martin also reported a positive association between brain tumours and the mother living with a smoker during pregnancy [12].

Although the data are inconclusive at present, smoking remains an exposure of interest because of its known carcinogenicity for numerous organs [13]. The present study in Shiraz, Islamic Republic of Iran, aimed to add to the evidence on this subject with an analysis of paternal and maternal smoking during pregnancy and after the birth with the risk of childhood cancer.

Methods

Data were obtained from a hospital-based case-control study conducted in Shiraz University of Medical Science (SUMS) between December 2007 and November 2008.

Sample

Eligible cases were all the children newly diagnosed with any type of cancer before the age of 14 years, whom the interviewers were authorized to contact by the physician. The inclusion criteria were having literate parents, no previous diagnosis of cancer and being diagnosed for at least 30 days (or since date of recurrence/relapse).

The sample size of the study with a power of 80%, $\alpha = 5\%$, prevalence of cancer in children = 12.9% and odds ratios of 2.8 was estimated to be 120 persons in the case and control groups. A total of 220 childhood cancer patients were newly diagnosed at the cancer centre of SUMS over the study period. Of these, 98 parents were eligible and participated in the study. The control subjects comprised 120 children without any disease or other birth defects who were selected randomly from the students in schools and day care in the 4 districts of the Ministry of Education, matched for age and sex. From the control group, 120 children/parents met the inclusion criteria and 100 of the parents consented to participate in the study and returned the questionnaire to the researcher. Therefore the final sample included 198 children and their parents.

Data collection

Medical interviewers conducted face-to-face interviews with the parents, using a specially designed questionnaire based on previous research [14,18]. This included questions on the parents' sociodemographic characteristics and the child's age and sex. Maternal smoking history included smoking status (ever smoked or current smoker: yes

or no), intensity of smoking (number of cigarettes smoked per day) and the timing of smoking (before the current pregnancy, during the pregnancy and after the birth). The history of paternal smoking included the same questions as for maternal smoking. The mothers were asked whether during pregnancy the atmosphere at home was smoky (maternal exposure to passive smoke during pregnancy).

The study protocol was reviewed and approved by the ethics committee of the cancer research centre of SUMS. The parents were informed about the study, both verbally and in writing. Participation was voluntary and the parents could stop their involvement without giving any reason. The questionnaires were coded in order to guarantee anonymity.

The internal consistency of the questionnaire was measured using Cronbach alpha reliability ($\alpha = 0.84$). Content validity for the questionnaire was also supported.

Analysis

Descriptive statistics were used to examine the data. The non-parametric chi-squared test and 2 independent samples *t*-test was used to assess the relationship between the variables. Statistical analysis was performed using unconditional logistic regression models including the stratification variables (age, sex and parental education) for measuring the risk of childhood cancer associated with parental smoking.

Separate analyses and regressions were also used to estimate specific odds ratios (ORs) and their 95% confidence intervals (CIs) for cancer patients. SPSS, version 10.0 was used to create descriptive statistics, including frequency statistics and measures of central tendency, to describe the demographic characteristics of the sample and the major variables of the study. A *P*-value ≤ 0.05 was considered statistically significant.

Results

Socioeconomic data

The distribution of cases and controls by socioeconomic variables is shown in Table 1. There were slightly more males (51.0%) than females with childhood cancer (49.0%). However, a significantly higher percentage of children in the control group were female (52.0% versus 48.0%; $\chi^2 = 0.26, P > 0.05$). The age distribution peaked in the case and control groups at ages 6–10 years (58.2% and 56.0%). The groups were nearly identical in age: mean 8.9 (SD 4.4) years versus 8.9 (SD 4.4) years for the case and control groups respectively ($t = 0.18, P > 0.05$). There were no statistically significant differences in the age and sex distributions between the case and control groups.

The mothers of the control group were significantly younger than those of the cases: mean age 32.2 (SD 5.4) years versus 35.3 (SD 6.9) years respectively ($t = 5.18, P \leq 0.05$). The father's age were also significantly different in the case and control groups: mean age 40.9 (SD 9.1) years versus 38.8 (SD 6.9) years respectively ($t = 4.69, P \leq 0.05$).

The case families were of significantly lower economic status than those of the controls ($\chi^2 = 7.13, P \leq 0.05$). In addition, the level of education of the case families was significantly lower than the control group (for mother's education $\chi^2 = 87.43, P < 0.001$; for father's education $\chi^2 = 58.68, P < 0.001$).

Smoking exposure and risk of cancer

Among the mothers of cases, 1 (1.0%) reported ever having smoked both prior to and during pregnancy, compared with 3 (3.0%) of the control mothers. After the birth, the proportions of case and control mothers who had smoked were the same (1.0%). The overall risk of cancer was not significantly associated with maternal smoking at any stage, prior to pregnancy ($\chi^2 = 0.64, P > 0.05$) (OR = 0.33; 95% CI: 0.4–3.9),

during pregnancy ($\chi^2 = 0.64, P > 0.05$) (OR = 0.33; 95% CI: 0.4–3.0) or after the birth ($\chi^2 = 0.11, P > 0.05$) (OR = .02; 95% CI: 0.6–2.5) (Table 2).

The mothers in the case and control groups did not vary by the number of cigarettes smoked daily ($t = 0.03, P > 0.05$). Only 1 of the case mothers and 3 of the control mothers reported having smoked ≥ 5 cigarettes during pregnancy. Thus there was no association with the number of cigarettes smoked by mothers (OR = 0.03, 95% CI: 0.3–2.5).

In the case group, 36.7% of fathers reported smoking prior to the mother's pregnancy compared with 29.0% of the control group fathers. Paternal smoking was associated with cancer prior to ($\chi^2 = 3.25, P < 0.05$) (OR = 1.8, 95% CI: 1.4–6.0) and during the mother's pregnancy ($\chi^2 = 3.18, P < 0.05$) (OR = 3.0, 95% CI: 1.4–5.0). In addition, there was an association between number of cigarettes smoked by fathers and childhood cancer ($t = 2.58, P < 0.05$); children whose fathers smoked ≥ 11 cigarettes per day during the mother's pregnancy had a > 2.7-fold higher risk of cancer (OR = 2.7, 95% CI: 1.4–6.0). However, the relationship between childhood cancer and paternal smoking after the birth was not significant (OR = 0.02, 95% CI: 0.3–5.9).

The regression analysis also showed a 3.6-fold increased risk of childhood cancer for mothers who reported being exposed to passive smoke during pregnancy ($\chi^2 = 4.23, P < 0.05$; OR = 3.6, 95% CI: 1.3–5.0).

Discussion

This study found no relationship between the risk of cancer childhood and maternal cigarette smoking at any stage—prior to pregnancy, during pregnancy or after the birth. There are currently no arguments in support of an influence of maternal smoking during pregnancy on the risk of childhood

cancer [14], tumours of the brain or central nervous system [15] and leukaemia [3,14], and the present results are consistent with this fact. In only a few studies was maternal smoking significantly associated with the risk of cancer [7,8,16]. All the smoker mothers in the study smoked only 5 or less cigarettes per day. The low number of cigarettes smoked per day by mothers may partially explain the lack of association between maternal smoking and the risk of childhood cancer in our study. Our findings agree with those of case-control studies conducted in Germany and the UK [3,17]. In addition, MacArthur et al. reported there was no relationship between childhood cancer and number of cigarettes smoked during pregnancy [18].

On the other hand, the data showed an association between childhood cancer and father's smoking prior to and during pregnancy. There was also a 2.7-fold higher risk of cancer in children whose fathers smoked more than 11 cigarettes per day compared with men who did not smoke. This was similar to the results of Memegaux et al. [14].

Fraga et al. reported that the level of 8-hydroxy-2'-deoxyguanosine, a product of oxidative DNA damage, was 50% higher in the sperm of smokers compared with that of non-smokers [19]. Shi et al. demonstrated that, compared with non-smoking men, light and heavy smoking men were more likely to manufacture abnormal sperm with disomy of chromosome 15, which could be linked to development of childhood cancer [20]. These data are consistent with a possible mechanism linking paternal preconception smoking to an enhanced risk of childhood cancer [21]. In a number of studies, paternal smoking, especially in the prenatal period, has been shown to increase the risk of childhood leukaemia [6–8,21–23]. In another study the associations with father's smoking in the absence of mother's smoking were found for all cancers combined, as well as for acute

Table 1 Description of the case and control children and parents

Variable	Cases (n = 98)		Controls (n = 100)		Statistics
	No.	%	No.	%	
Child's age (years)					
< 2	3	3.1	3	3.0	
2-5.9	13	13.3	14	14.0	
6-9.9	58	58.2	56	56.0	
10-14	24	24.5	27	27.0	<i>t</i> = 0.18
Mean (SD)	8.87 (4.42)		8.93 (4.40)		<i>P</i> > 0.05
Child's sex					
Female	48	49.0	52	52.0	$\chi^2 = 0.26$
Male	50	51.0	48	48.0	<i>P</i> > 0.05
Mother's age (years)					
< 20	3	3.1	4	4.0	
20-24.9	10	10.2	13	13.0	
25-29.9	24	24.5	31	31.0	
30-34.9	38	38.8	42	42.0	
≥ 35	23	23.5	10	10.0	<i>t</i> = 5.18
Mean (SD)	35.25 (6.87)		32.24 (5.40)		<i>P</i> ≤ 0.05
Father's age (years)					
< 20	0	0.0	0	0.0	
20-24.9	1	1.0	2	2.0	<i>t</i> = 4.69
25-29.9	26	26.5	29	29.0	<i>P</i> ≤ 0.05
30-34.9	29	29.6	32	32.0	
≥ 35	42	42.9	37	37.0	
Mean (SD)	40.92 (9.12)		38.81 (6.94)		
Mother's education					
Uneducated	37	37.8	2	2.0	
1-8 grade	43	43.9	28	28.0	$\chi^2 = 78.43$
9-12 grade	14	14.3	31	31.0	<i>P</i> < 0.001
College degree	4	4.1	39	39.0	
Father's education					
Uneducated	27	27.6	2	2.0	
1-8 grade	40	40.8	26	26.0	$\chi^2 = 58.68$
9-12 grade	20	20.4	31	31.0	<i>P</i> < 0.001
College degree	11	11.2	42	42.0	
Economic status					
Good	11	11.2	20	20.0	
Moderate	58	59.2	73	73.0	$\chi^2 = 7.13$
Poor	29	29.6	7	7.0	<i>P</i> < 0.05

SD = standard deviation.

lymphocytic leukaemia, lymphomas and brain cancer [7].

The findings of the study indicated that there was no relationship between childhood cancer and paternal cigarette smoking after the birth. This result was

similar to that of other studies [14,22]. However, Lee et al. reported that post-natal paternal smoking might play a role in the development of childhood leukaemia and that paternal smoking at home, rather than paternal smoking

itself, significantly increased the risk of childhood leukaemia [22].

In the current study mother's exposure to smoke during pregnancy was associated with a significant increase in the risk of childhood cancer (OR = 3.6, 95%

Table 2 Smoking exposure and risk of childhood cancer: logistic regression

Variable	Mothers			Fathers			
	Cases (n = 98) %	Controls (n = 100) %	OR (95% CI)	Cases (n = 98) %	Controls (n = 100) %	OR (95% CI)	P-value
Smoked prior to pregnancy							
Yes	1.0	3.0	0.33 (0.4-3.9)	36.7	29.0	1.80 (1.4-6.0)	
No	99.0	97.0	1 (Ref)	62.2	71.0	1 (Ref)	< 0.05
Smoked during pregnancy							
Yes	1.0	3.0	0.33 (0.4-3.9)	36.7	12.0	3.00 (1.4-5.0)	
No	99.0	97.0	1 (Ref)	62.2	88.0	1 (Ref)	< 0.05
Smoked after birth							
Yes	1.0	1.0	1.02 (0.6-2.5)	33.6	36.0	0.02 (0.3-5.9)	
No	99.0	99.0	1 (Ref)	66.3	54.0	1 (Ref)	> 0.05
Number of cigarettes smoked/day							
≤ 5	100.0	100.0	1 (Ref)	5.5	17.8	1 (Ref)	< 0.05
6-10	0.0	0.0	0.02 (0.3-2.9)	19.4	53.6	1.20 (1.1-3.0)	
≥ 11	0.0	0.0	0.03 (0.3-2.5)	75.1	28.6	2.70 (1.4-6.0)	
Mother's exposure to passive smoke during pregnancy							
Yes	54.1	30.0	3.6 (1.3-5.0)	-	-	-	-
No	45.9	70.0	1 Ref	-	-	-	-

OR = odds ratio; CI = confidence interval; Ref = reference category.

CI: 1.3-5.0). Maternal exposure to passive smoke during pregnancy has been associated with cancer in children [11]. However, other researchers indicated no association between cancers such as leukaemia and passive smoking at home [14]. Environmental exposure to cigarette smoking among children has been related to the level of biomarkers of genetic damage, such as an increased rate of sister chromatid exchange, a cytogenetic biomarker [24].

One limitation of the present study was the small number of cases with cancer, which led to high statistical uncertainty in the estimated associations.

There were also other important limitations in the study design. The children included in the study were aged from 0-14 years. Therefore, especially for the older age groups of children with cancer, mothers and fathers were asked to remember specific details of smoking habits from a long time ago and this may have affected the accuracy of their recall. Furthermore, the lifetime duration of exposure to tobacco smoke was much longer for some children than others and this may also have affected their risk of developing cancer.

Conclusion

The results from the current study suggest that the paternal smoking and maternal exposure to passive smoke during pregnancy may be important in the development of childhood cancer.

Currently, the public is becoming generally more aware of the detrimental impact of passive maternal smoking during pregnancy on the health of the fetus. Parents need more information on the adverse effects of environmental tobacco smoke and the benefits of stopping smoking. The knowledge of a potentially harmful effect of paternal smoking exposure may give parents a strong incentive to quit smoking.

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