

# Paternal Cigarette Smoking and the Risk of Childhood Cancer Among Offspring of Nonsmoking Mothers

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**Background:** Cigarette smoking has been shown to increase oxidative DNA damage in human sperm cells. Assessment of the role of cigarette smoking in the etiology of childhood cancer has focused primarily on the effect of maternal smoking. Similar studies in relation to paternal smoking, however, have been inconclusive. Few studies have evaluated the effect of paternal smoking in the preconception period, and most of these could not disentangle the effects of paternal from maternal smoking. **Purpose:** We investigated the relationship of paternal smoking, particularly in the preconception period, with childhood cancer among offspring of the nonsmoking mothers. **Methods:** We conducted a population-based, case-control study in Shanghai, People's Republic of China, where the prevalence of smoking is high among men but extremely low among women. The study included 642 childhood cancer case patients (<15 years of age) and their individually matched control subjects. Information concerning parental smoking, alcohol drinking, and other exposures of the index child was obtained by direct interview of both parents of the study subjects. Odds ratios (ORs), derived from conditional logistic regression models, were used to measure the association between paternal smoking and risk of childhood cancers. **Results and Conclusions:** Paternal preconception smoking was related to a significantly elevated risk of childhood cancers, particularly acute leukemia and lymphoma. The risks rose with increasing pack-years of paternal preconception smoking for acute lymphocytic leukemia (ALL) ( $P$  for trend = .01), lymphoma ( $P$  for trend = .07), and total cancer ( $P$  for trend = .006). Compared with children whose fathers had never smoked cigarettes, children whose fathers smoked more than five pack-years prior to their conception had adjusted ORs of 3.8 (95% confidence interval [CI] = 1.3-12.3) for ALL, 4.5 (95% CI = 1.2-16.8) for lymphoma, 2.7 (95% CI = 0.8-9.9) for brain tumors, and 1.7 (95% CI = 1.2-2.5) for all cancers combined. Statistically significant increased risks of cancer were restricted to children under the age of 5 years at diagnosis or those whose fathers had smoked during all of the 5 years prior to conception. **Implications:** Further studies are needed to confirm the association of paternal smoking with increased risk of cancer in offspring, to clarify the pattern of risks in relation to the timing of cigarette smoking, and to elucidate the biologic mechanism involved in predisposing the offspring to cancer. For example, it may be that paternal smoking induces prezygotic genetic damage that, in turn, acts as the predisposing factor. [J Natl Cancer Inst 1997;89:238-43]

The relationship of paternal cigarette smoking with childhood cancer has not been extensively evaluated, and the results have

been inconsistent. Assessment of the role of cigarette smoking in the cause of childhood cancer has focused primarily on the effect of maternal smoking (1-7). A few studies (8-10) have reported a positive association between paternal smoking and childhood cancer after adjusting for maternal smoking, but others (11-18) have found no effect of paternal smoking on the development of cancer in the offspring.

Most previous studies have not separately examined the effects of paternal smoking during different exposure windows, including preconception or postconception periods. Nor have many studies adjusted for potentially important confounding effects, particularly maternal smoking, on the association between paternal smoking and childhood cancer. To address these and other possible limitations of earlier studies, we analyzed data from a population-based, case-control study of childhood cancer in Shanghai, People's Republic of China, where the prevalence of cigarette smoking is high among men but extremely low among women [ $<1\%$  of young adult females are smokers (19,20)]. This study provided a unique opportunity to evaluate the role of paternal smoking in the absence of maternal smoking on the cause of childhood cancer.

## Materials and Methods

The methods for our comprehensive population-based, case-control study of childhood cancer in Shanghai, People's Republic of China, have been described in detail elsewhere (21,22). Briefly, eligible case patients were permanent residents of urban Shanghai under the age of 15 years who were newly diagnosed with acute leukemia during 1985 through 1991 or with lymphoma, brain tumors, or other childhood cancers during 1981 through 1991. All cases were ascertained from the population-based Shanghai Cancer Registry, which was established in 1963. A total of 680 case patients (response rate = 83% of eligible case patients) were successfully interviewed.

Control subjects were selected from the general population of urban Shanghai using a household group (a local government administrative unit, total number = 65 363) as the primary sampling unit and were individually matched to cases on sex and year of birth. A total of 642 control subjects were successfully recruited and there were no refusals. Because of financial constraints, however, matched control subjects were not obtained for 38 case patients, resulting in 642 case-control pairs for the current analysis.

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See "Notes" following "References."

Mothers and fathers of the study subjects (index children) were interviewed independently in person by trained nurses. A structured questionnaire was used to obtain information on demographic characteristics, birth-related factors, childhood medications, residential history, and familial and genetic factors, as well as on maternal and paternal medications, occupation, and other environmental and lifestyle factors, such as smoking and alcohol use prior to and following the conception of the index child. A cigarette smoker was defined as one who smoked at least one cigarette per day for 6 months or longer. Only three mothers of study subjects (one case subject and two control subjects) ever smoked, and these subjects were excluded from the present analyses. Fathers who were current or former cigarette smokers were asked detailed information about the number of cigarettes smoked per day and the cumulative duration of smoking before the conception of the index subject (henceforth referred to as preconception smoking) and after the birth of the index child, respectively. Since maternal passive smoking during pregnancy was not considered to be a major risk factor when the study was initiated, information was not obtained about paternal smoking during the index pregnancy.

Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to measure the association of paternal smoking and alcohol drinking with childhood cancer. Conditional logistic regression analysis was performed to derive ORs and CIs after adjustment for potential confounding variables (Table 1) (23). Categorical variables were analyzed by assigning indicators for each category in the model. Trend tests were calculated by using the median value for control subjects as the score for each category. Data were analyzed for all cancers combined and separately for three major categories of childhood cancers: acute leukemia (International Classification of Diseases [ICD], 9th Revision 204.0, 205.0, 206.0, 207.0, and 208.0), lymphoma (ICD-9 200-202), and brain tumors (ICD-9 191). Further analyses were also conducted for acute lymphocytic leukemia (ALL) and acute myelocytic leukemia (AML).

## Results

Of the 642 case patients included in the current analysis, acute leukemia ( $n = 166$ ), lymphoma ( $n = 87$ ), and brain tumors ( $n = 107$ ) accounted for 25.9%, 13.6%, and 16.7%, respectively. Approximately two thirds of the acute leukemia cases were ALL ( $n = 114$ ), and one third were AML ( $n = 52$ ). The majority of the patients with lymphoma (72 [83%] of 87) in this study were diagnosed with non-Hodgkin's lymphoma. The remaining cancers included 48 (7.5%) soft-tissue sarcomas, 32 (5%) bone cancers, 25 (3.9%) retinoblastomas, and 177 (27.6%) cancers of other sites. Approximately 93% (154 of 166) of acute leukemia cases, 96% (84 of 87) of lymphoma cases, and 56% (60 of 107) of brain tumors were histologically confirmed. Of the nonhistologically confirmed brain tumors (47 of 107), 71% (33 of 47) were diagnosed by computer-assisted tomographic scans. Almost half of all cancer case patients (48%) were under the age of 5 years at diagnosis (Table 1). Cancers were generally more common in boys than girls, except for brain tumors, which affected similar proportions of boys (49%) and girls (51%). The birth weight was almost the same between case patients (median = 3200 g) and control subjects (median = 3200 g), although a small, but statistically significant, increase was found for acute leukemia case patients compared with control subjects (median = 3250 g for case patients versus 3200 g for control subjects) (Table 1). Fathers of the cancer patients tended to be older, more educated, and have higher per capita income than those of the control children. Paternal alcohol drinking was similar for acute leukemia case patients versus control subjects, but fathers of control subjects were more likely to have consumed alcohol than fathers of children with brain tumors and lymphoma (Table 1). Therefore, paternal alcohol consumption was treated as a potential confounder in the analysis.

Fathers of case patients were more likely to have smoked

cigarettes at some point during their lifetime than control subject fathers. After adjustment for birth weight, family income, paternal age, education, and alcohol consumption, fathers who had ever smoked cigarettes were 30% more likely (OR = 1.3; 95% CI = 1.0-1.7) to have an offspring who developed cancer than control fathers (Table 2). Risks by type of cancer among offspring of fathers who had ever smoked cigarettes were 1.3 (95% CI = 0.7-2.4), 4.0 (95% CI = 1.3-12.5), and 1.4 (95% CI = 0.6-3.2) for acute leukemia, lymphoma, and brain tumors, respectively. Considering all childhood cancers, elevated risks, however, were mainly confined to offspring of fathers who started smoking before the age of 20 years, those who smoked for more than 15 years, and fathers whose cumulative smoking was more than 10 pack-years (Table 2). No clear dose-response relationships were observed between the number of cigarettes smoked per day and the risk of total or specific types of childhood cancer.

Further analyses were performed to examine potential differences in cancer risk among offspring according to the exposure period (e.g., before conception or after the birth of the index child) (Table 3). Excess risks of childhood cancer concentrated mainly among children whose fathers smoked for longer periods and more heavily before conception. Elevated risks were observed for acute leukemia (OR = 2.4; 95% CI = 1.1-5.6), ALL (OR = 3.8; 95% CI = 1.3-12.3), AML (OR = 2.3; 95% CI = 0.4-14.8), lymphoma (OR = 4.5; 95% CI = 1.2-16.8), brain tumors (OR = 2.7; 95% CI = 0.8-9.9), and for all cancers combined (OR = 1.7; 95% CI = 1.2-2.5) among offspring of fathers who smoked more than 5 pack-years before conception of the index child. Statistical testing to determine whether childhood cancer risks rose with increasing cumulative paternal preconception cigarette smoking revealed a marginal or significant trend for acute leukemia ( $P = .02$ ), ALL ( $P = .01$ ), lymphoma ( $P = .07$ ), and all sites combined ( $P = .006$ ) (Table 3). In contrast, levels of paternal smoking after the birth of the index child were generally not associated with a significant increase in risk of childhood cancers, except for lymphoma. Similar patterns were observed when cancer risks were assessed separately according to the duration of smoking or the number of cigarettes smoked per day, but estimates were less consistent for the latter (data not shown).

Only 1% of the fathers of control subjects and 2% of the fathers of case patients who smoked before the child's conception quit after the birth of the child; however, about 13% of fathers of control subjects and 12% of fathers of case patients who had not smoked before the conception of the index subject began smoking following the birth of the child. Paternal smoking initiated subsequent to the birth of the index child was not associated with an excess risk of childhood cancer (OR for overall childhood cancers = 1.0; 95% CI = 0.6-1.7), nor were the increased smoking levels following birth of the index child (seen in 40% of the fathers who had smoked prior to the birth) related to higher risks of childhood cancer (data not shown).

Further analysis was performed to assess risks associated with various durations of smoking according to the number of cigarettes smoked per day. Risk of childhood cancer was not linked with the number of cigarettes smoked per day among short-term smokers (e.g., those fathers whose total duration of cigarette smoking prior to conception was <5 years), with ORs of 1.2, 0.9,

**Table 1.** Comparison of demographic characteristics and potential confounders for case patients and control subjects, Shanghai, People's Republic of China, 1981 through 1991

Characteristic	All cancers (n = 642 pairs)		Acute leukemias (n = 166 pairs)		Lymphoma (n = 87 pairs)		Brain tumors (n = 107 pairs)	
	Case patients, %*	Control subjects, %	Case patients, %	Control subjects, %	Case patients, %	Control subjects, %	Case patients, %	Control subjects, %
Age, y								
0-4	48	48	50	50	45	45	42	42
5-9	32	32	38	38	40	40	34	34
10-14	20	20	12	12	15	15	24	24
Sex								
Boys	57	57	63	63	68	68	49	49
Girls	43	43	37	37	32	32	51	51
Birth weight, g								
<3000	25	26	19	31	29	24	28	26
3000-3250	32	33	34	29	32	39	23	35
3251-3700	30	29	28	26	28	26	27	29
>3700	14	13	13	14†	11	10	12	10
Paternal age, y								
<30	28	32	30	33	45	47	33	25
30-34	50	47	51	49	38	34	44	59
≥35	22	17	19	18	17	18	23	16
Paternal education, y								
<10	44	44	48	42	24	34	39	47
10-12	37	39	36	44	55	52	21	32
≥13	19	17	16	14	21	14	20	21
Per capita income, yuan‡/mo								
30-49	27	26	20	18	26	29	29	33
50-79	34	32	39	41	28	25	36	28
≥80	27	29	33	35	25	32	25	25
Paternal alcohol drinking, %								
Never	67	65	64	64	71	67	66	58
Ever	12	14	16	16	10	15	5	14†

\*Less than 100% of the total percentage is due to missing values.

† $\chi^2$  test,  $P \leq .05$ .

‡One dollar is approximately equal to 8 yuan.

and 0.7 for all cancers combined among fathers smoking less than 10, 10-14, and 15 cigarettes or more per day, respectively. Risks increased with the number of cigarettes smoked per day only among those who had smoked cigarettes for more than 5 years before conception (Table 4).

When we evaluated the relationship of paternal preconception cigarette smoking with age at onset of childhood cancers, we found that the elevated childhood cancer risks were confined to children under the age of 5 years, with an 80% (OR = 1.8; 95% CI = 1.2-2.6) excess risk observed for all cancer sites combined (Table 5). Among children under the age of 5 years, the risk of childhood cancer rose with increased duration ( $P$  for trend = .0002) or greater number of pack-years ( $P$  = .0002) of paternal preconception smoking. This pattern was also observed for children ages 1-2 and 3-4 years old at diagnosis, but not for children diagnosed under age 1 year (the latter characterized by small numbers, however). Childhood cancer diagnosed among children 5 years and older was not linked with paternal preconception smoking (Table 5). Similar patterns were observed when acute leukemia, lymphoma, and brain tumors were examined separately, although the risk estimates were based on a small number of subjects. For example, fathers of 37% of the case patients versus 25% of the control subjects had smoked 5 pack-years or more, fathers of 43% of the lymphoma case patients versus 11% of the control subjects had smoked, and fathers of

36% of brain tumor case patients versus 13% of control subjects had also smoked 5 pack-years or more (data not shown).

Adjustment for maternal age at diagnosis of the childhood cancer, maternal education, and paternal occupational exposures at work did not materially alter the associations reported above for childhood cancer risk in relation to paternal cigarette smoking (data not shown).

## Discussion

Our study was unique in presenting an opportunity to evaluate the role of paternal cigarette smoking on the risk of childhood cancer in the absence of maternal cigarette smoking. We found that paternal smoking beginning in the preconception period was associated with elevated risks of childhood acute leukemia, lymphoma, brain tumors, and all cancers combined. The significantly increased relative risks were mainly confined to cancers diagnosed in young children under 5 years old.

A few case-control studies have suggested that paternal smoking before the birth or during fetal development of the index child is associated with an increased risk of cancer in the offspring (8-10,24-29). Increased risks of cancer have been reported for paternal smoking in relation to childhood brain tumors (24,27,28), neuroblastoma (25), and rhabdomyosarcoma (8). There have been five case-control studies (8,10,24,25,29) in

**Table 2.** Odds ratios\* (ORs) and 95% confidence intervals (CIs) for childhood cancers in relation to paternal smoking, Shanghai, People's Republic of China, 1981 through 1991

	All sites			Acute leukemia			Lymphoma			Brain tumor		
	Case patients, % <sup>†</sup>	Control subjects, %	OR (95% CI)	Case patients, %	Control subjects, %	OR (95% CI)	Case patients, %	Control subjects, %	OR (95% CI)	Case patients, %	Control subjects, %	OR (95% CI)
Smoking status												
Never	29	31	1.0 —	23	26	1.0 —	28	34	1.0 —	24	29	1.0 —
Ever	61	59	1.3 (1.0-1.7)	68	66	1.3 (0.7-2.4)	66	59	4.0 (1.3-12.5)	60	55	1.4 (0.6-3.2)
Age started smoking, y <sup>‡</sup>												
≥25	14	15	1.1 (0.7-1.6)	9	14	0.9 (0.4-2.1)	20	16	4.3 (1.0-17.9)	15	21	0.7 (0.2-2.0)
20-24	28	30	1.1 (0.8-1.5)	33	37	1.1 (0.5-2.2)	20	26	1.9 (0.5-7.3)	32	25	1.9 (0.7-5.5)
<20	19	13	1.9 (1.3-2.7)	25	15	1.7 (0.8-3.8)	24	15	5.6 (1.5-21.2)	12	7	2.5 (0.7-9.1)
(P for trend)			.28			.26			.92			.37
Cigarettes per day												
<10	19	16	1.5 (1.1-2.3)	14	14	1.6 (0.7-3.9)	22	17	3.4 (0.8-14.0)	19	20	1.5 (0.5-4.5)
10-14	18	20	1.1 (0.8-1.6)	23	28	0.9 (0.4-1.5)	16	24	1.1 (0.3-4.8)	20	12	1.6 (0.6-4.7)
≥15	15	14	1.5 (1.0-2.3)	20	15	1.9 (0.8-4.6)	17	9	3.8 (0.9-16.5)	11	11	2.1 (0.6-8.1)
(P for trend)			.07			.27			.09			.23
Duration, y												
<10	10	11	1.2 (0.7-1.8)	8	10	0.9 (0.3-2.3)	8	11	1.3 (0.2-7.0)	12	13	0.8 (0.2-3.8)
10-14	18	19	1.1 (0.8-1.7)	24	28	1.0 (0.5-2.2)	21	17	3.4 (0.9-12.7)	16	17	1.3 (0.4-4.1)
≥15	24	19	1.7 (1.2-2.5)	28	19	1.7 (0.8-3.7)	26	22	3.5 (0.9-13.7)	21	13	3.4 (0.9-12.5)
(P for trend)			.007			.23			.05			.10
Pack-years												
≤5	17	17	1.2 (0.8-1.8)	13	16	0.9 (0.4-2.2)	17	16	2.8 (0.6-12.8)	15	21	1.0 (0.3-3.2)
>5 to <10	17	17	1.3 (0.9-2.0)	21	22	1.1 (0.5-2.6)	16	24	1.3 (0.3-5.5)	18	10	2.6 (0.8-8.6)
≥10	19	16	1.6 (1.1-2.4)	25	19	1.9 (0.8-4.6)	22	10	5.7 (1.3-26.0)	17	12	2.3 (0.6-8.3)
(P for trend)			.01			.06			.03			.16

\*Adjusted for birth weight, income, paternal age, education, and alcohol drinking.

<sup>†</sup>Less than 100% of the total percentage is due to missing values of covariates.

<sup>‡</sup>Nonsmokers were excluded for trend test.

which the adverse effects were associated with paternal smoking but not maternal smoking, but only one study in which the positive association of paternal smoking was reported in the absence of maternal smoking (9). Other studies, however, have failed to find associations between paternal smoking and childhood AML (17), central nervous system tumors (14), brain tumors (12,16), Ewing's sarcoma (15), hepatoblastoma (11), Wilms' tumor (18), or retinoblastoma (13). Most of the studies (30,31) characterized by negative findings limited investigation of childhood cancer risks in relation to paternal smoking to the pregnancy period only and did not specifically evaluate the effect of paternal preconception smoking. In the absence of knowledge about the relevant male germ cell stage for mutagenic/carcinogenic effects leading to subsequent cancer in offspring, the key time window for exposure relative to conception is unknown. Thus, the limited time interval (during pregnancy or within a short time period prior to conception) assessed in previous studies may have failed to reveal the cumulative effects of preconception cigarette smoking (such as duration of smoking), especially if the number of cigarettes smoked per day does not predict cancer risk in the offspring. Also, the relatively small number of control subjects and, particularly, the small number of smokers who quit during or after the index pregnancy make it difficult to separately evaluate effects of smoking during different time periods (preconception, pregnancy related, and postnatal). Misclassification of exposure may be another explanation for some of the inconsistencies because paternal smoking information was not directly obtained from the fathers in most previous studies. In addition, most ear-

lier studies have failed to control adequately for the potential effects of maternal smoking.

The mechanisms involved in a possible association between paternal smoking and cancer risk in offspring are unclear. It has been hypothesized that carcinogenic effects of paternal cigarette smoking on offspring may result from passive maternal smoking or direct effects on paternal germ cells or both (32). Many constituents of cigarette smoke can be detected in amniotic fluid (33,34) and in the fetal blood (35,36) of offspring of mothers who smoke or are passively exposed to cigarette smoke, thus underscoring the transplacental passage of cigarette smoke constituents. However, direct evidence that in utero exposure to maternal smoking (active or passive) increases the risk of childhood cancer is lacking (7,17). In two studies (10,30), it was postulated that carcinogenic effects may occur in paternal germ cells after exposure to cigarette smoking. Because carcinogenicity associated with paternal smoking was mostly restricted to fathers who smoked more than 5 years during the preconception period and to children under the age of 5 years at diagnosis, our findings imply an effect on paternal germ cells. Further support of this hypothesis is provided by in vitro evidence that cigarette smoking increases oxidative DNA damage in human sperm cells (37) and causes mutations in germ cells (38). The excess cancer risk observed in progeny of male mice (39) and rats (40,41) exposed to various physical or chemical carcinogens before mating also supports the biologic plausibility of a germ-cell effect.

Accuracy in recall of past exposure is always a concern in

**Table 3.** Odds ratios\* (ORs) and 95% confidence intervals (CIs) for childhood cancers in relation to pack-years smoked by fathers before conception and after birth of the index child, Shanghai, People's Republic of China, 1981 through 1991

	Pack-years before conception					Pack-years after birth				
	0	≤2	>2 to <5	≥5	<i>P</i> for trend	0	≤2	>2 to <5	≥5	<i>P</i> for trend
All case patients, %	29	15	18	20		29	23	19	18	
All control subjects, %	31	16	18	16		31	23	17	18	
All sites	1.0	1.2 (0.8-1.8)	1.3 (0.9-2.0)	1.7 (1.2-2.5)	.006	1.0	1.2 (0.9-1.7)	1.4 (1.0-2.0)	1.1 (0.8-1.7)	.57
Acute leukemia†	1.0	0.7 (0.3-1.8)	1.0 (0.4-2.1)	2.4 (1.1-5.6)	.02	1.0	1.3 (0.6-2.6)	1.6 (0.7-3.5)	1.0 (0.4-2.4)	.94
ALL	1.0	0.8 (0.2-2.5)	1.0 (0.4-2.7)	3.8 (1.3-12.3)	.01	1.0	1.1 (0.4-2.8)	1.8 (0.6-5.2)	1.8 (0.6-5.5)	.33
AML	1.0	0.9 (0.1-7.3)	0.6 (0.1-3.1)	2.3 (0.4-14.8)	.36	1.0	5.0 (0.8-32.5)	6.1 (0.8-45.1)	0.5 (0.1-2.7)	.24
Lymphoma	1.0	3.1 (0.8-11.4)	1.8 (0.4-7.8)	4.5 (1.2-16.8)	.07	1.0	3.9 (0.9-16.0)	2.7 (0.8-9.6)	5.0 (1.2-22.4)	.08
Brain tumor	1.0	1.5 (0.5-4.4)	1.7 (0.5-5.8)	2.7 (0.8-9.9)	.14	1.0	1.3 (0.4-3.7)	1.8 (0.6-5.2)	1.0 (0.3-3.3)	.96

\*Adjusted for birth weight, income, paternal age, education, and alcohol drinking.

†ALL = acute lymphocytic leukemia (n = 114 pairs); AML = acute nonlymphocytic leukemia (n = 52 pairs).

**Table 4.** Odds ratios\* (ORs) and 95% confidence intervals (CIs) for childhood cancers in relation to number of cigarettes smoked per day and duration of smoking by fathers before conception, Shanghai, People's Republic of China, 1981 through 1991

Cigarettes per day	Duration of smoking		
	<5 y	5-9 y	≥10 y
<10	OR (95% CI)	OR (95% CI)	OR (95% CI)
10-14	1.2 (0.7-2.1)	1.2 (0.7-2.0)	1.5 (0.9-2.5)
≥15	0.9 (0.5-1.9)	1.2 (0.8-1.9)	1.3 (0.8-2.3)
	0.7 (0.2-2.9)	2.4 (1.3-4.4)	2.0 (1.2-3.4)

\*Adjusted for birth weight, income, paternal age, education, and alcohol drinking. Reference group was never smokers.

retrospective studies. Fathers of children with cancer may remember more accurately or overreport their exposures in comparison with fathers of control children. However, it seems unlikely that such a bias would apply only to cigarette smoking and not to other lifestyles or exposures, such as alcohol drinking. In addition, the prevalence of cigarette smoking among control fathers was comparable to that in the general population of the People's Republic of China. The good response rate (83%) for fathers of case patients and the absence of refusals among fathers of control subjects minimized the likelihood of potential selection bias in this study. Survival bias may be possible. Paternal smoking may increase risk of embryologic defects and neonatal deaths, even though the results of investigations evaluating these outcomes have not been consistent (42,43). If the outcomes of paternal smoking include increased fetal or perinatal deaths due to undiagnosed neoplasms in fetuses or infants, the cancer risks estimated in the present study could represent an underestimate of the true risks. Another limitation of our investigation is the absence of information about paternal smoking during pregnancy. Therefore, the possibility that paternal smoking might result in carcinogenic effects due to passive maternal smoking cannot be ruled out. However, the consistency of our results and the dose-response association argue against chance as an explanation. Finally, it should be noted that because of the relatively small number of subjects, the ORs in some subgroups of cancer were not very precise.

Despite the possible limitations, this population-based, case-control study in Shanghai suggests that paternal smoking prior to

**Table 5.** Age-specific odds ratios\* (ORs) and 95% confidence intervals (CIs) for childhood cancers (all sites combined) in relation to paternal smoking before conception, Shanghai, People's Republic of China, 1981 through 1991

	Age at diagnosis of cancer		
	0-4 y	5-9 y	10-14 y
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Smoking status			
Nonsmokers	1.0 (referent)	1.0 (referent)	1.0 (referent)
Smokers	1.8 (1.2-2.6)	0.9 (0.5-1.5)	1.9 (0.5-1.8)
Cigarettes per day			
<10	2.1 (1.2-3.5)	1.0 (0.5-2.1)	1.0 (0.3-4.2)
10-14	1.6 (0.9-2.7)	0.8 (0.4-1.6)	1.1 (0.3-3.4)
≥15	2.5 (1.4-4.5)	0.7 (0.3-1.6)	0.8 (0.3-2.5)
( <i>P</i> for trend)	.004	.38	.76
Duration, y			
<5	1.7 (0.9-3.2)	0.8 (0.3-1.7)	0.3 (0.1-1.1)
5-9	1.5 (0.9-2.6)	1.1 (0.5-2.1)	2.4 (0.7-8.4)
≥10	2.3 (1.4-3.8)	0.9 (0.4-2.0)	0.9 (0.3-2.5)
( <i>P</i> for trend)	.0002	.92	.93
Pack-years			
≤2	1.6 (1.0-2.7)	0.7 (0.3-1.7)	0.8 (0.1-4.2)
>2-<5	1.8 (1.8-3.1)	1.0 (0.5-2.1)	0.8 (0.2-2.8)
≥5	3.5 (1.8-6.6)	0.7 (0.3-1.6)	0.9 (0.4-2.4)
( <i>P</i> for trend)	.0002	.71	.77

\*Adjusted for birth weight, income, paternal age, education, and alcohol drinking.

conception may be associated with an increased risk for all childhood cancers combined and particularly for childhood ALL, lymphoma, and brain tumors. The elevated cancer risk was confined to children under age 5 years at diagnosis and associated with paternal smoking starting prior to conception, suggesting the possibility of prezygotic genetic damage. The results of our investigation warrant further evaluation in very large, perhaps multinational studies in populations in which fathers, but not mothers, are cigarette smokers. Large study populations are needed to provide sufficient numbers of fathers who begin smoking in the preconception period but quit at or around conception, fathers who smoke only during the mother's pregnancy, and fathers who first initiate smoking after the child's birth, so that effects of the timing of paternal cigarette smoking in relation to childhood cancer can be disentangled. In addition, it is critical that information on paternal smoking be obtained directly from fathers. If our findings are confirmed and further clarified with

respect to the timing of cigarette smoking, additional studies should be undertaken to clarify the mechanism for this association.

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## Notes

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