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Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study

D Pang¹, R McNally¹ and JM Birch¹* on behalf of the UK Childhood Cancer Study Investigators²

¹Cancer Research UK, Paediatric and Familial Cancer Research Group, Royal Manchester Children’s Hospital, Stanscliffe, Hospital Road, Manchester M27 4HA, UK

There are strong a priori reasons for considering parental smoking behaviour as a risk factor for childhood cancer but case–control studies have found relative risks of mostly only just above one. To investigate this further, self-reported smoking habits in parents of 3838 children with cancer and 7629 control children included in the United Kingdom Childhood Cancer Study (UKCCS) were analysed. Separate analyses were performed for four major groups (leukaemia, lymphoma, central nervous system tumours and other solid tumours) and more detailed diagnostic subgroups by logistic regression. In the four major groups, after adjustment for parental age and deprivation there were nonsignificant trends of increasing risk with number of cigarettes smoked for paternal preconception smoking and nonsignificant trends of decreasing risk for maternal preconception smoking (all P-values for trend >0.05). Among the diagnostic subgroups, a statistically significant increased risk of developing hepatoblastoma was found in children whose mothers smoked preconceptionally (OR = 2.68, P = 0.02) and strongest (relative to neither parent smoking) for both parents smoking (OR = 4.74, P = 0.003). This could be a chance result arising from multiple subgroup analysis. Statistically significant negative trends were found for maternal smoking during pregnancy for all diagnoses together (P < 0.001) and for most individual groups, but there was evidence of under-reporting of smoking by case mothers. In conclusion, the UKCCS does not provide significant evidence that parental smoking is a risk factor for any of the major groups of childhood cancers.

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There are strong a priori reasons for considering parental smoking behaviour as a risk factor for childhood cancer. Many proven carcinogens are present in tobacco and tobacco smoke (Hecht, 1999; Hoffmann and Hoffmann, 1997). Tobacco-related compounds have also been detected in human placenta, fetal blood, urine of offspring and in breast milk of smoking mothers (Perlman et al, 1999; Hoffmann and Hoffmann, 1997). Tobacco-related carcinogens are present in tobacco and tobacco smoke (Hecht, 1997a, b; 2001). This effect has been attributed to germ-cell mutations during spermatogenesis caused by tobacco products (Wyrobek, 1993; Wyrobek and Adler, 1996; Woodall and Ames, 1997). Relevant studies are reviewed by Thornton and Lee (1998).

The United Kingdom Childhood Cancer Study (UKCCS) is a nationwide population-based case–control study of possible aetiological factors in childhood cancer. We have examined the possible effect of paternal and maternal cigarette smoking in the development of childhood cancers by analysing self-reported parental smoking habits in relation to such cancers at a preconceptional time period and maternal smoking during pregnancy. Information on paternal smoking during pregnancy was not collected as maternal passive smoking during pregnancy was not considered important when the study was designed.

 MATERIALS AND METHODS

The UKCCS study design, case and control selection, and data collection procedures have already been published in detail (McKinney et al, 1995; UK Childhood Cancer Study Investigators, 2000). A summary is provided here.
Case ascertainment

The study sought to interview the parents of children, resident in England, Scotland and Wales, who were diagnosed with a confirmed malignancy or any central nervous system (CNS) tumour under the age of 15 years between 1991–1994 in Scotland and 1992–1994 in England and Wales. Case accrual continued in England and Wales for non-Hodgkin’s lymphoma and leukaemias during 1995 and leukaemias alone during 1996. A total of 10 study regions were defined. Cases were usually ascertained from regional paediatric oncology units. Completeness of ascertainment was assessed by cross-reference to regional and national cancer registries. Leukaemia diagnoses and subclassification were based on all available data including data from national clinical trials. For solid tumours, consensus diagnoses were made by panels of pathologists with special interests in specific types of tumours after histopathological review. All diagnoses were coded according to the International Classification of Diseases for Oncology (2nd ed.) (Percy et al, 1990) and regrouped into Birch and Kelsey diagnostic subcategories (UKCCS Investigators, 2000), available at http://www.biomed2.man.ac.uk/crcplcrg/crukplcrg/pfcrz.htm.

Control selection

For each case child, similar data were sought for two control children matched for sex, date of birth and geographical area of residence at diagnosis and randomly selected from Family Health Services Authorities (FHSA) lists in England and Wales and Health Boards in Scotland. Control parents were contacted and given permission from their general practitioners (GP). The parents of 3838 case children and 7629 control children were interviewed, representing participation rates of 87 and 64%, respectively.

Parental smoking behaviour

Evaluation of parental smoking data obtained from face-to-face structured interviews with parents were available on 3585 case fathers, 6987 control fathers, 3814 case mothers and 7581 control mothers. We developed software to derive the preconception smoking variable from the social habits section of the questionnaire on the basis of the starting and stopping dates of smoking, specific questions relating to smoking 1 year before birth of the index child and at other time points and the birth date of the index child. Parental smoking status was categorised as: (a) lifelong nonsmokers; (b) ex-smokers, who stopped smoking more than 1 year before the birth of the index child; and (c) current smokers, who smoked cigarettes during the year before the birth of the index child. When smoking status was unknown (8% of parents overall) because of missing information or contradictory information, these were excluded from statistical analyses to avoid bias of odds ratios (ORs) because of possible misclassification of smoking status (Lee, 1998; Infante-Rivard and Jacques, 2000). A smoking variable defining numbers of cigarettes smoked per day during specific periods of pregnancy was derived from the interview data. Maternal smoking during the second trimester of pregnancy is reported since fetal organs have by then developed and have begun to function. It was considered that fetal organ exposure to products of tobacco smoking in this period might replicate the tissue-specific effects suggested by animal studies.

Statistical methods

As in previous UKCCS reports (UKCCS Investigators, 1999; Beral et al, 2001), case and control data relating to cigarette consumption were compared by means of unconditional logistic regression (Breslow and Day, 1980) using Stata, version 6, program (StataCorp, 1999). The original matching variables were accounted for by adjustment, with all analyses being routinely adjusted for child’s age at diagnosis in single years (0–14) treated as a continuous variable, sex and UKCCS region (Beral et al, 2001). All controls were used as the comparison group for each diagnostic group. Since it is known that spontaneous mutation rates can increase with age, especially in males (Penrose, 1955, 1957; Vogel and Rathenberg, 1975), adjustments were made for parental ages at the birth of the child (in single years) and for deprivation score. The latter is a small area seven-level index based on car ownership, overcrowding and unemployment. Individual scores were obtained by linking to the 1991 census of Great Britain via the postcode of their residence at diagnosis/pseudodiagnosis of the index children (UKCCS Investigators, 2000).

Analyses were performed with respect to paternal and maternal preconception smoking, and maternal smoking in pregnancy, initially by the following broad diagnostic groups: all cancers, leukaemia, lymphoma, central nervous system tumours (CNS) and other solid tumours. Possible dose–response relations between smoking and childhood cancer were examined using three smoking categories of 0, 1–19, and 20 or more cigarettes smoked per day (cpd). Relative risks were estimated for light/moderate (1–19 cpd) and heavy (20+ cpd) smokers relative to nonsmokers. ORs were computed and shown relative to a baseline risk of unity for the nonsmokers together with two-sided P-values and 95% confidence intervals (CI). The trend of risk by amount smoked was examined by coding the three smoking groups to 1, 2 and 3, respectively, and treating as a continuous variable (Sorahan et al, 1997a, b).

Work on single gene cancer predisposition syndromes, on specific somatic mutations in human cancers and on laboratory animals suggests that any mutagenic/carcinogenic effects of tobacco smoke would be tissue specific and/or organ specific (Correa et al, 1990; Beebe et al, 1993; Hecht, 1998; Birch, 1999; Hollstein et al, 1999). Therefore, separate analyses were performed for Birch and Kelsey diagnostic subgroups, which group biologically similar tumours together (UKCCS Investigators, 2000). In those groups showing a statistically significantly elevated OR, the relation was explored in more detail as follows: father’s smoking in the absence of mother’s smoking, mother’s smoking in the absence of father’s smoking, and both father and mother smoking were compared with neither smoking for data on parental preconception smoking.

If parental smoking is a risk factor for childhood cancer, germline mutations caused by a preconceptional exposure might lead to earlier age of cancer onset in the child, whereas a placental exposure may be associated with later age of onset. To investigate this possibility, analyses were carried out for children, under and above the median age at diagnosis, respectively, in diagnostic groups with elevated ORs.

RESULTS

Table 1 shows details of subjects and their biological parents. In total 56% are boys and about 50% are under 5 years old at diagnosis. Case and control children have similar distributions by sex and age at diagnosis. The mother’s mean age at birth of the index child is 27 years and the father’s is 30 years. Case parents are slightly younger than control parents. For all cancers, ORs for the child’s age at diagnosis and sex are close to 1 due to matching (all OR = 1.0, all P-values > 0.5). Nevertheless, these matching variables were included in the model to avoid a biased estimate of the parental smoking effect (Clayton and Hills, 1993). There is a significant negative trend for maternal age at the birth of the index child (P-value for trend < 0.001), but a nonsignificant positive trend for paternal age (P-value for trend = 0.4). There is a significant positive trend for deprivation (P-value for trend < 0.05).
DISCUSSION

The UKCCS does not provide evidence that parental preconception smoking is a risk factor for childhood cancers in general. Statistically significant point estimates of risks just above unity can be accounted for by the potential confounders. There are no statistically significant trends with increasing number of cigarettes smoked. Failure to replicate the findings of two nationwide and multiregional case–control studies in the UK (Sorahan et al, 1995, 1997a, b), which found significant associations with paternal preconception smoking, may be due, in part, to a higher smoking prevalence, and a larger proportion of heavy smokers in those earlier studies. More importantly, perhaps, the present study is more likely to be subject to reporting bias because of increased public awareness of adverse effects of smoking and blinding parents with respect to the study hypothesis regarding smoking pressure on mothers to stop smoking during pregnancy and therefore less liability to bias.

Table 2 shows ORs for paternal preconception smoking for the main diagnostic groups. Overall, there was a nonsignificant trend of increasing risks with amount smoked after adjustment for parental age and deprivation. Although some statistically significant ORs were shown among fathers with 1–19 cpd, adjustment for parental age and deprivation removed these.

For maternal preconception smoking, Table 3 shows a statistically significant decreased OR of 0.86 among heavy smokers after adjustment (P = 0.03), also seen for other solid tumours (OR = 0.75, P = 0.02).

For all diagnoses considered together, the OR for paternal preconception smoking in cases below, or at or above, the median age was 1.03 (P = 0.7) and 1.05 (P = 0.4), respectively. For maternal preconception smoking, the corresponding ORs were 0.91 (P = 0.2) and 1.00 (P = 1.0). Therefore, there was no evidence of a general tendency for increased risk at younger ages that may have been associated with germline mutations in relevant genes.

Table 4 shows, for maternal smoking during pregnancy, statistically significant monotonic decreasing trends with increasing number of cigarettes after adjustment for parental age and deprivation. For the other subgroups, ORs were close to unity. For maternal smoking during pregnancy, ORs in most diagnostic subgroups were below unity and not statistically significant, but for primitive neuroectodermal tumours the OR was 0.55 (P = 0.01).

Table 5 shows ORs by the Birch–Kelsey diagnostic subgroup. For paternal preconception smoking, most subgroups showed ORs close to unity, but choroid plexus tumours and hepatoblastoma showed statistically nonsignificant elevated ORs (OR = 2.1 and 2.2) after adjustment for parental age and deprivation. For maternal preconception smoking, only hepatoblastoma showed a significantly elevated OR (OR = 2.68, P = 0.02) after adjustment for parental age and deprivation. For the other subgroups, ORs were close to unity. For maternal smoking during pregnancy, ORs in most diagnostic subgroups were below unity and not statistically significant, but for primitive neuroectodermal tumours the OR was 0.55 (P = 0.01).

For hepatoblastoma, Table 6 shows results for parental smoking by age, number of cpd, and number of parents smoking. For maternal preconception smoking, there was a statistically significantly elevated OR of 12 for children older than the median age at diagnosis after adjustment for parental age and deprivation (P = 0.002) and a positive trend with number of cigarettes smoked per day of borderline statistical significance (P = 0.06). The strongest effect is seen for both parents smoking preconceptionally (OR = 4.74, P = 0.003).
The adjusted analyses in Table 4 show statistically significant negative trends for maternal smoking during pregnancy for most diagnostic groups. A protective effect for these types does not seem biologically plausible here, and it is more likely that these trends reflect an underestimation of the amount smoked by case mothers during the index pregnancy.

Birth weights of index children reported by mothers at interview were analysed in cases and controls for trend with reported numbers of cigarettes smoked during the second trimester of pregnancy. In controls, there was a trend of monotonic decrease in birth weights with numbers of cigarettes smoked (differences in mean birth weights from nonsmokers were –144.9, –237.8, –240.5, –247.1 and –252.9 g for 1–9, 10–19, 20–29, 30–39 and 40+ cpd, respectively). However, no such trend was observed among the cases (differences from nonsmokers were –209.2, –222.7, –245.6, –260.5 and –286.1 g for 1–9, 10–19, 20–29, 30–39 and 40+ cpd, respectively). These results would tend to indicate inaccurate reporting of smoking by case mothers, but they should be interpreted with caution, given the maternal source of the birth weight data. Furthermore, unusual birth weight distributions have been reported for certain childhood cancers (Yeazel et al., 1997), which also complicates interpretation.

Participating controls lived in more affluent areas than the originally selected controls and the cases (Law et al., 2002). This bias could not explain the observed case-control difference in reported maternal smoking since the risk should move in the opposite direction. Since smoking is such a well-known risk factor for cancer and for unfavourable pregnancy outcomes (e.g. low birth weight), the possibility of guilt feelings leading to under-reporting, especially in case mothers, must be considered (Heller et al., 1998). This is suggested by the smoking prevalence at various time points (Table 7). Slightly more case than control mothers reported giving up smoking in pregnancy. In addition, it is known that some smokers deny having smoked, denial rates varying with the phrasing of questions and whether medical advice against smoking had been given (Lee, 1998).

A separate study on reactions of parents before, during and after interview was independently carried out by sending questionnaires to a subset of 371 cases and 380 controls as soon as the interview was completed (Jenkinson et al., 2001). The results lend support to the proposition that the pattern shown in Table 7 is because of reporting bias in the case mothers since differential reactions between case and control mothers were found. Case mothers felt more difficulty than controls (20% vs 11%, P = 0.02) when

### Table 2: Paternal preconception cigarette smoking in relation to childhood cancer risks

| Diagnostic group | Cases | Controls | OR 95% CI | OR 95% CI |
|------------------|-------|----------|-----------|-----------|
| **All cancer**   | 3585  | 6987     |           |           |
| Lifelong nonsmoker | 1543  | 3082     | 1.00      | 1.00      |
| 1–19 cpd         | 583   | 1003     | 1.16*     | 1.03      | 1.31      |
| 20+ cpd          | 757   | 1440     | 1.05      | 0.94      | 1.17      |
| Trend P          |       |          |           | 0.198     | 0.635     |
| Ex-smoker        | 421   | 827      | 1.02      | 0.89      | 1.16      |
| Smoking status n/k | 281   | 635      |           |           |
| **Leukaemia**    | 1630  | 6987     |           |           |
| Lifelong nonsmoker | 697   | 3082     | 1.00      | 1.00      |
| 1–19 cpd         | 269   | 1003     | 1.19*     | 1.01      | 1.39      |
| 20+ cpd          | 342   | 1440     | 1.07      | 0.93      | 1.24      |
| Trend P          |       |          |           | 0.216     | 0.743     |
| Ex-smoker        | 192   | 827      | 1.03      | 0.86      | 1.23      |
| Smoking status n/k | 130   | 635      |           |           |
| **Lymphoma**     | 331   | 6987     |           |           |
| Lifelong nonsmoker | 124   | 3082     | 1.00      | 1.00      |
| 1–19 cpd         | 55    | 1003     | 1.34      | 0.96      | 1.87      |
| 20+ cpd          | 72    | 1440     | 1.15      | 0.85      | 1.56      |
| Trend P          |       |          |           | 0.260     | 0.419     |
| Ex-smoker        | 45    | 827      | 1.32      | 0.93      | 1.89      |
| Smoking status n/k | 35    | 635      |           |           |
| **CNS**          | 635   | 6987     |           |           |
| Lifelong nonsmoker | 271   | 3082     | 1.00      | 1.00      |
| 1–19 cpd         | 101   | 1003     | 1.13      | 0.89      | 1.43      |
| 20+ cpd          | 138   | 1440     | 1.07      | 0.86      | 1.33      |
| Trend P          |       |          |           | 0.466     | 0.706     |
| Ex-smoker        | 71    | 827      | 0.98      | 0.74      | 1.28      |
| Smoking status n/k | 54    | 635      |           |           |
| **Other solid tumours** | 989   | 6987     |           |           |
| Lifelong nonsmoker | 451   | 3082     | 1.00      | 1.00      |
| 1–19 cpd         | 158   | 1003     | 1.08      | 0.89      | 1.31      |
| 20+ cpd          | 205   | 1440     | 0.99      | 0.83      | 1.18      |
| Trend P          |       |          |           | 0.981     | 0.909     |
| Ex-smoker        | 113   | 827      | 0.95      | 0.76      | 1.19      |
| Smoking status n/k | 62    | 635      |           |           |

*P<0.05. For deprivation and parental age at birth of index child. cpd=cigarettes per day, n/k=not known.
responding to questions about smoking in pregnancy. In contrast, case and control mothers reported a similar level of difficulty over questions about employment history (11 vs 11%, $P = 0.91$). Occupations are not generally perceived to be associated with the risk of childhood cancer (McKinney et al., 2002).

While smoking during pregnancy is well-known to have adverse effects on the fetus, the possible mutational effects of tobacco products on germ cells would not generally be understood. It is unlikely therefore that responses to questions about preconceptional smoking would be influenced in the same way, so these data are likely to be more reliable.

The only clear positive association to emerge from these analyses is between maternal preconceptional smoking and hepatoblastoma. This may be a chance finding arising because of multiple testing. However, detailed results support the finding, and potential confounders (deprivation, maternal/paternal ages at diagnosis of the index child) have not accounted for it. Trends with numbers of cigarettes smoked approached statistical significance ($P = 0.058$). Smoking by both parents increased the risk more than four-fold ($P = 0.003$). Furthermore, maternal smoking was strongly associated with cases diagnosed above the median age, suggesting specificity in the timing of a putative carcinogenic event. Since a chance association would predict a random distribution among subgroups analysed, the results suggest that parental smoking might increase the risk of hepatoblastoma. Alternatively, other unknown risk factors associated with parental smoking may explain the results. If causal, the most plausible explanation would be a transplacental carcinogenic effect of tobacco products, including passive smoking from the father’s cigarettes affecting the embryonal and/or fetal liver rather than maternal germ cells. We did not collect information on paternal smoking during the pregnancy and analyses of reported maternal smoking during pregnancy do not support this explanation. However, for reasons mentioned above regarding probable under-reporting of maternal smoking, preconception smoking can be used as a proxy for pregnancy smoking.

Tobacco-specific carcinogens can cross the placental barrier to reach the fetal liver and potentially lead to mutations in oncogenes or tumour suppressor genes. Fifty-five proven carcinogens have been found in cigarettes, including polycyclic aromatic hydrocarbons, N-nitrosamines, aromatic amines, heterocyclic aromatic amines, aldehydes, aza-arenes, other organic compounds and

### Table 3  Maternal preconception cigarette smoking in relation to childhood cancer risks

| Diagnostic group | Cases | Controls | OR  | 95% CI | OR  | 95% CI |
|------------------|-------|----------|-----|--------|-----|--------|
|                  | Before adjustment |        | After adjustment $^a$ |        |       |
| All cancer       | 3814  | 7581     | 1.00|        | 1.00|        |
| Lifelong nonsmoker| 1991  | 3916     | 1.00|        | 1.00|        |
| I - 19 cpd       | 795   | 1490     | 1.05| 0.95   | 1.16| 1.00   |
| 20+ cpd          | 394   | 882      | 0.88| 0.77   | 1.00| 0.86   |
| Trend P          |       |          |     |        |     |        |
| Ex-smoker        | 353   | 758      | 0.92| 0.80   | 1.05| 0.95   |
| Smoking status n/k | 281   | 535      |     |        |     |        |
| Leukaemia        | 1723  | 7581     | 1.00|        | 1.00|        |
| Lifelong nonsmoker| 899   | 3916     | 1.00|        | 1.00|        |
| I - 19 cpd       | 351   | 1490     | 1.04| 0.90   | 1.19| 0.99   |
| 20+ cpd          | 191   | 882      | 0.96| 0.81   | 1.14| 0.96   |
| Trend P          |       |          |     |        |     |        |
| Ex-smoker        | 153   | 758      | 0.86| 0.71   | 1.04| 0.88   |
| Smoking status n/k | 129   | 535      |     |        |     |        |
| Lymphoma         | 351   | 7581     | 1.00|        | 1.00|        |
| Lifelong nonsmoker| 180   | 3916     | 1.00|        | 1.00|        |
| I - 19 cpd       | 67    | 1490     | 0.95| 0.71   | 1.27| 0.87   |
| 20+ cpd          | 38    | 882      | 0.93| 0.65   | 1.34| 0.86   |
| Trend P          |       |          |     |        |     |        |
| Ex-smoker        | 39    | 758      | 1.15| 0.80   | 1.65| 1.25   |
| Smoking status n/k | 27    | 535      |     |        |     |        |
| CNS              | 684   | 7581     | 1.00|        | 1.00|        |
| Lifelong nonsmoker| 349   | 3916     | 1.00|        | 1.00|        |
| I - 19 cpd       | 143   | 1490     | 1.06| 0.86   | 1.30| 1.00   |
| 20+ cpd          | 67    | 882      | 0.84| 0.64   | 1.10| 0.78   |
| Trend P          |       |          |     |        |     |        |
| Ex-smoker        | 67    | 758      | 1.01| 0.77   | 1.33| 1.05   |
| Smoking status n/k | 58    | 535      |     |        |     |        |
| Other solid tumours | 1056  | 7581    | 1.00|        | 1.00|        |
| Lifelong nonsmoker| 563   | 3916     | 1.00|        | 1.00|        |
| I - 19 cpd       | 234   | 1490     | 1.09| 0.93   | 1.29| 1.05   |
| 20+ cpd          | 98    | 882      | 0.77| 0.61   | 0.96| 0.75   |
| Trend P          |       |          |     |        |     |        |
| Ex-smoker        | 94    | 758      | 0.86| 0.68   | 1.09| 0.92   |
| Smoking status n/k | 67    | 535      |     |        |     |        |

$^a$For deprivation and parental age at the birth of the index child. $^p < 0.05$. cpd=cigarettes per day. $[^]$ indicates negative trend, n/k=not known.
### Table 4  Maternal cigarette smoking during pregnancy in relation to childhood cancer risks

| Diagnostic group | Cases | Controls | Before adjustment | After adjustment* |
|------------------|-------|----------|-------------------|-------------------|
|                  | OR    | 95% CI   | OR 95% CI         |                   |
| **All cancer**   |       |          |                   |                   |
| Nonsmoker        | 2958  | 5743     | 1.00              | 1.00              |
| 1–19 cpd         | 648   | 1306     | 0.96**            | 0.76**            |
| 20+ cpd          | 207   | 528      | 0.76**            | 0.64              |
| Trend P          |        |          | (0.004)           | [0.029]           |
| **Leukaemia**    |       |          |                   |                   |
| Nonsmoker        | 1341  | 5743     | 1.00              | 1.00              |
| 1–19 cpd         | 286   | 1306     | 0.95              | 0.74              |
| 20+ cpd          | 95    | 528      | 0.80              | 0.64              |
| Trend P          |        |          | (0.004)           | (0.029)           |
| **Lymphoma**     |       |          |                   |                   |
| Nonsmoker        | 269   | 5743     | 1.00              | 1.00              |
| 1–19 cpd         | 60    | 1306     | 0.99              | 0.74              |
| 20+ cpd          | 22    | 528      | 0.82              | 0.62              |
| Trend P          |        |          | (0.048)           | (0.011)           |
| **CNS**          |       |          |                   |                   |
| Nonsmoker        | 538   | 5743     | 1.00              | 1.00              |
| 1–19 cpd         | 111   | 1306     | 0.89              | 0.72              |
| 20+ cpd          | 35    | 528      | 0.69*             | 0.48              |
| Trend P          |        |          | (0.048)           | (0.030)           |

*For parental age and deprivation. **P<0.05; ***P<0.01; ****P<0.001. cpd=cigarettes per day. [ ] indicates negative trend.

### Table 5  Parental smoking in relation to childhood cancer risks by selected diagnostic subgroups

| Diagnostic group | Father preconception | Mother preconception | Mother pregnancy |
|------------------|----------------------|----------------------|------------------|
|                  | Cases | OR | 95% CI | Cases | OR | 95% CI | Cases | OR | 95% CI |
| 110 Acute lymphocytic leukaemia | 1375   | 1.04 | 0.91 1.18 | 1449   | 1.02 | 0.89 1.16 | 1449   | 0.89 | 0.77 1.03 |
| 120 Acute myeloid leukaemia | 230   | 1.07 | 0.80 1.43 | 249   | 0.82 | 0.60 1.12 | 249   | 0.76 | 0.54 1.07 |
| 130 Chronic myeloid leukaemia | 22   | 1.44 | 0.59 3.50 | 22   | 1.44 | 0.57 3.65 | 22   | 1.70 | 0.68 4.26 |
| 210 Hodgkin’s disease | 105 | 1.16 | 0.75 1.70 | 114 | 0.75 | 0.47 1.19 | 114 | 0.91 | 0.57 1.45 |
| 220 Non-Hodgkin’s lymphoma | 218   | 1.03 | 0.76 1.40 | 229   | 0.90 | 0.65 1.23 | 229   | 0.86 | 0.61 1.22 |
| 311 Pilocytic astrocytoma | 158   | 1.08 | 0.76 1.52 | 169   | 0.89 | 0.62 1.28 | 169   | 0.92 | 0.62 1.37 |
| 315 Other astrocytoma | 119   | 0.92 | 0.61 1.39 | 132   | 0.94 | 0.62 1.43 | 132   | 0.84 | 0.53 1.33 |
| 320 Other glioma | 66 | 1.09 | 0.64 1.84 | 67 | 1.07 | 0.55 1.71 | 67 | 1.12 | 0.63 1.99 |
| 330 Ependymoma | 61 | 1.03 | 0.59 1.78 | 69 | 0.73 | 0.40 1.35 | 69 | 0.77 | 0.40 1.47 |
| 340 Choroid plexus tumours | 20 | 2.11 | 0.81 5.49 | 20 | 1.29 | 0.44 3.79 | 20 | 0.49 | 0.14 1.75 |
| 350 Primitive neuroectodermal tumours | 150 | 0.90 | 0.63 1.30 | 161 | 0.96 | 0.65 1.42 | 161 | 0.55* | 0.34 0.88 |
| 360 Mx. brain and spinal neoplasms | 61 | 1.33 | 0.77 2.28 | 66 | 0.82 | 0.46 1.45 | 66 | 0.74 | 0.39 1.40 |
| 360 Retinoblastoma | 86 | 0.66 | 0.40 1.09 | 87 | 0.60 | 0.40 1.10 | 87 | 0.60 | 0.30 1.10 |
| 370 Neuroblastoma | 180 | 1.35 | 0.97 1.88 | 188 | 1.04 | 0.73 1.49 | 188 | 0.91 | 0.62 1.34 |
| 380 Mis. brain and spinal neoplasms | 74 | 1.12 | 0.68 1.80 | 78 | 1.52 | 0.93 2.48 | 78 | 1.48 | 0.88 2.47 |
| 390 Wilms’ tumour | 170 | 1.01 | 0.73 1.42 | 182 | 0.82 | 0.57 1.17 | 182 | 0.82 | 0.55 1.22 |
| 400 Other unspecified renal tumours | 10 | 1.76 | 0.37 8.31 | 12 | 0.96 | 0.26 3.71 | 12 | 0.98 | 0.24 3.99 |
| 410 Hepatoblastoma | 27 | 2.19 | 0.94 5.12 | 28 | 2.68* | 1.16 6.21 | 28 | 1.10 | 0.44 2.72 |
| 420 Other sarcoma | 48 | 1.18 | 0.65 2.14 | 56 | 1.06 | 0.56 2.01 | 56 | 0.46 | 0.20 1.06 |
| 430 Other skeletal sarcoma | 125 | 0.84 | 0.57 1.25 | 132 | 0.83 | 0.55 1.25 | 132 | 1.02 | 0.66 1.56 |
| 440 Soft tissue sarcoma | 62 | 0.81 | 0.46 1.43 | 69 | 1.02 | 0.57 1.80 | 69 | 0.98 | 0.53 1.83 |
| 450 Other germ cell tumours | 34 | 0.98 | 0.47 2.03 | 35 | 0.82 | 0.37 1.84 | 35 | 0.70 | 0.28 1.75 |
| 500 Other non-germ cell tumours | 57 | 0.81 | 0.46 1.46 | 61 | 0.74 | 0.41 1.37 | 61 | 0.53 | 0.25 1.10 |
| 510 Other non-germ cell tumours | 51 | 1.14 | 0.62 2.08 | 57 | 1.21 | 0.66 2.22 | 57 | 1.16 | 0.62 2.18 |
| 520 Choroid plexus tumours | 46 | 0.73 | 0.38 1.40 | 49 | 0.74 | 0.37 1.48 | 49 | 0.47 | 0.20 1.15 |

*Birch – Kelsey classification (UKCCS Investigators, 2000), excluding diagnostic subgroups with less than 10 cases. **Corresponding controls: 6987. ***Corresponding controls: 7581.

*aAfter adjustment for parental age and deprivation. *P<0.05.
inorganic compounds (Hecht, 1999). Of these, N-nitroso compounds are the most likely candidate transplacental liver carcinogens (Anderson et al., 1989; Correa et al., 1990; Beebe et al., 1993; Schuller et al., 1993, 1994; Hecht, 1998). These compounds can cross the human placenta, and their metabolites have been found both in the urine and bound to the fetal haemoglobin of newborns whose mothers smoked cigarettes (Coghlin et al., 1991; Lackmann et al., 1999) and in the fetus in early pregnancy (Milunsky et al., 2000). Cord blood T lymphocytes from newborns has revealed an increased level of mutations (deletions in infants of mothers who smoked (Finette et al., 1997)). The liver is a target organ for transplacental carcinogenesis in experimental animals and, indeed, the enzymes necessary for their bioactivation are more active in human than in animal fetal liver (Everson, 1980).

For adults, carcinogens in cigarettes mainly target the first exposed organ, the lung, (Hecht, 1999), but in the fetus, the first exposed organ may be the liver, so a role for parental smoking during pregnancy may be biologically plausible in childhood hepatoblastoma. However, although a causal association with hepatoblastoma should be considered, given the number of comparisons made the apparent association could well be due to chance.

In conclusion, no statistically significant positive associations between parental smoking behaviour and major groups of cancers in children were identified by the UKCCS. However, causal associations cannot be ruled out. If there is under-reporting of smoking in the case parents, the true effects would be expected to be higher than observed in the present study. To resolve this question, new approaches are required and the integration of biomarkers for genotypes and phenotypes specific to tobacco products would be helpful in pursuing the possible role of parental smoking in the aetiology of childhood cancer.

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Table 6  Parental smoking in relation to risk of developing hepatoblastoma (all results adjusted for parental age and deprivation)

|                  | Cases | Controls | OR   | 95% CI |
|------------------|-------|----------|------|--------|
| Father preconception | 27    | 6987     | 2.19 | 0.94   | 5.12  |
| Mother preconception | 28    | 7581     | 1.16 | 0.61   | 2.18  |
| Mother 2nd trimester | 10    | 6684     | 1.72 | 1.20   | 2.45  |
| Total             | 57    | 14572    |      |        |      |

Table 7  Prevalence (%) of maternal cigarette smoking in cases and controls

| Time point               | Cases | Controls | OR   | 95% CI |
|--------------------------|-------|----------|------|--------|
| Preconception            | 33.7  | 33.7     |      |        |
| 1st trimester            | 25.7  | 26.9     |      |        |
| 2nd trimester            | 22.4  | 22.4     |      |        |
| 3rd trimester            | 22.4  | 22.4     |      |        |

Table 8  Prevalence (%) of maternal cigarette smoking in cases and controls by trend

| Cases | Controls | OR   | 95% CI |
|-------|----------|------|--------|
| Total | 57       | 14572|        |

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APPENDIX

Management Committee – KK Cheng, Central region; NE Day, East Anglia region; R Cartwright, A Craft, North East region; JM Birch, OB Eden, North West region; PA McKinney, Scotland; J Peto, South East region; V Beral, E Roman, South Midlands region; P Elwood, South Wales region; FE Alexander, South West region; CED Chilvers, Trent region; R Doll, Epidemiological Studies Unit, University of Oxford, Oxford; GM Taylor, Immunogenetics Laboratory, University of Manchester, Manchester; M Greaves, Leukaemia Research Fund Centre, Institute of Cancer Research; D Goodhead, Radiation and Genome Stability Unit, Medical Research Council, Harwell; FA Fry, National Radiological Protection Board; G Adams, UK Coordinating Committee for cancer research.

Regional Investigators – KK Cheng, E Gilman, Central region; NE Day, J Skinner, D Williams, East Anglia region; R Cartwright, A Craft, North East region; JM Birch, OB Eden, North West region; PA McKinney, Scotland; J Deacon, J Peto, South East region; V Beral, E Roman, South Midlands region; P Elwood, South Wales region; FE Alexander, M Mott, South West region; CED Chilvers, K Muir, Trent region.

Data Processing Group – GR Law, J Simpson, E Roman.

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