

## CANCER IN THE PARENTS OF CHILDREN WITH CANCER

JØRGEN H. OLSEN, M.D., JOHN D. BOICE, JR., SC.D., NIELS SEERSHOLM, M.D., ANDREA BAUTZ,  
AND JOSEPH F. FRAUMENI, JR., M.D.

**Abstract Background.** Certain types of cancer in children and young adults have been linked with an increased risk of cancer in close relatives. However, the relation between childhood cancer and familial risk remains to be fully assessed in population-based studies.

**Methods.** We conducted a nationwide study in Denmark of 11,380 parents of children with cancer. The children were identified from records in the Danish Cancer Registry; their parents were identified from population registers. The occurrence and rate of cancer in the parents were determined with use of the Cancer Registry's files and compared with national incidence rates for various categories of tumor.

**Results.** Overall, 1445 cancers were diagnosed in the parents, as compared with 1496 expected from national

incidence rates, to yield standardized incidence ratios of 1.0 (95 percent confidence interval, 0.9 to 1.0) for all parents, 1.0 for mothers, and 0.9 for fathers. The lower rate of cancer among fathers reflected their lower standardized incidence ratio for lung cancer (0.8; 95 percent confidence interval, 0.6 to 0.9), as calculated from 114 observations.

**Conclusions.** Genetic determinants are important in several types of childhood cancer, but the genetic susceptibility to tumors does not generally extend to the parents of children with cancer, nor do the patterns of incidence point to the influence of shared environmental factors. Thus, cancer in children should not be viewed as a general marker for an increased risk of cancer in the patients' parents. (N Engl J Med 1995;333:1594-9.)

NEOPLASIA in early life has characteristics that suggest the importance of heritable factors in the causation of cancer.<sup>1</sup> Clinical and epidemiologic surveys<sup>2-10</sup> have revealed that close relatives of children with cancer have an overall rate of cancer<sup>7-10</sup> and rates of certain types of cancer<sup>2-6</sup> that are higher than those in the general population. This finding implies that the occurrence of cancer in a child can predict an increased risk of cancer in the child's parents or other relatives. An inherited susceptibility to tumors has been well documented for bilateral retinoblastoma<sup>1</sup> and for Li-Fraumeni syndrome, in which families are prone to breast cancer and neoplasms of early life, such as childhood sarcoma.<sup>11</sup> These two hereditary disorders have been linked to germ-line mutations of the tumor-suppressor genes *RBI* and *p53*, respectively. It has been suggested that the mothers of children with sarcoma should be screened for breast cancer in early adulthood.<sup>12,13</sup> However, whether the occurrence of childhood cancer can predict an increased familial risk of cancer has heretofore not been assessed in large, population-based studies.

### METHODS

In this nationwide study in Denmark, covering a period of almost 50 years, the incidence of various types of cancer was measured in large cohorts of the parents of patients with childhood cancer and then compared with the rates of cancer in the general population.

#### Study Population

In Denmark, during the period 1943 to 1985, 5917 children under 15 years of age were given a diagnosis of some type of cancer, including tumors of the brain. We identified the children through the files of the Danish Cancer Registry, which in each case provided information on the tumor, the name and sex of the child, and the child's date of birth.<sup>14</sup> For children alive on April 1, 1968, when the Central Pop-

ulation Register was established, and children born after that date, a unique personal identification number was also available. Only children born in Denmark were included in the study; this led to the exclusion of 17 children (0.3 percent) who were born elsewhere. The emigration of persons born in Denmark has been negligible since the early 1960s, never exceeding 0.5 percent per year.<sup>15</sup>

Cases of childhood cancer reported during the period 1943 to 1977 were reevaluated on the basis of the initial information given by the clinicians and pathologists,<sup>16</sup> so that all cases occurring between 1943 and 1985 could be classified according to the system set forth in the *International Classification of Diseases for Oncology*.<sup>17</sup> In our analyses, we used a defined set of diagnostic categories (Table 1) formed by aggregating groups of codes, as proposed by the International Agency for Research on Cancer in an international study of childhood cancer.<sup>18</sup>

The parents of children with cancer were traced in one of two ways. With the personal identification numbers of the children with cancer who were alive on April 1, 1968 (or who were born later) as the key identifiers, the name, identification number, and date of death or emigration (if applicable) of the parents of each child were determined by computerized records linkage. For families in which the child with cancer or a parent had died before April 1, 1968, information about the parents had to be obtained manually from the local population registers of the municipalities in which the families had lived at the time of the diagnosis of cancer. Parents in this latter group were then traced by computer in the Central Population Register or traced manually in the Death Certificate File at the National Board of Health, to verify personal data and dates of death or emigration. More details of the tracing procedures have been described elsewhere.<sup>19</sup> A total of 37 adopted children with cancer (0.6 percent) were excluded from the study, leaving a total of 5863 children with cancer in the study group (Table 1).

#### Identifying Cancer in the Parents

We linked data on the parents with data in the Danish Cancer Registry, using the parents' personal identification numbers or, if they had died before April 1, 1968, their dates of birth, dates of death, and names. The period of follow-up for the occurrence of cancer among parents of a child with cancer extended from the date of birth of the child (or from January 1, 1943, when the registry began, for children born before that date) to the date of the parent's death or emigration, or until December 31, 1989, whichever came first. Cancers in the parents, including benign tumors of the brain and papillomas of the urinary tract, were classified according to the modified Danish version of the *International Classification of Diseases, 7th Revision (ICD-7)*.<sup>20</sup> National incidence rates for these categories of tumor, calculated according to sex, age (in five-year groups), and five-year historical periods were applied to the person-years of observation in the parental co-

From the Division for Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (J.H.O., N.S., A.B.); and the Epidemiology and Biostatistics Program, National Cancer Institute, Bethesda, Md. (J.D.B., J.F.F.). Address reprint requests to Dr. Olsen at the Danish Cancer Society, Division for Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen, Denmark.

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Table 1. Characteristics of the 5863 Children with Cancer.\*

| CHARACTERISTIC  | NO. OF CHILDREN (%) |
|---|---------------------|
| Sex   |                     |
| Male  | 3303 (56)           |
| Female  | 2560 (44)           |
| Year of birth   |                     |
| 1929–1947   | 1457 (25)           |
| 1948–1966   | 2683 (46)           |
| 1967–1985   | 1723 (29)           |
| Year of diagnosis                                     |                     |
| 1943–1957   | 1952 (33)           |
| 1958–1971   | 2021 (35)           |
| 1972–1985   | 1890 (32)           |
| Age at diagnosis (yr)                                 |                     |
| 0–4   | 2801 (48)           |
| 5–9   | 1573 (27)           |
| 10–14   | 1489 (25)           |
| Diagnostic group†                                     |                     |
| Leukemias   | 2067 (35)           |
| Lymphomas and other reticuloendothelial neoplasms     | 541 (9)             |
| Central nervous system neoplasms                      | 1368 (23)           |
| Sympathetic nervous system neoplasms                  | 319 (5)             |
| Retinoblastomas                                       | 178 (3)             |
| Renal tumors  | 381 (7)             |
| Hepatic tumors  | 51 (1)              |
| Malignant bone tumors                                 | 274 (5)             |
| Soft-tissue sarcomas                                  | 306 (5)             |
| Germ-cell, trophoblastic, and other gonadal neoplasms | 125 (2)             |
| Carcinomas and other malignant epithelial neoplasms   | 176 (3)             |
| Other and unspecified malignant neoplasms             | 77 (1)              |

\*Excluding 37 children with adoptive parents and 17 children born outside Denmark.

†According to a classification scheme for childhood cancers.<sup>18</sup>

horts to obtain the number of cancers expected in the parents if they had the same rates of incidence as the general population.

### Statistical Analysis

The statistical methods were chosen on the basis of the assumption that the observed number of cases of cancer in any specific category follows a Poisson distribution. Tests of significance and confidence intervals for the standardized incidence ratio — the ratio of the observed to the expected number of cancers — were calculated with use

of the Miettinen exact confidence limits if the observed number of cases was small; otherwise, an accurate asymptotic approximation was used.<sup>21</sup> Separate analyses were performed for a number of diagnostic categories of childhood cancer. Account was also taken of the age of the child and the parent at the time of the diagnosis of cancer.

### RESULTS

Table 1 shows characteristics of the children with cancer. Of the parents of the 5863 children, 5747 mothers (98.4 percent) and 5633 fathers (96.5 percent) were successfully traced (23 pairs of parents had 2 children with cancer, and 1 pair had 3). On average, each parent was at risk for cancer for 28 years (range, 3 months to 47 years), beginning at the date of birth of the index child; 2364 parents (21 percent) died and 112 (1 percent) emigrated during follow-up. By the end of the study period, 320,000 person-years of parents' exposure to risk had been observed. Overall, 1445 cancers were diagnosed, and 1496 were expected (Table 2), which yielded a standardized incidence ratio of 1.0 (95 percent confidence interval, 0.9 to 1.0). The standardized incidence ratio was 1.0 (95 percent confidence interval, 0.9 to 1.1) for mothers and 0.9 (95 percent confidence interval, 0.9 to 1.0) for fathers. The slightly lower overall ratio for fathers was due to their standardized incidence ratio for lung cancer (0.8, significantly lower than the overall ratio in all parents), calculated on the basis of 114 observed cases, and their ratios for prostatic cancer (0.9) and testicular cancer (0.7). No similarly lower rate of lung cancer was seen in mothers (50 cases observed vs. 43.8 expected).

Table 3 shows the patterns of cancer among 1135 parents of 580 children with osteogenic or soft-tissue sarcomas, the childhood tumors most consistently associated with an increased risk of cancer in parents. Overall, 177 cancers were reported, and 188.3 were ex-

Table 2. Standardized Incidence Ratios for Cancer in the Parents of 5863 Children with Cancer.\*

| SITE OF CANCER IN PARENT (ICD-7 CODE)         | MOTHERS (N = 5747) |              |               | FATHERS (N = 5633) |              |               |
|---|--------------------|--------------|---------------|--------------------|--------------|---------------|
|   | NO. OBSERVED       | NO. EXPECTED | SIR (95% CI)  | NO. OBSERVED       | NO. EXPECTED | SIR (95% CI)  |
| All sites (140–204)                           | 718                | 723.1        | 1.0 (0.9–1.1) | 727                | 772.4        | 0.9 (0.9–1.0) |
| Buccal cavity and pharynx (140–148)           | 10                 | 8.0          | 1.2 (0.6–2.2) | 31                 | 25.5         | 1.2 (0.8–1.7) |
| Digestive organs (150–159)                    | 135                | 128.0        | 1.1 (0.9–1.3) | 198                | 192.3        | 1.0 (0.9–1.2) |
| Respiratory system (160–164)                  | 54                 | 48.9         | 1.1 (0.8–1.4) | 129                | 171.6        | 0.8 (0.6–0.9) |
| Larynx (161)                                  | 3                  | 2.4          | 1.2 (0.2–3.6) | 12                 | 13.8         | 0.8 (0.5–1.5) |
| Lung (162)                                    | 50                 | 43.8         | 1.1 (0.8–1.5) | 114                | 150.3        | 0.8 (0.6–0.9) |
| Breast (170)                                  | 168                | 176.0        | 1.0 (0.8–1.1) | 0                  | 1.2          | 0.0 (0.0–3.1) |
| Female genital organs (171–176)               | 162                | 168.4        | 1.0 (0.8–1.1) | —                  | —            | —             |
| Male genital organs (177–179)                 | —                  | —            | —             | 71                 | 81.8         | 0.9 (0.7–1.1) |
| Prostate (177)                                | —                  | —            | —             | 58                 | 65.1         | 0.9 (0.7–1.2) |
| Testis (178)                                  | —                  | —            | —             | 10                 | 13.6         | 0.7 (0.4–1.3) |
| Urinary system (180–181)                      | 32                 | 31.2         | 1.0 (0.7–1.5) | 88                 | 90.4         | 1.0 (0.8–1.2) |
| Skin (190–191)                                | 79                 | 84.1         | 0.9 (0.7–1.2) | 102                | 107.2        | 1.0 (0.8–1.2) |
| Brain and nervous system (193)                | 19                 | 21.2         | 0.9 (0.5–1.4) | 22                 | 23.0         | 1.0 (0.6–1.5) |
| Bone and connective tissue (196–197)          | 2                  | 3.4          | 0.6 (0.1–2.0) | 7                  | 4.6          | 1.5 (0.7–3.0) |
| Lymphatic and hematopoietic tissues (200–205) | 36                 | 33.3         | 1.1 (0.8–1.5) | 57                 | 52.3         | 1.1 (0.8–1.4) |
| Other specified organs (192, 194–195)         | 7                  | 6.8          | 1.0 (0.5–2.0) | 7                  | 5.8          | 1.2 (0.5–2.4) |
| Secondary and unspecified sites (198–199)     | 14                 | 13.8         | 1.0 (0.6–1.7) | 15                 | 16.7         | 0.9 (0.5–1.4) |

\*Expected numbers of cancers are from national incidence rates adjusted for sex, age, and date of diagnosis. SIR denotes standardized incidence ratio, and CI confidence interval.

Table 3. Standardized Incidence Ratios for Cancer in the Parents of 580 Children with Osteogenic or Soft-Tissue Sarcomas.\*

| SITE OF CANCER IN PARENT (ICD-7 CODE)               | MOTHERS (N = 573) |              |               | FATHERS (N = 562) |              |               |
|---|-------------------|--------------|---------------|-------------------|--------------|---------------|
|   | NO. OBSERVED      | NO. EXPECTED | SIR (95% CI)  | NO. OBSERVED      | NO. EXPECTED | SIR (95% CI)  |
| All sites (140–204)                                 | 93                | 86.7         | 1.1 (0.9–1.3) | 84                | 101.6        | 0.8 (0.7–1.0) |
| Digestive organs (150–159)                          | 22                | 16.6         | 1.3 (0.8–2.0) | 27                | 26.4         | 1.0 (0.7–1.5) |
| Stomach (151)                                       | 2                 | 2.3          | 0.9 (0.1–2.9) | 8                 | 6.0          | 1.3 (0.6–2.5) |
| Colon (153)   | 6                 | 6.3          | 1.0 (0.4–2.0) | 6                 | 7.0          | 0.9 (0.3–1.8) |
| Rectum (154)  | 2                 | 1.8          | 1.1 (0.2–3.6) | 4                 | 6.0          | 0.7 (0.2–1.6) |
| Respiratory system (160–164)                        | 6                 | 5.8          | 1.0 (0.4–2.2) | 10                | 22.4         | 0.4 (0.2–0.8) |
| Larynx (161)  | 0                 | 0.3          | 0.0 (0.0–12)  | 1                 | 1.7          | 0.6 (0.0–2.9) |
| Lung (162)  | 6                 | 5.2          | 1.2 (0.5–2.4) | 9                 | 19.8         | 0.5 (0.2–0.8) |
| Breast (170)  | 20                | 20.3         | 1.0 (0.6–1.5) | 0                 | 0.2          | 0.0 (0.0–18)  |
| Female genital organs (171–176)                     | 20                | 20.0         | 1.0 (0.6–1.5) | —                 | —            | —             |
| Male genital organs (177–179)                       | —                 | —            | —             | 11                | 11.4         | 1.0 (0.5–1.7) |
| Urinary system (180–181)                            | 3                 | 3.9          | 0.8 (0.2–2.1) | 8                 | 11.8         | 0.7 (0.3–1.3) |
| Kidney (180)  | 1                 | 1.9          | 0.5 (0.0–2.6) | 1                 | 3.3          | 0.3 (0.0–1.5) |
| Urinary bladder (181)                               | 2                 | 2.0          | 1.0 (0.2–2.2) | 7                 | 8.5          | 0.8 (0.4–1.6) |
| Skin (190–191)                                      | 12                | 9.8          | 1.2 (0.7–2.1) | 10                | 13.5         | 0.7 (0.4–1.3) |
| Melanoma of skin (191)                              | 0                 | 2.1          | 0.0 (0.0–1.6) | 1                 | 1.5          | 0.7 (0.0–3.2) |
| Brain and nervous system (193)                      | 0                 | 2.4          | 0.0 (0.0–1.5) | 2                 | 2.6          | 0.8 (0.1–2.5) |
| Bone and connective tissue (196–197)                | 0                 | 0.4          | 0.0 (0.0–9.2) | 2                 | 0.6          | 3.6 (0.6–12)  |
| Lymphatic and hematopoietic tissues (200–205)       | 7                 | 4.1          | 1.7 (0.8–3.4) | 11                | 6.6          | 1.7 (0.9–2.9) |
| Non-Hodgkin's lymphoma (200–202)                    | 0                 | 1.4          | 0.0 (0.0–2.1) | 2                 | 2.0          | 1.0 (0.1–3.4) |
| Hodgkin's disease (201)                             | 1                 | 0.5          | 2.2 (0.1–11)  | 2                 | 0.7          | 2.9 (0.5–9.5) |
| Multiple myeloma (203)                              | 3                 | 0.7          | 4.3 (1.1–12)  | 1                 | 1.1          | 0.9 (0.0–4.4) |
| Leukemia (204)                                      | 3                 | 1.6          | 1.9 (0.5–5.3) | 6                 | 2.8          | 2.2 (0.9–4.5) |
| Other and unspecified sites (192, 194–195, 198–199) | 3                 | 3.4          | 0.9 (0.2–2.4) | 3                 | 6.1          | 0.5 (0.1–1.3) |

\*Expected numbers of cancers are from national incidence rates adjusted for sex, age, and date of diagnosis. SIR denotes standardized incidence ratio, and CI confidence interval.

pected (standardized incidence ratio, 0.9); 93 were reported in mothers (standardized incidence ratio, 1.1) and 84 in fathers (standardized incidence ratio, 0.8). With the exception of lung cancer in fathers, which occurred at a 54 percent lower rate than expected (9 cases observed vs. 19.8 expected), and a slightly elevated risk of multiple myeloma in mothers, no meaningful deviation from the expected figures was seen in parents for any of the categories of cancer (Table 3). Specifically, the observation of 20 breast cancers in mothers was close to the 20.3 cases expected, although if the risk of breast cancer is analyzed only for mothers of children given a diagnosis of sarcoma before the age of three, a significant, threefold increase in risk is seen on the basis of 9 observed cases (Table 4). The association with

breast cancer was particularly strong for mothers under 45 years of age (standardized incidence ratio, 5.4).

There was a tendency for most forms of cancer in children under the age of 3 to be associated to some extent with breast cancer in mothers under the age of 45, with a significantly increased incidence ratio for such women, for all cancers combined, of 1.9 (21 observed cancers vs. 11.0 expected). These findings suggest that the excess of 10 cases of breast cancer in mothers under the age of 45 was related to the occurrence of cancer in their offspring; the 10 cases represent 6 percent of the 168 cases of breast cancers observed in the study and 22 percent of the 45 breast cancers in mothers under the age of 45. A total of 17 cases of breast cancer in mothers were observed in association with childhood cancers other than sarcomas, whereas 10.3 were expected, for a standardized incidence ratio of 1.7 (95 percent confidence interval, 1.0 to 2.6). Cancers of other types occurred in mothers at the expected rates (28 observed vs. 27.9 expected).

Table 5 shows the standardized incidence ratios for all types of cancer combined in the mothers and fathers of children with cancers other than sarcomas. The overall risk of cancer was slightly lower in the parents of children with leukemia and was significantly lower in the fathers of children with renal tumors (mainly Wilms' tumor); the latter finding was based on 33 observed cases and 49.5 expected cases (standardized incidence ratio, 0.7) and was not explained by a lower number of any particular type of cancer in the fathers. Also included in

Table 4. Standardized Incidence Ratios for Breast Cancer in Mothers of Children with Osteogenic or Soft-Tissue Sarcomas, According to the Age of the Child at Diagnosis and the Age of the Mother.\*

| AGE OF CHILD AT DIAGNOSIS (YR) | AGE OF MOTHER (YR) | NO. OBSERVED | NO. EXPECTED | SIR (95% CI)   |
|--------------------------------|--------------------|--------------|--------------|----------------|
| 0–2                            | All ages           | 9†           | 3.1          | 2.9 (1.4–5.3)  |
| 3–14                           | All ages           | 11           | 17.2         | 0.6 (0.4–1.1)  |
| 0–14                           | <45                | 5†           | 3.7          | 1.4 (0.5–3.0)  |
| 0–14                           | ≥45                | 15           | 16.6         | 0.9 (0.5–1.5)  |
| 0–2                            | <45                | 4†           | 0.7          | 5.4 (1.7–12.9) |

\*Expected numbers of cancers are from national incidence rates adjusted for sex, age, and date of diagnosis. SIR denotes standardized incidence ratio, and CI confidence interval.

†One case of bilateral breast cancer is included as a single observation.

Table 5. Standardized Incidence Ratios for All Cancers Combined and Cancers at Selected Sites in the Parents of 5155 Children with Cancers Other Than Osteogenic and Soft-Tissue Sarcomas.\*

| TYPE OF CANCER IN CHILD†                                      | TYPE OF CANCER IN PARENT | MOTHERS      |              |               | FATHERS      |              |               |
|---|--------------------------|--------------|--------------|---------------|--------------|--------------|---------------|
|   |                          | NO. OBSERVED | NO. EXPECTED | SIR (95% CI)  | NO. OBSERVED | NO. EXPECTED | SIR (95% CI)  |
| Leukemia (n = 2067)   | All sites                | 243          | 258.9        | 0.9 (0.8–1.1) | 242          | 269.6        | 0.9 (0.8–1.0) |
|   | Rectum                   | 8            | 9.2          | 0.9 (0.4–1.7) | 6            | 15.2         | 0.4 (0.1–0.9) |
|   | Lung                     | 18           | 15.7         | 1.1 (0.7–1.8) | 37           | 52.5         | 0.7 (0.5–1.0) |
|   | Kidney                   | 12           | 5.5          | 2.1 (1.1–3.8) | 12           | 8.9          | 1.4 (0.7–2.4) |
|   | Leukemias                | 6            | 4.5          | 1.3 (0.5–2.9) | 5            | 7.4          | 0.7 (0.2–1.6) |
| Lymphoma or other reticulo-endothelial neoplasm (n = 541)     | All sites                | 87           | 70.2         | 1.2 (1.0–1.5) | 73           | 73.6         | 1.0 (0.8–1.2) |
|   | Cervix uteri             | 15           | 7.6          | 2.0 (1.1–3.3) | —            | —            | —             |
|   | Brain and nervous system | 6            | 2.1          | 2.9 (1.1–6.3) | 2            | 2.2          | 0.9 (0.1–3.3) |
|   | Malignant lymphoma       | 0            | 1.4          | 0.0 (0.0–2.6) | 1            | 2.1          | 0.5 (0.0–2.3) |
| Central nervous system neoplasm (n = 1368)                    | All sites                | 153          | 166.4        | 0.9 (0.8–1.1) | 184          | 173.8        | 1.1 (0.9–1.2) |
|   | Rectum                   | 5            | 5.9          | 0.9 (0.3–2.0) | 19           | 9.8          | 1.9 (1.2–3.0) |
|   | Brain and nervous system | 6            | 4.9          | 1.2 (0.8–2.7) | 7            | 5.3          | 1.3 (0.5–2.7) |
| Sympathetic nervous system neoplasm (n = 319)                 | All sites                | 29           | 25.1         | 1.2 (0.8–2.7) | 22           | 25.7         | 0.9 (0.5–1.3) |
| Retinoblastoma (n = 178)                                      | All sites                | 12           | 16.1         | 0.8 (0.4–1.3) | 25           | 17.9         | 1.4 (0.9–2.1) |
|   | Melanoma of skin         | 1            | 0.5          | 1.9 (0.0–11)  | 3            | 0.4          | 7.5 (1.5–22)  |
| Renal tumor (n = 381)   | All sites                | 44           | 43.0         | 1.0 (0.7–1.4) | 33           | 49.5         | 0.7 (0.5–0.9) |
|   | Kidney                   | 0            | 0.9          | 0.0 (0.0–4.1) | 3            | 1.6          | 1.9 (0.4–5.4) |
| Germ-cell, trophoblastic, or other gonadal neoplasm (n = 125) | All sites                | 13           | 12.6         | 1.0 (0.5–1.8) | 14           | 13.1         | 1.1 (0.6–1.8) |
|   | Lip                      | 0            | 0.0          | —             | 3            | 0.2          | 14.7 (3.0–43) |
|   | Breast                   | 3            | 3.2          | 0.9 (0.2–2.7) | 0            | 0.0          | —             |
|   | Cervix uteri             | 3            | 1.5          | 2.1 (0.4–6.0) | —            | —            | —             |
|   | Corpus uteri             | 0            | 0.7          | 0.0 (0.0–5.3) | —            | —            | —             |
|   | Prostate                 | —            | —            | —             | 0            | 0.9          | 0.0 (0.0–4.1) |
|   | Ovary                    | 0            | 0.8          | 0.0 (0.0–4.6) | —            | —            | —             |
| Carcinoma or other malignant epithelial neoplasm (n = 176)    | All sites                | 25           | 27.9         | 0.9 (0.6–1.3) | 10           | 12.8         | 0.8 (0.4–1.4) |
|   | Testis                   | —            | —            | —             | 1            | 0.3          | 3.5 (0.0–20)  |

\*Parents of 51 children with hepatic tumors and 77 children with other and unspecified malignant neoplasms are not shown in this table because these groups were too small to yield meaningful results. Expected numbers of cancers are from national incidence rates adjusted for sex, age, and date of diagnosis. SIR denotes standardized incidence ratio, and CI confidence interval.

†According to a classification scheme for childhood cancers.<sup>18</sup>

Table 5 are the few significant relations — each derived from at least three observations — between a particular type of childhood cancer and the type of cancer, if any, that developed in parents. The most striking of these are the relations between childhood leukemia and kidney cancer in mothers (standardized incidence ratio, 2.1) and, to a lesser extent, fathers (standardized incidence ratio, 1.4), and those between non-Hodgkin's lymphoma in children and cancers of the brain (standardized incidence ratio, 2.9) and uterine cervix (standardized incidence ratio, 2.0) in mothers. A positive association between cancers of the same type was identified only for childhood tumors of the central nervous system, which were associated with a slight excess of central nervous system tumors in both mothers (standardized incidence ratio, 1.2) and fathers (standardized incidence ratio, 1.3).

To evaluate whether some characteristics of the distribution of childhood cancer might be especially predictive of parental risk, we examined 24 families in which more than one child had cancer and 54 families in which a child with cancer eventually had a second primary tumor. The overall standardized incidence ratio for cancer in the parents of the first group was 1.0 (95 percent confidence interval, 0.3 to 2.4), calculated on the basis of 5 cases of cancer in parents, and in the

parents of the second group, 0.9 (95 percent confidence interval, 0.5 to 1.5), calculated on the basis of 16 cases.

## DISCUSSION

Our main finding is that the overall occurrence of cancer in the parents of children with cancer, 1445 observed cases, was remarkably close to that expected from incidence rates in the general adult population. The parents' risk of cancer was not increased by having a child with any of the 10 major categories of disease, including osteogenic and soft-tissue sarcomas (of which there were 580 cases). These findings conflict with those of some earlier studies, which found that first-degree relatives of children with cancer, especially sarcomas, had an overall increased risk of cancer.<sup>7-10</sup> The earlier studies involved 177 children with soft-tissue sarcomas (1.7 times the average risk of cancer was found in mothers);<sup>7</sup> 159 children with soft-tissue sarcomas (1.3 times the average risk of cancer was found in first-degree relatives);<sup>9</sup> 47 cases of bilateral retinoblastoma (1.3 times the average risk of cancer was found in first-degree relatives);<sup>8</sup> and 326 children with a variety of types of cancer (1.7 times the average risk of cancer was found in mothers).<sup>10</sup> Our findings are more in line with hospital-based studies in Italy,<sup>22</sup> the United States,<sup>13</sup> and France,<sup>23</sup> which reported no overall increased risk

of cancer in the first-degree relatives of 195 children with soft-tissue sarcomas, 88 children with sarcomas of the bone and soft tissue, and 501 children with Wilms' tumor, respectively.

We have no reason to believe that our failure to find a general link between the occurrence of cancer in children and that in their parents is due to bias in our study. The Danish Cancer Registry records data from the country's entire population, so practically all cases of childhood cancer occurring after 1943 were identified, as were more than 97 percent of the parents of the children involved; this minimizes the possibility of bias due to the selection of study subjects. Similarly, very few persons born in Denmark emigrate to other countries. Information bias is also unlikely; the study groups were established and parenthood determined before files were searched for evidence of cancer in the parents, and the study relied on population registers that are kept for administrative purposes.

We saw a few noteworthy relations between childhood cancer and specific types of cancer in parents, including an increase in breast cancer in mothers under the age of 45 whose children had been given a diagnosis of cancer before the age of 3. This link was based on an excess of 10 breast cancers (about 20 percent) among the 45 observed in mothers under the age of 45, which suggests that cancer in young children (that diagnosed before the age of 3) is a useful predictor of breast cancer in relatively young mothers. The strength of the association may be somewhat underestimated, because the national rates for breast cancer that we used are influenced by an approximately 30 percent higher risk of breast cancer among nulliparous women than among parous women.<sup>24</sup> Since any group of mothers would therefore be likely to have a lower risk of breast cancer than the group of all women in the country, the standardized incidence ratio is an underestimate. On the other hand, the large-scale, quantitative importance of familial susceptibility seems limited, since the 10 cases of breast cancer predicted by the occurrence of cancer in young children make up only about 0.1 percent of the 11,911 cases of breast cancer that were diagnosed during the study period in Danish women under the age of 45.

The association with breast cancer was particularly strong for mothers of children with sarcoma diagnosed before the age of 3. This finding is in accordance with the familial syndrome of soft-tissue sarcomas, breast cancer, and other neoplasms in young adults and children initially described by Li and Fraumeni in 1969<sup>11</sup> and confirmed by longitudinal studies of high-risk families<sup>25,26</sup> and by a British population-based study that found the risk of breast cancer in the mothers of children with soft-tissue sarcoma to be three times the average for the population at large.<sup>6,7</sup> Susceptibility to breast cancer also occurs in the families of children with osteosarcoma and chondrosarcoma,<sup>26</sup> as indicated both by our study and by another population-based study from England.<sup>3</sup>

The substantially lower risk of lung cancer that we

found in the fathers of children with cancer has not been reported previously and was not paralleled by a lower risk among mothers. Although fathers may have changed their smoking habits after cancer developed in their children, this seems an insufficient explanation for the effect, since even former smokers are prone to have lung cancer. Because genetic factors also seem unlikely to play a part, the finding may be a matter of chance. Our general finding that the risk of lung cancer is not elevated in the parents of children with cancer is consistent with recent studies that have shown no relation between parental smoking habits and childhood neoplasms.<sup>27,28</sup>

In our study, the overall risk of cancer was also significantly lower than expected in the fathers of children with Wilms' tumor; no particular risk pattern according to the father's type of cancer was seen, and no similar effect was noticed in mothers. We have no plausible explanation for this finding other than its being a result of multiple statistical testing; we tested 22 types of cancer in parents, both men and women, against each of 11 diagnostic groups of childhood cancer. Given 484 such comparisons and our practice of establishing significance with 95 percent confidence intervals, chance alone might result in 24 "significant" findings. We in fact observed 11 positive and 7 negative associations that had statistical significance.

Aside from those already mentioned, our study revealed few associations between cancer in children and cancer in their parents. The increased risk of kidney cancer observed in mothers and fathers of children with leukemia, irrespective of the child's age at diagnosis, calls for further studies of shared risk factors, as does the increased risk of cervical cancer observed in the mothers of children with non-Hodgkin's lymphoma. The slight elevation of the risk of brain tumors in the mothers of children with lymphoma, although based on few observations, is consistent with previous reports of familial tumor complexes.<sup>29</sup> The high risk of melanoma among fathers of children with retinoblastoma is an intriguing finding, given that children with heritable retinoblastoma are prone to have melanoma as a second tumor<sup>30</sup> (however, the finding in our study occurred in children with unilateral disease<sup>19</sup>). A link between melanoma and retinoblastoma has also been noted in case reports,<sup>31</sup> as well as an accompanying association with the dysplastic nevus syndrome.<sup>32</sup> Except for the link between sarcoma in children and early-onset breast cancer in their mothers, which has been previously reported, the associations in our study must be interpreted with caution because of the increased effects of chance in multiple comparisons.

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