Long-term Risks of Subsequent Primary Neoplasms Among Survivors of Childhood Cancer

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Survivors of childhood cancer are at increased risk of developing subsequent primary neoplasms with the risk being estimated at 3- to 6-fold that expected. However, the magnitude of the long-term risks of developing a subsequent primary neoplasm, in particular beyond ages at which the background cancer incidence in the general population starts to increase substantially, are unknown. Thus far, only 1 study has sufficient follow-up to start to explore the risk of subsequent primary neoplasms in childhood cancer survivors older than 40 years.

It is essential to investigate the long-term risks of subsequent primary neoplasms since any increased relative risk (RR) sustained into old age would lead to a substantial number of survivors being diagnosed with a subsequent primary neoplasm. To reduce the number of subsequent primary neoplasms, prevention, screening, and other intervention strategies should focus on subsequent primary neoplasm types with the highest absolute excess risks (AERs); however, it is unclear which subsequent primary neoplasm types contribute most to the total AER, particularly at older than 40 years. Several important clinical and policy issues, including the creation and revision of guidelines for clinical follow-up, require the identification of specific survivor subgroups that are at substantially increased risk of particular subsequent primary neoplasms.
A principal advantage of the current study, in addition to being population based and large scale, is that many of the childhood cancer survivors included were older than 40 years and thus, we can explore the risks of subsequent primary neoplasms as the survivors reach those ages during which general population cancer rates increase substantially.

The objectives of this large-scale study were to: (1) investigate the long-term risks of subsequent primary neoplasms in survivors of childhood cancer; (2) identify subsequent primary neoplasm types that contribute most to the long-term excess risk; and (3) to identify subgroups of survivors at substantially increased risk of particular subsequent primary neoplasms who may require specific interventions.

METHODS
British Childhood Cancer Survivor Study
The British Childhood Cancer Survivor Study comprises 17,981 individuals who were diagnosed with cancer at younger than 15 years, from 1940 through 1991 in Great Britain, and survived at least 5 years. The cohort was identified using the population-based National Registry of Childhood Tumours. Ascertainment is estimated to be very high (=99%) because the registry receives notifications from multiple sources and cross checks and validates reports with other sources. Approval to process personal data without individual consent was obtained from the Patient Information Advisory Group and the National Research Ethics Service.

Ascertainment of Subsequent Primary Neoplasms
Ascertainment of subsequent primary neoplasms was population based through flagging survivors at the National Health Service Central Registers. Flagging informs the British Childhood Cancer Survivor Study when a survivor develops a subsequent primary neoplasm or dies, and provides linkage between the population-based cohort and the national population-based death and cancer registration systems. Confirmation of all subsequent primary neoplasms was undertaken by writing to the relevant clinician(s) to obtain all diagnostic reports to confirm site, type, and date of diagnosis, with particular reference to the pathology reports.

Subsequent primary neoplasms were grouped according to the edition of the International Classification of Diseases (ICD) appropriate to the calendar year in which the neoplasm was diagnosed, as national general population cancer rates for these classifications are available. The exception was for the category of glioma and other neuroepithelial neoplasms (ie, the glioma group) that was identified by histology type (ICD-O-3 codes: 9380-9523, excluding 9470-9473). Nonmelanoma skin cancers (NMSC) and nonglioma central nervous system (CNS) tumors were ascertained but excluded from analyses involving comparisons with the general population because general population registration rates for these neoplasms are known to be variably underascertained. We included all tumors of the bladder irrespective of whether they were classified as malignant, benign, in-situ or of uncertain behavior because of the known difficulty of classifying the malignant potential of bladder tumors.

Statistical Analysis
Time at risk for a subsequent primary neoplasm began at 5 years subsequent to initial childhood cancer diagnosis and ended at the first occurrence of loss to follow-up, death, or reaching the study exit date (December 31, 2006, the most recent available data). Unless otherwise specified, all analyses allowed for multiple subsequent primary neoplasms per survivor.

To compare subsequent primary neoplasm rates in survivors with neoplasm rates in the general population, standardized incidence ratios (SIRs) and AERs were computed. SIRs were computed as the ratio of observed (Obs) to expected (Exp) numbers of neoplasms (Obs/Exp). Expected numbers were estimated by accumulating person-years at risk within specific sex, 5-year age and 1-year calendar period strata and multiplying by the corresponding neoplasm rates in the general population of England and Wales. The range of calendar years available for the general population neoplasm rates were from 1971 to 2006, and for years prior to 1971, the mean was taken from the earliest 4 years (1971-1974). AERs were computed as: ([Obs − Exp]/person-years at risk) × 10,000. The AER may be interpreted as the mean excess number of subsequent primary neoplasms observed per 10,000 survivors per year. For those subsequent primary neoplasm types with 75 or more observed cases, SIRs and AERs were provided by sex, type of childhood cancer, and attained age.

To compare subsequent primary neoplasm rates between survivors with different characteristics (sex, type of childhood cancer, age at childhood cancer diagnosis, treatment with radiotherapy, treatment with chemotherapy, and attained age), special multivariable Poisson regression models that incorporated the relevant expected population rates were used to derive RRs and relative excess risks (RERs). Cumulative incidence for the first occurrence of a subsequent primary neoplasm was computed by attained age with death considered as a competing risk. Expected cumulative incidence was estimated using the conditional (Ederer II) method. The cumulative incidence of developing a subsequent colorectal cancer was specifically estimated for survivors treated with direct radiotherapy to the abdomen, pelvis, or lumbar/sacral spine (ie, direct abdominopelvic irradiation). Colorectal cancer was not only a large enough and homogeneous enough subsequent primary neoplasm group to investigate in more detail, but it was also possible to compare the cumulative incidence among this group of survivors with that of other subgroups from the general population at excess risk, such as individuals with at least 2 first-degree relatives affected by colorectal cancer. The cumulative incidence for individuals with at least 2 first-degree relatives affected by colorectal cancer was de-
Overall Risk of Subsequent Neoplasm
After excluding NMSC and nonglioma CNS neoplasms, 837 subsequent primary neoplasms were observed, whereas 215.5 were expected (Table 1). Overall, survivors were 4 times more likely to develop a subsequent primary neoplasm than expected (SIR, 3.9; 95% CI, 3.6-4.2). An overall SIR of 16.8 subsequent primary neoplasms per 10 000 person-years (95% CI, 15.3-18.3) was observed. While the SIR declined significantly with increasing attained age, the AER increased from 12.2 per 10 000 person-years (95% CI, 10.3-14.1) in survivors younger than 20 years to 38.6 per 10 000 person-years (95% CI, 17.5-59.7) in those older than 50 years ($P_{\text{trend}} < .001$). All types of childhood cancer exhibited significantly increased SIRs, with survivors of heritable retinoblastoma exhibiting the highest SIR (13.4; 95% CI, 11.1-16.1; AER, 69.0/10 000 person-years). The multivariable Poisson models revealed that type of childhood cancer, radiotherapy, chemotherapy, and attained age were significantly associated with the risk of developing any subsequent primary neoplasm (all $P$ values < .001) (eTable 2).

Digestive
The SIR for a digestive subsequent primary neoplasm was 4.6 times more than expected (95% CI, 3.8-5.6; AER, 2.2/10 000 person-years) (Table 1). The SIR was particularly high for survivors younger than aged 20 years (SIR, 28.3; 95% CI, 16.7-47.7), but declined sharply with increasing attained age ($P_{\text{trend}} < .001$). In contrast, the AER was low in survivors younger than 20 years (AER, 1.0/10 000 person-years; 95% CI, 0.4-1.5), but increased with attained age to 6.1 per 10 000 person-years in survivors older than 40 years (95% CI, 2.5-9.7). Greatest SIRs were observed following Wilms tumor (SIR, 13.0; 95% CI, 8.1-20.8; AER, 4.6/10 000 person-years) and heritable retinoblastoma (SIR, 12.5; 95% CI, 6.9-22.6; AER, 6.7/10 000 person-years). Initial treatment including direct abdominopelvic irradiation increased the RR of developing a digestive subsequent primary neoplasm by 3.3 fold (95% CI, 1.6-6.8) relative to initial treatment, which excluded radiotherapy (eTable 2).

Genitourinary
The overall SIR for developing a genitourinary subsequent primary neoplasm was the lowest of all subsequent primary neoplasm categories (SIR, 1.9; 95% CI, 1.6-2.4; AER, 1.3/10 000 person-years) (Table 1). However, the SIR remained relatively uniform throughout all age groups and as a consequence, the AER increased sharply with attained age reaching 12.7 subsequent primary neoplasms per 10 000 person-years (95% CI, 1.7-23.7) in survivors older than aged 50 years ($P_{\text{trend}} < .001$). Survivors of heritable retinoblastoma were at particularly high risk both in terms of SIR and AER (SIR, 7.9; 95% CI, 4.8-13.1; AER, 8.6/10 000 person-years; 95% CI, 3.6-13.7). The multivariable Poisson regression revealed that females were at a 70% higher risk than males (RR, 1.7; 95% CI, 1.1-2.6) for a genitourinary subsequent primary neoplasm (eTable 2).

Glioma
The overall SIR for a glioma subsequent primary neoplasm was 6.5 times more than expected (95% CI, 5.4-7.8; AER, 2.4/10 000 person-years). Although it declined with attained age, it remained high even at older than 50 years (SIR, 3.1; 95% CI, 1.2-8.3) (Table 2). The AER was 2.6 per 10 000 person-years (95% CI, 1.7-3.5) at younger than 20 years and did not increase significantly with attained age ($P_{\text{trend}} = .48$), but remained elevated nonetheless. SIRs for a glioma subsequent primary neoplasm were highest following a diagnosis of CNS tumor (SIR, 12.3; 95% CI, 9.3-16.2; AER, 5.3/10 000 person-years) and leukemia (SIR, 9.4; 95% CI, 6.5-13.7; AER, 3.0/10 000 person-years). Treatment involving cranial irradiation increased the RR of a glioma subsequent primary neoplasm by a factor of 5.5 (95% CI, 2.4-12.3) (eTable 2).
SUBSEQUENT PRIMARY NEOPLASMS AFTER CHILDHOOD CANCER

Breast

The SIR for a breast subsequent primary neoplasm was 2.2 times more than expected (95% CI, 1.8–2.7; AER, 1.4/10 000 person-years) and highest following Hodgkin lymphoma (SIR, 8.9; 95% CI, 5.9–13.2; AER, 7.8/10 000 person-years) (Table 2). The RR decreased significantly with increasing attained age ($P_{trend} < .001$) while the RER increased with attained age ($P_{trend} < .001$) (eTable 2).

Bone

The highest overall SIR for any specific subsequent primary neoplasm category was observed for bone subsequent primary neoplasms (SIR, 30.5; 95% CI, 24.9–37.3; AER, 2.5/10 000 person-years), but the SIR declined sharply with increasing attained age ($P_{trend} = .002$) (Table 2). The SIR and AER were particularly high for heritable retinoblastoma (SIR, 289.2; 95% CI, 207.6–402.8; AER, 23.0/10 000 person-years) and bone tumors (SIR, 136.3; 95% CI, 79.2–234.8; AER, 10.0/10 000 person-years).

Table 1. Standardized Incidence Ratios and Absolute Excess Risks for All Combined, Digestive, and Genitourinary Subsequent Primary Neoplasms by Sex, Childhood Cancer Type, and Attained Age

<table>
<thead>
<tr>
<th>Person-Years</th>
<th>No. Obs/Exp</th>
<th>SIR (95% CI)a</th>
<th>AER (95% CI)b</th>
<th>Person-Years</th>
<th>No. Obs/Exp</th>
<th>SIR (95% CI)a</th>
<th>AER (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>369 909.9</td>
<td>837/215.5</td>
<td>3.9 (3.6 to 4.2)</td>
<td>16.8 (15.3 to 18.3)</td>
<td>105/22.7</td>
<td>4.6 (3.8 to 5.6)</td>
<td>2.2 (1.7 to 2.8)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>200 390.0</td>
<td>429/95.6</td>
<td>4.5 (4.1 to 4.9)</td>
<td>16.6 (14.6 to 18.7)</td>
<td>75/14.0</td>
<td>5.4 (4.3 to 6.7)</td>
<td>3.0 (2.2 to 3.9)</td>
</tr>
<tr>
<td>Female</td>
<td>169 519.9</td>
<td>408/119.9</td>
<td>3.4 (3.1 to 3.6)</td>
<td>17.0 (14.7 to 19.3)</td>
<td>30/8.7</td>
<td>3.5 (2.4 to 4.9)</td>
<td>1.3 (0.6 to 1.9)</td>
</tr>
<tr>
<td>Attained age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–9</td>
<td>140 017.6</td>
<td>189/18.2</td>
<td>10.4 (9.0 to 12.0)</td>
<td>12.2 (10.3 to 14.1)</td>
<td>14/0.5</td>
<td>28.3 (16.7 to 47.7)</td>
<td>1.0 (0.4 to 1.5)</td>
</tr>
<tr>
<td>10–19</td>
<td>125 942.9</td>
<td>207/42.5</td>
<td>4.9 (4.3 to 5.6)</td>
<td>10.8 (8.9 to 12.9)</td>
<td>20/1.9</td>
<td>10.4 (6.7 to 16.2)</td>
<td>1.4 (0.7 to 2.1)</td>
</tr>
<tr>
<td>20–29</td>
<td>69 626.9</td>
<td>231/56.9</td>
<td>4.4 (3.6 to 5.6)</td>
<td>20.0 (17.7 to 22.5)</td>
<td>35/4.5</td>
<td>8.5 (5.6 to 10.9)</td>
<td>4.4 (2.7 to 6.4)</td>
</tr>
<tr>
<td>30–39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>26 157.7</td>
<td>133/52.4</td>
<td>2.5 (2.1 to 3.0)</td>
<td>30.8 (22.3 to 39.6)</td>
<td>23/7.1</td>
<td>3.2 (2.1 to 4.8)</td>
<td>6.1 (2.5 to 9.7)</td>
</tr>
<tr>
<td>≥50</td>
<td>8 164.7</td>
<td>77/45.5</td>
<td>1.5 (1.4 to 2.1)</td>
<td>38.6 (17.5 to 79.7)</td>
<td>13/8.7</td>
<td>1.5 (0.9 to 2.6)</td>
<td>5.3 (3.3 to 14.0)</td>
</tr>
<tr>
<td>$P_{trend}$</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: AER, absolute excess risk; CI, confidence interval; Exp, expected; Obs, observed; SIR, standardized incidence ratio.

aCIs should be interpreted cautiously if based on fewer than 5 observed events.
bAER is shown per 10 000 person-years; CIs should be interpreted cautiously if based on fewer than 5 observed events.
cBased on International Classification of Childhood Cancer.
dHeritable retinoblastoma defined as bilateral retinoblastoma or family history of retinoblastoma.

2314 JAMA, June 8, 2011—Vol 305, No. 22 ©2011 American Medical Association. All rights reserved.
Survivors treated with direct abdominopelvic radiotherapy had a 3.1 times increased RR (95% CI, 1.5-6.5) compared with those not treated with radiotherapy (eTable 2).

AER by Attained Age

AERs for specific subsequent primary neoplasm categories by attained age and the percentage of the total age-specific AER associated with each subsequent primary neoplasm category are shown in Table 3. At younger than 20 years, glioma and bone subsequent primary neoplasms accounted for 57% of the total AER of developing a subsequent primary neoplasm, whereas at older than 40 years, these subsequent primary neoplasms accounted for only 6% of the total AER. In contrast, digestive and genitourinary subsequent primary neoplasms contributed the largest AER at older than 40 years compared with other subsequent primary neoplasm categories (P < .001); 36% of the total AER was attributable to genitourinary and digestive subsequent primary neoplasms. Overall, 52% of the total AER was attributable to digestive, genitourinary, breast, or respiratory sites at older than 40 years.

Table 2. Standardized Incidence Ratios and Absolute Excess Risks for Glioma, Breast, and Bone Subsequent Primary Neoplasms by Sex, Childhood Cancer Type, and Attained Age

<table>
<thead>
<tr>
<th>Glioma</th>
<th>Breast</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Obs/Exp</td>
<td>SIR (95% CI)</td>
<td>AER (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>105/16.2</td>
<td>6.5 (5.4 to 7.8)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53/9.4</td>
<td>5.7 (4.3 to 7.4)</td>
</tr>
<tr>
<td>Female</td>
<td>52/6.8</td>
<td>7.6 (5.8 to 10.0)</td>
</tr>
<tr>
<td>P heterogeneity</td>
<td>0.13</td>
<td>0.38</td>
</tr>
<tr>
<td>Childhood cancer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>50/4.1</td>
<td>12.3 (9.3 to 16.2)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>27/2.9</td>
<td>9.4 (8.5 to 13.7)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>4/1.4</td>
<td>2.9 (1.1 to 7.7)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>6/0.9</td>
<td>6.8 (2.9 to 14.6)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>2/0.7</td>
<td>3.0 (0.8 to 12.2)</td>
</tr>
<tr>
<td>Heritable retinoblastoma</td>
<td>3/0.6</td>
<td>4.7 (1.5 to 14.5)</td>
</tr>
<tr>
<td>Nonheritable retinoblastoma</td>
<td>1/0.8</td>
<td>1.3 (0.2 to 8.9)</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>3/1.3</td>
<td>2.2 (0.7 to 7.0)</td>
</tr>
<tr>
<td>Bone tumor</td>
<td>2/0.7</td>
<td>3.0 (0.7 to 12.0)</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>4/1.3</td>
<td>3.2 (1.2 to 8.5)</td>
</tr>
<tr>
<td>Other</td>
<td>3/1.6</td>
<td>1.9 (0.6 to 5.8)</td>
</tr>
<tr>
<td>P heterogeneity</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: AER, absolute excess risk; CI, confidence interval; Exp, expected; Obs, observed; SIR, standardized incidence ratio.

1. CI should be interpreted cautiously if based on fewer than 5 observed events.
2. AER is shown per 10,000 person-years; Cls should be interpreted cautiously if based on fewer than 5 observed events.
3. Based on International Classification of Childhood Cancer.
4. CI could not be calculated because observed number of events was zero.
5. Heritable retinoblastoma defined as bilateral retinoblastoma or family history of retinoblastoma.

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Table 3. Absolute Excess Risk for Specific Subsequent Neoplasm Types by Attained Age as a Proportion of the Total Specific Absolute Excess Risk

<table>
<thead>
<tr>
<th>Subsequent Neoplasm</th>
<th>5-19</th>
<th>20-29</th>
<th>30-39</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of Total</td>
<td>% of Total</td>
<td>% of Total</td>
<td>% of Total</td>
</tr>
<tr>
<td>Digestive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14/0.5 (0.4 to 1.5)</td>
<td>7.9</td>
<td>20/1.9 (0.7 to 2.1)</td>
<td>11.0</td>
</tr>
<tr>
<td>Glioma</td>
<td>40/3.6 (1.7 to 3.5)</td>
<td>21.3</td>
<td>29/4.6 (1.1 to 2.8)</td>
<td>14.8</td>
</tr>
<tr>
<td>Genitourinary&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5/1.8 (–0.1 to 0.5)</td>
<td>1.9</td>
<td>22/13.1 (0.7 to –0.0)</td>
<td>5.4</td>
</tr>
<tr>
<td>Breast</td>
<td>1/0.1 (–0.1 to 0.2)</td>
<td>0.5</td>
<td>16/2.4 (0.5 to 1.7)</td>
<td>1.1</td>
</tr>
<tr>
<td>Bone</td>
<td>63/1.7 (3.3 to 5.5)</td>
<td>35.9</td>
<td>22/0.9 (0.9 to 2.4)</td>
<td>12.8</td>
</tr>
<tr>
<td>Connective and soft tissue</td>
<td>10/0.9 (0.2 to 1.1)</td>
<td>0.7</td>
<td>20/1.1 (0.5 to 1.7)</td>
<td>1.5</td>
</tr>
<tr>
<td>Thyroid</td>
<td>10/0.4 (0.2 to 1.1)</td>
<td>0.7</td>
<td>19/1.6 (0.7 to 2.1)</td>
<td>1.4</td>
</tr>
<tr>
<td>Leukemia</td>
<td>15/3.5 (0.2 to 1.4)</td>
<td>6.7</td>
<td>10/2.5 (0.1 to 1.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Oral</td>
<td>10/0.4 (0.2 to 1.1)</td>
<td>0.7</td>
<td>14/0.7 (0.5 to 1.1)</td>
<td>1.1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6/0.7 (0.0 to 0.7)</td>
<td>3.1</td>
<td>13/4.6 (0.1 to 1.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Respiratory</td>
<td>3/0.2 (0.0 to 0.4)</td>
<td>1.6</td>
<td>4/0.7 (0.3 to 0.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Other and unspecified</td>
<td>12/4.4 (0.1 to 1.0)</td>
<td>0.5</td>
<td>18/8.5 (0.1 to 1.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td>189/18.2 (10.3 to 14.1)</td>
<td>12.2</td>
<td>207/42.5 (9.5 to 15.3)</td>
<td>13.1</td>
</tr>
</tbody>
</table>

Abbreviations: AER, absolute excess risk; CI, confidence interval; Exp, expected; Obs, observed.
<sup>a</sup>AER is shown per 10 000 person-years; CIs should be interpreted cautiously if based on fewer than 5 observed events.
<sup>b</sup>Subcategories: lower abdominal (57), upper abdominal (28), peritoneum (18), and other (2).
<sup>c</sup>Subcategories: urinary bladder (25), urinary kidney (17), female genital organs (41), and male genital organs (17).

Table 4. Absolute Excess Risk for Digestive, Genitourinary, Breast, and Respiratory Subsequent Primary Neoplasms in Survivors Older Than 40 Years by Type of Childhood Cancer

<table>
<thead>
<tr>
<th>Type of Childhood Cancer</th>
<th>Digestive</th>
<th>Genitourinary</th>
<th>Breast</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Obs/Exp</td>
<td>AER (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No. Obs/Exp</td>
<td>AER (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No. Obs/Exp</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>9/3.5</td>
<td>3.6 (–1.8 to 9.0)</td>
<td>13/6.8</td>
<td>5.9 (–0.6 to 12.4)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0/0.3</td>
<td>–2.8 (–11.8 to 19.7)</td>
<td>1/0.5</td>
<td>4.0 (–6.8 to 12.6)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4/1.3</td>
<td>11.5 (–5.0 to 28.1)</td>
<td>5/1.5</td>
<td>14.7 (–3.8 to 33.3)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>0/0.4</td>
<td>–3.9 (–14.1 to 22.7)</td>
<td>1/0.5</td>
<td>4.3 (–6.8 to 12.6)</td>
</tr>
<tr>
<td>Heritable retinoblastoma</td>
<td>3/0.6</td>
<td>15.4 (–6.8 to 37.4)</td>
<td>8/0.8</td>
<td>46.5 (10.5 to 82.5)</td>
</tr>
<tr>
<td>Nonheritable retinoblasta</td>
<td>1/0.9</td>
<td>–6.9 (–10.3 to 8.8)</td>
<td>1/1.2</td>
<td>–1.1 (–11.1 to 8.8)</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>5/0.8</td>
<td>20.7 (–0.7 to 42.1)</td>
<td>0/1.0</td>
<td>–5.1 (–13.1 to 8.0)</td>
</tr>
<tr>
<td>Bone tumor</td>
<td>1/1.0</td>
<td>–0.1 (–10.1 to 9.8)</td>
<td>1/1.4</td>
<td>–1.9 (–11.8 to 8.1)</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>2/1.6</td>
<td>–7.2 (–26.2 to 23.3)</td>
<td>6/2.1</td>
<td>11.5 (–9.9 to 6.8)</td>
</tr>
<tr>
<td>Other</td>
<td>4/2.0</td>
<td>–4.3 (–13.5 to 6.2)</td>
<td>2/2.6</td>
<td>–1.7 (–8.0 to 4.5)</td>
</tr>
</tbody>
</table>

Abbreviations: AER, absolute excess risk; CI, confidence interval; Exp, expected; Obs, observed.
<sup>a</sup>AER per 10 000 person-years; CIs should be interpreted cautiously if based on fewer than 5 observed events.
<sup>b</sup>CI could not be calculated because observed number of events is zero.
Table 4 shows AERs at older than 40 years for digestive, genitourinary, breast, and respiratory subsequent primary neoplasms by type of childhood cancer. At this age, Wilms tumor, heritable retinoblastoma, and Hodgkin lymphoma survivors had the highest AERs for developing a digestive subsequent primary neoplasm. For genitourinary subsequent primary neoplasms, the AER at older than 40 years was greatest among heritable retinoblastoma survivors. With regard to breast subsequent primary neoplasms, Hodgkin survivors exhibited the highest AERs at this age. The AER for respiratory subsequent primary neoplasms at older than 40 years was highest for heritable retinoblastoma, and Hodgkin lymphoma survivors.

**Cumulative Incidence**

The cumulative percentage of survivors developing a subsequent primary neoplasm increased steadily with attained age from 1.6% (95% CI, 1.4%-1.9%) at age 20 years to 13.8% (95% CI, 12.3%-15.5%) at age 60 years, whereas 8.4% was expected at the latter age based on rates from the general population (Figure 1). Five percent (95% CI, 4.6%-5.5%) of survivors had developed a subsequent primary neoplasm by age 38 years, whereas it took until age 54 years for 5% of a comparable cohort (based on the general population rates) to develop a cancer.

The cumulative incidence of developing colorectal cancer by age 50 years was 1.4% (95% CI, 0.7%-2.6%) for survivors treated with direct abdominopelvic irradiation (Figure 2). This risk is comparable to the equivalent percentage (1.2%) for individuals with at least 2 first-degree relatives affected by colorectal cancer.

**COMMENT**

In this large-scale population-based study, we demonstrated, to our knowledge for the first time, that survivors of childhood cancer treated with direct abdominopelvic irradiation have a risk of developing colorectal cancer that is comparable to that of individuals with a strong family history of colorectal cancer. In Great Britain, individuals with at least 2 first-degree relatives affected by colorectal cancer are currently being considered for routine screening colonoscopy under the National Health Service bowel cancer screening program, but survivors treated with direct abdominopelvic irradiation are not, despite having a comparable risk. In Great Britain, there are currently no survivorship guidelines relating to the risk of colorectal cancer in survivors treated with direct abdominopelvic irradiation.

In the United States, current survivorship guidelines recommend colonoscopy every 5 years from age 35 years for survivors treated with at least 30 Gy of irradiation to the abdomen, pelvis, or spine; however, to our knowledge, there are no accurate published risk estimates to justify this recommendation. A recent North American study showed that the vast majority of survivors treated with at least 30 Gy of irradiation to the abdomen, pelvis, or spine do not undergo colonoscopy. Clearly, there is potential for reducing the number of colorectal cancers among survivors of childhood cancer treated with direct abdominopelvic irradiation.

Another important finding of this study is that childhood cancer survivors remain at risk for developing subsequent primary neoplasms at older than 40 years. Among survivors younger than 20 years, bone tumor and glioma subsequent primary neoplasms account for more than 50% of the total AER of developing a subsequent primary neoplasm, but as survivors age, this proportion decreases rapidly.

In contrast, the AER for digestive and genitourinary subsequent primary neoplasms is low among survivors younger than 20 years, but increases substantially with attained age, and at older than 40 years, these subsequent primary neoplasms account for 36% of the total AER. At older than 40 years, the AER of developing a digestive subsequent primary neoplasm is highest among survivors of Wilms tumor, heritable retinoblastoma, and Hodgkin lymphoma. These increased risks of digestive subsequent primary neoplasms are likely to be related to previous exposure of the digestive tract to radiation, except following heritable retinoblastoma. We found a 3-fold increased RR for survivors treated with direct abdominopelvic irradiation.

The highest AER for genitourinary subsequent primary neoplasms was
observed after heritable retinoblas-
toma, suggesting that this excess risk
is at least partially attributable to
genetic predisposition. AERs for geni-
tourinary subsequent primary neo-
plasms were also high after non-
Hodgkin lymphoma and soft tissue
sarcoma, which suggests that treat-
ments for these neoplasms may be
implicated in the development of the
observed excess genitourinary sub-
sequent primary neoplasms. Rigorous
investigation of the elements of treat-
ment will require large case-control
studies. Two such nested case-control
studies investigating the risks of diges-
tive and genitourinary subsequent pri-
mary neoplasms in relation to cumula-
tive dose of radiation and specific
chemotherapeutic agents are funded
and currently being undertaken as
part of a collaboration throughout
Europe—Pan-European Network for
Care of Survivors after Childhood and
Adolescent Cancer (PanCareSurFup
[http://www.pancare.eu/en/]).

Our finding that the majority (52%)
of the total AER at older than 40 years
was attributable to digestive, genito-
urinary, breast, and respiratory subse-
quent primary neoplasms is broadly
consistent with the only previous large-
scale population-based cohort study
with sufficient follow-up at older than
40 years to satisfactorily assess risk. In
the general population of the United
Kingdom, cancer at these 4 sites ac-
counted for 74% of all incident can-
cers. Even small increased RRs of can-
cers occurring so commonly in the
general population will result in large
numbers of additional cancers occur-
ing in survivors compared with ex-
pected numbers.

Given the excesses observed among
those older than 40 years, these survi-
ors should be encouraged to partici-
pate in existing general population
screening programs. In the United
Kingdom, the National Health Service
has ongoing screening programs that
are related to breast, cervical, and bowel
cancers. Table 4 provides useful risk
stratification information concerning
the groups of survivors at particularly
high excess risk of specific second pri-
mary cancers at older than 40 years. It
should be emphasized that the AER for
most subsequent primary neoplasms
was still relatively low; although for
genitourinary and digestive subse-
quent primary neoplasms, it increased
rapidly with attained age, and if con-
tinued into old age, a substantial num-
er of survivors would develop such
subsequent primary neoplasms.

Study Limitations

A potential limitation of our study is the
lack of detailed data on radiotherapy
and chemotherapy exposures that pre-
cluded detailed examination of dose-
response patterns of treatment expo-
sures in relation to subsequent primary
neoplasm risk. Survivors included in the
current cohort were treated between
1940 and 1991 and consequently, find-
ings may not be translatable to survi-
ors treated in more recent years. Fur-
ter follow-up is necessary to address
the risks of subsequent primary neo-
plasms of survivors treated more re-
cently, mainly because of substantial
changes in exposure to radiotherapy.
Radiotherapy has developed over the
decades to provide more focused de-
ivery of the maximal dose to the tu-
mor tissue, with minimal levels of ex-
posure to adjacent tissue. Therefore,
more modern radiotherapy treatment
techniques are likely to result in fewer
cancers of surrounding tissue.

Survelliance bias might explain some of
the excess risk observed beyond that
expected from the general population.
However, it is unlikely to account for
more than a small element of the ex-
cess observed for most cancers be-
cause we specifically excluded NMSCs
and nonglioma brain CNS tumors. These
2 groups of neoplasms are known
to be subject to the highest levels of un-
derascertainment in the general popu-
lation, and because of the indolent
natural history of development char-
acterizing these neoplasms, there is the
possibility of disproportionately bet-
ter ascertainment in cancer surviv-
ors because of greater surveillance. Al-
most all cancers found to be in excess
of that expected in this investigation are
not characterized by such an indolent
history of development and they pre-
sent fairly rapidly as invasive cancer that
is unlikely to missed.
In conclusion, survivors of childhood cancer remain at increased risk of developing a subsequent primary neoplasm at older than 40 years, although the AERs of developing a subsequent primary neoplasm are generally small. The AER at older than 40 years is highest for digestive and genitourinary subsequent primary neoplasms. Effects to reduce the absolute number of survivors developing a subsequent primary neoplasm should therefore focus on digestive and genitourinary subsequent primary neoplasms. The risk of developing colorectal cancer in survivors treated with direct abdominopelvic irradiation is comparable to that of individuals who have at least 2 first-degree relatives affected and for whom routine colonoscopy is currently being considered. This raises the question of whether childhood cancer survivors treated with direct abdominopelvic irradiation should be similarly considered for routine colonoscopy for colorectal cancer.

Author Contributions: Drs Reulen and Frobisher had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Reulen and Frobisher contributed equally to this article.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Funding/Support: This work was supported by Cancer Research UK and Kay Kendall Leukaemia Fund. The Childhood Cancer Research Group receives funding from the Department of Health and the Scottish Ministers. Role of the Sponsor: Cancer Research UK, Kay Kendall Leukaemia Fund, Department of Health, and the Scottish Ministers had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Disclaimer: The views expressed here are not necessarily those of Cancer Research UK, Kay Kendall Leukaemia Fund, the Department of Health, or the Scottish Ministers.

Previous Presentation: This study was presented in part at the 11th International Conference of Long-term Complications of Treatment of Children and Adolescents for Cancer, June 11–12, 2010: Williamsburg, Virginia.

Online-Only Material: eTable 1 and eTable 2 are available at http://www.jama.com.

Additional Contributions: The British Childhood Cancer Survivor Study (BCCSS) benefits from the contributions of the officers, centers, and individual members of the Children’s Cancer and Leukaemia Group, the Childhood Cancer Research Group, and the Regional Pediatric Cancer Registers. However, the Work acknowledges the role of the Office of National Statistics, the General Register Office for Scotland, the National Health Service Central Register, the regional cancer registries, health authorities, and area health boards for providing general practitioner names and addresses and the general practitioners nationwide who facilitated direct contact with survivors. The BCCSS would not have been possible without the support of our 2 funders: Cancer Research UK and the Kay Kendall Leukaemia Fund, to whom we owe our profound thanks. We thank Trevor Cole, MD, of the West Midlands Regional Genetics Service, for his comments on earlier drafts of the manuscript and all BCCSS staff who have given many years of dedicated work to bring the BCCSS to fruition. The BCCSS staff and Dr Cole were not compensated in association with their contributions to this article.

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JAMA. June 8, 2011—Vol 305, No. 22 2319