

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.¹⁻⁸ 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.¹

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 currently unclear which

Context Survivors of childhood cancer are at excess risk of developing subsequent primary neoplasms but the long-term risks are uncertain.

Objectives To investigate long-term risks of subsequent primary neoplasms in survivors of childhood cancer, to identify the types that contribute most to long-term excess risk, and to identify subgroups of survivors at substantially increased risk of particular subsequent primary neoplasms that may require specific interventions.

Design, Setting, and Participants British Childhood Cancer Survivor Study—a population-based cohort of 17 981 5-year survivors of childhood cancer diagnosed with cancer at younger than 15 years between 1940 and 1991 in Great Britain, followed up through December 2006.

Main Outcome Measures Standardized incidence ratios (SIRs), absolute excess risks (AERs), and cumulative incidence of subsequent primary neoplasms.

Results After a median follow-up time of 24.3 years (mean = 25.6 years), 1354 subsequent primary neoplasms were ascertained; the most frequently observed being central nervous system (n = 344), nonmelanoma skin cancer (n = 278), digestive (n = 105), genitourinary (n = 100), breast (n = 97), and bone (n = 94). The overall SIR was 4 times more than expected (SIR, 3.9; 95% confidence interval [CI], 3.6-4.2; AER, 16.8 per 10 000 person-years). The AER at older than 40 years was highest for digestive and genitourinary subsequent primary neoplasms (AER, 5.9 [95% CI, 2.5-9.3]; and AER, 6.0 [95% CI, 2.3-9.6] per 10 000 person-years, respectively); 36% of the total AER was attributable to these 2 subsequent primary neoplasm sites. The cumulative incidence of colorectal cancer for survivors treated with direct abdominopelvic irradiation was 1.4% (95% CI, 0.7%-2.6%) by age 50 years, comparable with the 1.2% risk in individuals with at least 2 first-degree relatives affected by colorectal cancer.

Conclusion Among a cohort of British childhood cancer survivors, the greatest excess risk associated with subsequent primary neoplasms at older than 40 years was for digestive and genitourinary neoplasms.

JAMA. 2011;305(22):2311-2319

www.jama.com

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.

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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.^{9,10} The cohort was identified using the population-based National Registry of Childhood Tumours. Ascertainment is estimated to be very high ($\approx 99\%$) because the registry receives notifications from multiple sources and cross checks and validates reports with other sources.^{11,12} 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 reg-

istration 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.¹³ 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).¹⁴ 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.^{15,16}

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).¹⁷ 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.¹³ 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: $([Obs - Exp]/person\text{-}years\text{ at risk}) \times 10\,000$. 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).¹⁷⁻¹⁹

Cumulative incidence for the first occurrence of a subsequent primary neoplasm was computed by attained age with death considered as a competing risk.^{20,21} Expected cumulative incidence was estimated using the conditional (Ederer II) method.²² 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-

rived from incidence rates that were estimated using age-specific RRs for such individuals from published meta-analyses^{23,24} and then multiplying these with the corresponding age-specific colorectal cancer incidence rates from the general population of England and Wales.¹³

All analyses were performed using Stata software, version 11 (StataCorp, College Station, Texas). Tests for linear trend in relation to a particular factor were performed by incorporating a parameter in the relevant Poisson regression model with consecutive nonnegative integer values corresponding to increasing or decreasing levels of the factor and comparing the deviance statistic with that of a model without the relevant parameter. To test the robustness of the Poisson regression in modeling the RRs, we reanalyzed the data using negative binomial regression; the results were almost identical and therefore we only provide those relating to the Poisson regression. Statistical significance was defined as a 2-sided *P* value of less than .05.

RESULTS

Cohort Characteristics

Through December 2006, 1354 subsequent primary neoplasms were diagnosed in 1222 of the 17 981 survivors in the cohort. Of the 1354 subsequent primary neoplasms ascertained, 1335 (98.6%) were confirmed with pathology reports. Total follow-up subsequent to 5-year survival was 369 910 person-years. The mean follow-up time from childhood cancer diagnosis was 25.6 years (median, 24.3 years; 25th-75th percentile, 17.9-32.4 years). The most commonly observed subsequent primary neoplasms were CNS tumors (*n*=344) of which 105 were gliomas, NMSC (*n*=278), digestive (*n*=105), genitourinary (*n*=100), breast (*n*=97), and bone (*n*=94) (eTable 1 available at <http://www.jama.com>). Subsequent primary neoplasms occurred most frequently in survivors who were originally diagnosed with a CNS neoplasm (*n*=338), leukemia (*n*=271), Hodgkin lymphoma (*n*=157), heritable retinoblastoma (*n*=131), and Wilms tumor (*n*=104).

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% confidence interval [CI], 3.6-4.2). An overall AER 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 abdominopel-

vic 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).

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 ($P_{\text{trend}} < .001$) while the RER increased with attained age ($P_{\text{trend}} < .001$) (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 ($P_{\text{trend}} = .002$) (Table 2). The SIR and AER were particularly high after 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

| | Subsequent Primary Neoplasms | | | | | | | | | |
|---------------------------------------|------------------------------|-------------|---------------------------|---------------------------|-------------|---------------------------|---------------------------|---------------|---------------------------|---------------------------|
| | All | | | | Digestive | | | Genitourinary | | |
| | Person-Years | No. Obs/Exp | SIR (95% CI) ^a | AER (95% CI) ^b | No. Obs/Exp | SIR (95% CI) ^a | AER (95% CI) ^b | No. Obs/Exp | SIR (95% CI) ^a | AER (95% CI) ^b |
| Overall | 369 909.9 | 837/215.5 | 3.9 (3.6 to 4.2) | 16.8 (15.3 to 18.3) | 105/22.7 | 4.6 (3.8 to 5.6) | 2.2 (1.7 to 2.8) | 100/51.3 | 1.9 (1.6 to 2.4) | 1.3 (0.8 to 1.8) |
| Sex | | | | | | | | | | |
| Male | 200 390.0 | 429/95.6 | 4.5 (4.1 to 4.9) | 16.6 (14.6 to 18.7) | 75/14.0 | 5.4 (4.3 to 6.7) | 3.0 (2.2 to 3.9) | 42/26.2 | 1.6 (1.2 to 2.2) | 0.8 (0.2 to 1.4) |
| Female | 169 519.9 | 408/119.9 | 3.4 (3.1 to 3.8) | 17.0 (14.7 to 19.3) | 30/8.7 | 3.5 (2.4 to 4.9) | 1.3 (0.6 to 1.9) | 58/25.1 | 2.3 (1.8 to 3.0) | 1.9 (1.1 to 2.8) |
| $P_{\text{heterogeneity}}$ | | | <.001 | .82 | | .04 | .001 | | .07 | .03 |
| Childhood cancer type ^c | | | | | | | | | | |
| Central nervous system | 86 150.9 | 165/60.1 | 2.7 (2.4 to 3.2) | 12.2 (9.3 to 15.1) | 25/6.9 | 3.6 (2.5 to 5.4) | 2.1 (1.0 to 3.2) | 23/14.3 | 1.6 (1.1 to 2.4) | 1.0 (-0.1 to 2.1) |
| Leukemia | 80 028.1 | 115/26.7 | 4.3 (3.6 to 5.2) | 11.0 (8.4 to 13.7) | 5/1.5 | 3.2 (1.3 to 7.8) | 0.4 (-0.1 to 1.0) | 10/6.5 | 1.5 (0.8 to 2.9) | 0.4 (-0.3 to 1.2) |
| Hodgkin lymphoma | 27 231.5 | 104/18.6 | 5.6 (4.6 to 6.8) | 31.3 (24.0 to 38.7) | 13/2.4 | 5.5 (3.2 to 9.4) | 3.9 (1.3 to 6.5) | 5/4.8 | 1.1 (0.4 to 2.5) | 0.1 (-1.5 to 1.7) |
| Non-Hodgkin lymphoma | 18 522.5 | 48/12.8 | 3.8 (2.8 to 5.0) | 19.0 (11.7 to 26.3) | 9/1.7 | 5.4 (2.8 to 10.4) | 4.0 (0.8 to 7.1) | 10/3.2 | 3.1 (1.7 to 5.8) | 3.7 (0.3 to 7.0) |
| Neuroblastoma | 16 970.4 | 20/7.2 | 2.8 (1.8 to 4.3) | 7.5 (2.4 to 12.7) | 3/0.7 | 4.5 (1.5 to 14.0) | 1.4 (-0.6 to 3.4) | 3/1.6 | 1.8 (0.6 to 5.7) | 0.8 (-1.2 to 2.8) |
| Heritable retinoblastoma ^d | 15 158.3 | 113/8.4 | 13.4 (11.1 to 16.1) | 69.0 (55.2 to 82.7) | 11/0.9 | 12.5 (6.9 to 22.6) | 6.7 (2.4 to 11.0) | 15/1.9 | 7.9 (4.8 to 13.1) | 8.6 (3.6 to 13.7) |
| Nonheritable retinoblastoma | 18 369.9 | 19/11.2 | 1.7 (1.1 to 2.7) | 4.2 (-0.4 to 8.9) | 1/1.2 | 0.8 (0.1 to 5.7) | -0.1 (-1.2 to 0.9) | 2/2.6 | 0.8 (0.2 to 3.1) | -0.3 (-1.8 to 1.2) |
| Wilms tumor | 34 287.6 | 72/15.2 | 4.7 (3.8 to 6.0) | 16.6 (11.7 to 21.4) | 17/1.3 | 13.0 (8.1 to 20.8) | 4.6 (2.2 to 6.9) | 9/3.5 | 2.6 (1.3 to 4.9) | 1.6 (-0.1 to 3.3) |
| Bone tumor | 12 913.4 | 49/11.2 | 4.4 (3.3 to 5.8) | 29.3 (18.7 to 39.9) | 3/1.3 | 2.3 (0.7 to 7.0) | 1.3 (-1.3 to 3.9) | 4/2.7 | 1.5 (0.6 to 4.0) | 1.0 (-2.0 to 4.0) |
| Soft tissue sarcoma | 26 667.1 | 57/17.9 | 3.2 (2.5 to 4.1) | 14.7 (9.1 to 20.2) | 7/2.1 | 3.3 (1.6 to 6.9) | 1.8 (-0.1 to 3.8) | 12/4.3 | 2.8 (1.6 to 5.0) | 2.9 (0.4 to 5.4) |
| Other | 33 610.1 | 75/26.1 | 2.9 (2.3 to 3.6) | 14.5 (9.5 to 19.6) | 11/2.7 | 4.1 (2.3 to 7.5) | 2.5 (0.5 to 4.4) | 7/6.0 | 1.2 (0.6 to 2.5) | 0.3 (-1.2 to 1.9) |
| $P_{\text{heterogeneity}}$ | | | <.001 | <.001 | | <.001 | <.001 | | <.001 | <.001 |
| Attained age, y | | | | | | | | | | |
| 5-19 | 140 017.6 | 189/18.2 | 10.4 (9.0 to 12.0) | 12.2 (10.3 to 14.1) | 14/0.5 | 28.3 (16.7 to 47.7) | 1.0 (0.4 to 1.5) | 5/1.8 | 2.7 (1.1 to 6.6) | 0.2 (-0.1 to 0.5) |
| 20-29 | 125 942.9 | 207/42.5 | 4.9 (4.3 to 5.6) | 13.1 (10.8 to 15.3) | 20/1.9 | 10.4 (6.7 to 16.2) | 1.4 (0.7 to 2.1) | 22/13.1 | 1.7 (1.1 to 2.5) | 0.7 (-0.0 to 1.4) |
| 30-39 | 69 626.9 | 231/56.9 | 4.1 (3.6 to 4.6) | 25.0 (20.7 to 29.3) | 35/4.5 | 7.8 (5.6 to 10.9) | 4.4 (2.7 to 6.0) | 32/15.9 | 2.0 (1.4 to 2.8) | 2.3 (0.7 to 3.9) |
| 40-49 | 26 157.7 | 133/52.4 | 2.5 (2.1 to 3.0) | 30.8 (22.2 to 39.5) | 23/7.1 | 3.2 (2.1 to 4.8) | 6.1 (2.5 to 9.7) | 20/9.8 | 2.0 (1.3 to 3.2) | 3.9 (0.5 to 7.2) |
| ≥50 | 8 164.7 | 77/45.5 | 1.7 (1.4 to 2.1) | 38.6 (17.5 to 59.7) | 13/8.7 | 1.5 (0.9 to 2.6) | 5.3 (-3.3 to 14.0) | 21/10.6 | 2.0 (1.3 to 3.0) | 12.7 (1.7 to 23.7) |
| P_{trend} | | | <.001 | <.001 | | <.001 | <.001 | | .96 | <.001 |

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.

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 genito-

urinary 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

| | Glioma | | | Breast | | | Bone | | |
|---------------------------------------|-------------|---------------------------|---------------------------|-------------|---------------------------|---------------------------|-------------|---------------------------|---------------------------|
| | No. Obs/Exp | SIR (95% CI) ^a | AER (95% CI) ^b | No. Obs/Exp | SIR (95% CI) ^a | AER (95% CI) ^b | No. Obs/Exp | SIR (95% CI) ^a | AER (95% CI) ^b |
| Overall | 105/16.2 | 6.5 (5.4 to 7.8) | 2.4 (1.9 to 2.9) | 97/43.6 | 2.2 (1.8 to 2.7) | 1.4 (0.9 to 2.0) | 94/3.1 | 30.5 (24.9 to 37.3) | 2.5 (1.9 to 3.0) |
| Sex | | | | | | | | | |
| Male | 53/9.4 | 5.7 (4.3 to 7.4) | 2.2 (1.5 to 2.9) | 2/0.2 | 12.8 (3.2 to 51.3) | 0.1 (-0.0 to 0.2) | 58/1.9 | 30.3 (23.4 to 39.2) | 2.8 (2.1 to 3.5) |
| Female | 52/6.8 | 7.6 (5.8 to 10.0) | 2.7 (1.8 to 3.5) | 95/43.4 | 2.2 (1.8 to 2.7) | 3.0 (1.9 to 4.2) | 36/1.2 | 30.7 (22.2 to 42.6) | 2.1 (1.4 to 2.7) |
| <i>P</i> _{heterogeneity} | | .13 | .38 | | .05 | <.001 | | .95 | .15 |
| Childhood cancer type ^c | | | | | | | | | |
| Central nervous system | 50/4.1 | 12.3 (9.3 to 16.2) | 5.3 (3.7 to 6.9) | 10/13.1 | 0.8 (0.4 to 1.4) | -0.4 (-1.1 to 0.4) | 6/0.7 | 8.7 (3.9 to 19.5) | 0.6 (0.1 to 1.2) |
| Leukemia | 27/2.9 | 9.4 (6.5 to 13.7) | 3.0 (1.7 to 4.3) | 7/3.5 | 2.0 (1.0 to 4.2) | 0.4 (-0.2 to 1.1) | 5/0.7 | 6.7 (2.8 to 16.1) | 0.5 (-0.0 to 1.1) |
| Hodgkin lymphoma | 4/1.4 | 2.9 (1.1 to 7.7) | 1.0 (-0.5 to 2.4) | 24/2.7 | 8.9 (5.9 to 13.2) | 7.8 (4.3 to 11.3) | 6/0.2 | 27.7 (12.4 to 61.6) | 2.1 (0.4 to 3.9) |
| Non-Hodgkin lymphoma | 6/0.9 | 6.5 (2.9 to 14.6) | 2.7 (0.2 to 5.3) | 2/2.1 | 1.0 (0.2 to 3.9) | -0.0 (-1.5 to 1.5) | 2/0.2 | 12.7 (3.2 to 50.8) | 1.0 (-0.5 to 2.5) |
| Neuroblastoma | 2/0.7 | 3.0 (0.8 to 12.2) | 0.8 (-0.8 to 2.4) | 1/1.3 | 0.8 (0.1 to 5.4) | -0.2 (-1.3 to 1.0) | 0/0.1 | 0 | -0.1 ^d |
| Heritable retinoblastoma ^e | 3/0.6 | 4.7 (1.5 to 14.5) | 1.6 (-0.7 to 3.8) | 9/1.9 | 4.7 (2.4 to 9.0) | 4.7 (0.8 to 8.6) | 35/0.1 | 289.2 (207.6 to 402.8) | 23.0 (15.4 to 30.7) |
| Nonheritable retinoblastoma | 1/0.8 | 1.3 (0.2 to 8.9) | 0.1 (-1.0 to 1.2) | 5/2.5 | 2.0 (0.8 to 4.8) | 1.4 (-1.0 to 3.7) | 4/0.1 | 26.9 (10.1 to 71.7) | 2.1 (-0.0 to 4.2) |
| Wilms tumor | 3/1.3 | 2.2 (0.7 to 7.0) | 0.5 (-0.5 to 1.5) | 9/2.9 | 3.1 (1.6 to 5.9) | 1.8 (0.1 to 3.5) | 6/0.3 | 20.2 (9.1 to 44.9) | 1.7 (0.3 to 3.1) |
| Bone tumor | 2/0.7 | 3.0 (0.7 to 12.0) | 1.0 (-1.1 to 3.2) | 12/2.6 | 4.5 (2.6 to 8.0) | 7.2 (2.0 to 12.5) | 13/0.1 | 136.3 (79.2 to 234.8) | 10.0 (4.5 to 15.5) |
| Soft tissue sarcoma | 4/1.3 | 3.2 (1.2 to 8.5) | 1.0 (-0.4 to 2.5) | 8/3.6 | 2.2 (1.1 to 4.5) | 1.7 (-0.4 to 3.7) | 8/0.2 | 36.6 (18.3 to 73.1) | 2.9 (0.8 to 5.0) |
| Other | 3/1.6 | 1.9 (0.6 to 5.8) | 0.4 (-0.6 to 1.4) | 10/7.3 | 1.4 (0.7 to 2.6) | 0.8 (-1.0 to 2.7) | 9/0.3 | 35.5 (18.5 to 68.3) | 2.6 (0.9 to 4.4) |
| <i>P</i> _{heterogeneity} | | <.001 | <.001 | | <.001 | <.001 | | <.001 | <.001 |
| Attained age, y | | | | | | | | | |
| 5-19 | 40/3.6 | 11.0 (8.1 to 15.0) | 2.6 (1.7 to 3.5) | 1/0.1 | 13.7 (1.9 to 97.4) | 0.1 (-0.1 to 0.2) | 63/1.7 | 38.0 (29.7 to 48.7) | 4.4 (3.3 to 5.5) |
| 20-29 | 29/4.6 | 6.3 (4.4 to 9.1) | 1.9 (1.1 to 2.8) | 16/2.4 | 6.7 (4.1 to 11.0) | 1.1 (0.5 to 1.7) | 22/0.9 | 25.3 (16.7 to 38.4) | 1.7 (0.9 to 2.4) |
| 30-39 | 26/4.3 | 6.1 (4.2 to 9.0) | 3.1 (1.7 to 4.6) | 44/13.0 | 3.4 (2.5 to 4.6) | 4.5 (2.6 to 6.3) | 8/0.3 | 23.1 (11.5 to 46.1) | 1.1 (0.3 to 1.9) |
| 40-49 | 6/2.5 | 2.4 (1.1 to 5.4) | 1.4 (-0.5 to 3.2) | 25/17.1 | 1.5 (1.0 to 2.2) | 3.0 (-0.7 to 6.8) | 1/0.1 | 7.1 (1.0 to 50.1) | 0.3 (-0.4 to 1.1) |
| ≥50 | 4/1.3 | 3.1 (1.2 to 8.3) | 3.3 (-1.5 to 8.1) | 11/11.0 | 1.0 (0.6 to 1.8) | 0.0 (-7.9 to 8.0) | 0/0.1 | 0 | -0.1 ^d |
| <i>P</i> _{trend} | | <.001 | .48 | | <.001 | <.001 | | .002 | <.001 |

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*.

^dCI could not be calculated because observed number of events was zero.

^eHeritable retinoblastoma defined as bilateral retinoblastoma or family history of retinoblastoma.

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

| Subsequent Neoplasm | Attained Age, y | | | | | | | | | | | |
|----------------------------|-----------------|---------------------------|------------|-------------|---------------------------|------------|-------------|---------------------------|------------|-------------|---------------------------|------------|
| | 5-19 | | | 20-29 | | | 30-39 | | | ≥40 | | |
| | No. Obs/Exp | AER (95% CI) ^a | % of Total | No. Obs/Exp | AER (95% CI) ^a | % of Total | No. Obs/Exp | AER (95% CI) ^a | % of Total | No. Obs/Exp | AER (95% CI) ^a | % of Total |
| Digestive ^b | 14/0.5 | 1.0 (0.4 to 1.5) | 7.9 | 20/1.9 | 1.4 (0.7 to 2.1) | 11.0 | 35/4.5 | 4.4 (2.7 to 6.0) | 17.5 | 36/15.8 | 5.9 (2.5 to 9.3) | 18.0 |
| Glioma | 40/3.6 | 2.6 (1.7 to 3.5) | 21.3 | 29/4.6 | 1.9 (1.1 to 2.8) | 14.8 | 26/4.3 | 3.1 (1.7 to 4.6) | 12.5 | 10/3.7 | 1.8 (0.0 to 3.6) | 5.6 |
| Genitourinary ^c | 5/1.8 | 0.2 (-0.1 to 0.5) | 1.9 | 22/13.1 | 0.7 (-0.0 to 1.4) | 5.4 | 32/15.9 | 2.3 (0.7 to 3.9) | 9.2 | 41/20.4 | 6.0 (2.3 to 9.6) | 18.3 |
| Breast | 1/0.1 | 0.1 (-0.1 to 0.2) | 0.5 | 16/2.4 | 1.1 (0.5 to 1.7) | 8.3 | 44/13.0 | 4.5 (2.6 to 6.3) | 17.8 | 36/28.1 | 2.3 (-1.1 to 5.7) | 7.0 |
| Bone | 63/1.7 | 4.4 (3.3 to 5.5) | 35.9 | 22/0.9 | 1.7 (0.9 to 2.4) | 12.8 | 8/0.3 | 1.1 (0.3 to 1.9) | 4.4 | 1/0.2 | 0.2 (-0.3 to 0.8) | 0.7 |
| Connective and soft tissue | 10/0.9 | 0.7 (0.2 to 1.1) | 5.3 | 20/1.1 | 1.5 (0.8 to 2.2) | 11.5 | 14/0.8 | 1.9 (0.8 to 2.9) | 7.6 | 10/0.7 | 2.7 (0.9 to 4.5) | 8.3 |
| Thyroid | 10/0.4 | 0.7 (0.2 to 1.1) | 5.6 | 19/1.6 | 1.4 (0.7 to 2.1) | 10.6 | 21/1.7 | 2.8 (1.5 to 4.1) | 11.1 | 10/1.0 | 2.6 (0.8 to 4.4) | 8.0 |
| Leukemia | 15/3.5 | 0.8 (0.3 to 1.4) | 6.7 | 10/2.5 | 0.6 (0.1 to 1.1) | 4.6 | 3/1.8 | 0.2 (-0.3 to 0.7) | 0.7 | 6/2.1 | 1.1 (-0.3 to 2.5) | 3.5 |
| Oral | 10/0.4 | 0.7 (0.2 to 1.1) | 5.6 | 14/0.7 | 1.1 (0.5 to 1.6) | 8.1 | 8/1.1 | 1.0 (0.2 to 1.8) | 4.0 | 13/3.1 | 2.9 (0.8 to 4.9) | 8.8 |
| Melanoma | 6/0.7 | 0.4 (0.0 to 0.7) | 3.1 | 13/4.6 | 0.7 (0.1 to 1.2) | 5.1 | 11/5.6 | 0.8 (-0.2 to 1.7) | 3.1 | 7/5.1 | 0.6 (-0.9 to 2.1) | 1.7 |
| Respiratory | 3/0.2 | 0.2 (0.0 to 0.4) | 1.6 | 4/0.7 | 0.3 (-0.0 to 0.6) | 2.0 | 9/1.7 | 1.1 (0.2 to 1.9) | 4.2 | 20/10.0 | 2.9 (0.4 to 5.5) | 9.0 |
| Other and unspecified | 12/4.4 | 0.5 (0.1 to 1.0) | 4.4 | 18/8.5 | 0.8 (0.1 to 1.4) | 5.8 | 20/6.3 | 2.0 (0.7 to 3.2) | 7.9 | 20/7.6 | 3.6 (1.0 to 6.2) | 11.0 |
| Total | 189/18.2 | 12.2 (10.3 to 14.1) | 100.0 | 207/42.5 | 13.1 (10.8 to 15.3) | 100.0 | 231/56.9 | 25.0 (20.7 to 29.3) | 100.0 | 210/97.9 | 32.7 (24.4 to 40.9) | 100.0 |

Abbreviations: AER, Absolute excess risk; CI, confidence interval; Exp, expected; Obs, observed.
^aAER is shown per 10 000 person-years; CIs should be interpreted cautiously if based on fewer than 5 observed events.
^bSubcategories: lower abdominal (57), upper abdominal (28), peritoneum (18), and other (2).
^cSubcategories: 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

| Type of Childhood Cancer | Digestive | | Genitourinary | | Breast | | Respiratory | |
|-----------------------------|-------------|---------------------------|---------------|---------------------------|-------------|---------------------------|-------------|---------------------------|
| | No. Obs/Exp | AER (95% CI) ^a | No. Obs/Exp | AER (95% CI) ^a | No. Obs/Exp | AER (95% CI) ^a | No. Obs/Exp | AER (95% CI) ^a |
| Central nervous system | 9/5.1 | 3.6 (-1.8 to 9.0) | 13/6.6 | 5.9 (-0.6 to 12.4) | 7/9.0 | -1.8 (-6.6 to 3.0) | 3/3.3 | -0.2 (-3.4 to 2.9) |
| Leukemia | 0/0.3 | -2.8 ^b | 1/0.5 | 4.0 (-11.8 to 19.7) | 0/0.9 | -7.3 ^b | 0/0.2 | -1.4 ^b |
| Hodgkin lymphoma | 7/1.7 | 15.1 (0.3 to 29.9) | 3/2.0 | 2.9 (-6.8 to 12.6) | 11/1.7 | 26.4 (7.9 to 44.9) | 7/1.1 | 16.9 (2.1 to 31.7) |
| Non-Hodgkin lymphoma | 4/1.3 | 11.5 (-5.0 to 28.1) | 5/1.5 | 14.7 (-3.8 to 33.3) | 1/1.5 | -2.0 (-10.3 to 6.3) | 2/0.8 | 5.0 (-6.7 to 16.7) |
| Neuroblastoma | 0/0.4 | -3.9 ^b | 1/0.5 | 4.3 (-14.1 to 22.7) | 1/0.7 | 2.7 (-15.7 to 21.2) | 0/0.2 | -2.3 ^b |
| Heritable retinoblastoma | 3/0.6 | 15.4 (-6.6 to 37.4) | 8/0.8 | 46.5 (10.5 to 82.5) | 3/1.3 | 10.7 (-11.3 to 32.8) | 5/0.4 | 30.0 (1.5 to 58.4) |
| Nonheritable retinoblastoma | 1/0.9 | 0.4 (-9.6 to 10.3) | 1/1.2 | -1.1 (-11.1 to 8.8) | 3/1.7 | 6.7 (-10.5 to 24.0) | 0/0.6 | -3.0 ^b |
| Wilms tumor | 5/0.8 | 20.7 (-0.7 to 42.1) | 0/1.0 | -5.1 ^b | 1/1.7 | -3.5 (-13.1 to 6.0) | 0/0.4 | -2.2 ^b |
| Bone tumor | 1/1.0 | -0.1 (-10.1 to 9.8) | 1/1.4 | -1.9 (-11.8 to 8.1) | 4/1.9 | 10.8 (-9.1 to 30.7) | 1/0.7 | 1.7 (-8.3 to 11.6) |
| Soft tissue sarcoma | 2/1.6 | 1.1 (-7.2 to 9.4) | 6/2.1 | 11.8 (-2.6 to 26.3) | 2/2.5 | -1.6 (-9.9 to 6.8) | 1/1.0 | -0.1 (-6.0 to 5.8) |
| Other | 4/2.0 | 4.6 (-4.3 to 13.5) | 2/2.8 | -1.7 (-8.0 to 4.5) | 3/5.2 | -4.9 (-12.6 to 2.8) | 1/1.2 | -0.5 (-5.0 to 3.9) |

Abbreviations: AER, absolute excess risk; CI, confidence interval; Exp, expected; Obs, observed.
^aAER per 10 000 person-years; CIs should be interpreted cautiously if based on fewer than 5 observed events.
^bCI 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

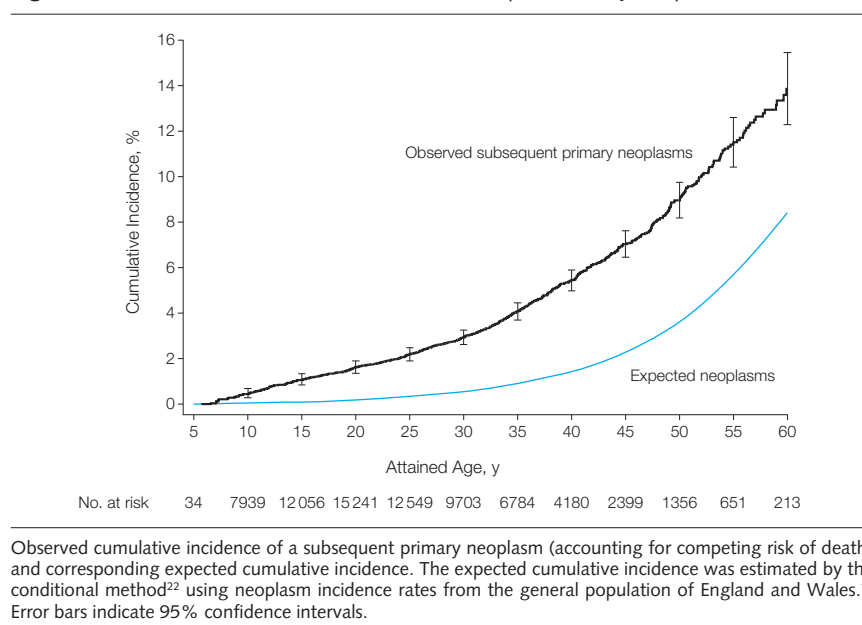
The cumulative percentage of survivors developing a subsequent primary neoplasm increased steadily with attained age from 1.6% (95% CI, 1.4%-1.9%) at age 20 years to 13.8% (95% CI, 12.3%-15.5%) at age 60 years, whereas 8.4% was expected at the latter age based on rates from the general population (FIGURE 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

Figure 1. Observed Cumulative Incidence of a Subsequent Primary Neoplasm



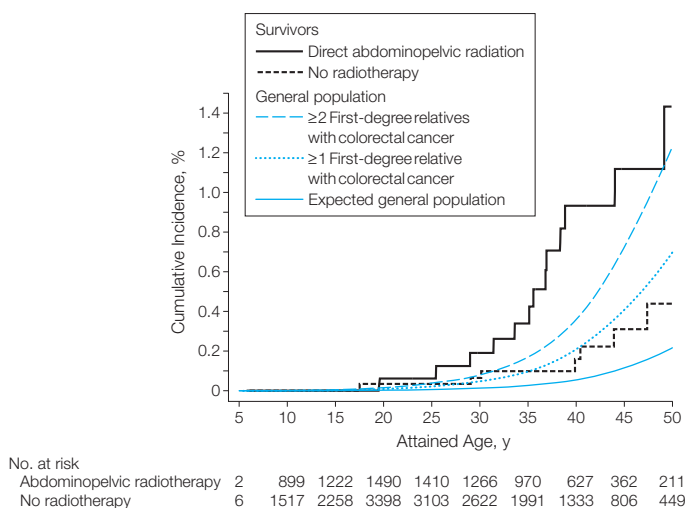
a strong family history of colorectal cancer. In Great Britain, individuals with at least 2 first-degree relatives affected by colorectal cancer are currently being considered for routine screening colonoscopy under the National Health Service bowel cancer screening program,^{25,26} but survivors treated 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 spine²⁷; 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.²⁸ 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

Figure 2. Cumulative Incidence of Developing Subsequent Colorectal Cancer for Survivors Treated With Direct Abdominopelvic Irradiation

Cumulative incidence of developing a second primary colorectal cancer for survivors treated with direct abdominopelvic irradiation, corresponding cumulative incidence based on incidence rates of colorectal cancer for individuals with specific family histories of colorectal cancer,^{23,24} and expected general population cumulative incidence of colorectal cancer. The expected cumulative incidence was estimated by the conditional method²² using colorectal cancer incidence rates from the general population of England and Wales.¹³

observed after heritable retinoblastoma, suggesting that this excess risk is at least partially attributable to genetic predisposition. AERs for genitourinary subsequent primary neoplasms were also high after non-Hodgkin lymphoma and soft tissue sarcoma, which suggests that treatments for these neoplasms may be implicated in the development of the observed excess genitourinary subsequent primary neoplasms. Rigorous investigation of the elements of treatment will require large case-control studies. Two such nested case-control studies investigating the risks of digestive and genitourinary subsequent primary neoplasms in relation to cumulative 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, genitourinary, 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.¹ In the general population of the United Kingdom, cancer at these 4 sites accounted for 74% of all incident cancers.²⁹ Even small increased RRs of cancers occurring so commonly in the general population will result in large numbers of additional cancers occurring in survivors compared with expected numbers.

Given the excesses observed among those older than 40 years, these survivors should be encouraged to participate 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.³⁰ Table 4 provides useful risk stratification information concerning the groups of survivors at particularly high excess risk of specific second primary 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 subsequent primary neoplasms, it increased rapidly with attained age, and if continued into old age, a substantial number 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 precluded detailed examination of dose-response patterns of treatment exposures in relation to subsequent primary neoplasm risk. Survivors included in the current cohort were treated between 1940 and 1991 and consequently, findings may not be translatable to survivors treated in more recent years. Further follow-up is necessary to address the risks of subsequent primary neoplasms of survivors treated more recently, mainly because of substantial changes in exposure to radiotherapy. Radiotherapy has developed over the decades to provide more focused delivery of the maximal dose to the tumor tissue, with minimal levels of exposure to adjacent tissue. Therefore, more modern radiotherapy treatment techniques are likely to result in fewer cancers of surrounding tissue.

Surveillance 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 excess observed for most cancers because we specifically excluded NMSCs and nonglioma brain CNS tumors. These 2 groups of neoplasms are known to be subject to the highest levels of underascertainment in the general population, and because of the indolent natural history of development characterizing these neoplasms, there is the possibility of disproportionately better ascertainment in cancer survivors because of greater surveillance. Almost 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 present fairly rapidly as invasive cancer that is unlikely to be 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. Efforts 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.

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Acquisition of data: Reulen, Frobisher, Winter, Kelly, Lancashire, Stiller, Hawkins.

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Drafting of the manuscript: Reulen, Frobisher, Hawkins. **Critical revision of the manuscript for important intellectual content:** Reulen, Frobisher, Winter, Kelly, Lancashire, Stiller, Prichard-Jones, Jenkinson, Hawkins. **Statistical analysis:** Reulen, Frobisher, Hawkins.

Obtained funding: Lancashire, Hawkins.

Administrative, technical, or material support: Winter, Kelly, Lancashire, Hawkins.

Study supervision: Hawkins.

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, the 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 Leukemia Group, the Childhood Cancer Research Group, and the Regional Pediatric Cancer Registries. The BCCSS acknowledges the collaboration of the Office for National Statistics, the General Register Office for Scotland, the National Health Service Central Registers, 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 offer 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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