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ORIGINAL REPORT

Risk of Adverse Health and Social Outcomes Up to 50 Years After Wilms Tumor: The British Childhood Cancer Survivor Study

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ABSTRACT

Purpose
Survivors of Wilms tumor (WT) are at risk for adverse health and social outcomes but risks beyond 30 years from diagnosis remain uncertain. We investigated the risks of adverse outcomes among 5-year survivors of WT, in particular, those between 30 and 50 years from diagnosis.

Patients and Methods
The British Childhood Cancer Survivor Study includes 1,441 5-year survivors of WT. We investigated cause-specific mortality, risk of subsequent primary neoplasms (SPNs), and, for those who completed a questionnaire, the extent of smoking and drinking, educational achievement, health status, and health service use compared with the general population.

Results
Cumulative risk of death from all causes, excluding recurrence, increased substantially from 5.4% to 22.7% at 30 years and 50 years, respectively, after WT diagnosis—75% of excess deaths beyond 30 years from diagnosis were attributable to SPNs (50%) and cardiac diseases (25%). Digestive cancer, most frequently bowel, accounted for 41% of excess cancers beyond 30 years.

Conclusion
Between 30 and 50 years from diagnosis, survivors of WT are at a substantially increased risk of premature mortality, and 75% of excess deaths were accounted for by SPNs and cardiac diseases. Radiotherapy exposure was a risk factor for both outcomes. The proportion of patients with WT who are exposed to radiotherapy has reduced substantially in recent decades because of initiatives such as the SIOP WT 2001 clinical trial, which sought to reduce late effects; however, the majority of current survivors, who are at least 30 years from diagnosis, received radiotherapy. Surveillance of this group should focus on SPNs, in particular, bowel and breast cancers, and cardiac conditions.

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INTRODUCTION

The 5-year survival rate after diagnosis with Wilms tumor (WT) has improved to 90% as a result of advances in anticancer therapy.[1] Although WT is increasingly curable, survivors are at risk for a range of treatment-related, long-term adverse health and social outcomes. Survivors of WT have increased mortality compared with the general population[2,3] and are at excess risk of developing second primary cancers,[3-6] adverse pregnancy outcomes,[7-9] cardiac disease, and renal dysfunction.[10]

Although a number of previous studies have investigated the risks of adverse health and social outcomes among survivors of WT,[9,11-16] none have had sufficient follow-up to satisfactorily investigate the risks beyond 30 years from WT diagnosis; hence, there remains considerable uncertainty regarding the magnitude of these risks. The main advantage of the current study—in addition to being large scale and population based—is that 65% of the cohort survived for > 30 years after WT diagnosis.

The objective of this study was to investigate the risks of adverse health and social outcomes among 5-year survivors of WT ≤ 50 years after diagnosis. Specific objectives were to investigate cause-specific late mortality; the risk of developing subsequent primary neoplasms (SPNs); the risk of adverse pregnancy outcomes; health status;

smoking and alcohol consumption, educational attainment, and marriage status; and health services use.

PATIENTS AND METHODS

British Childhood Cancer Survivor Study

The British Childhood Cancer Survivor Study (BCCSS) is a large-scale, population-based cohort study established to investigate adverse health and social outcomes among such survivors. The BCCSS includes 1,441 survivors of WT who were diagnosed at age < 15 years between 1940 and 1991 in Great Britain and who survived for ≥ 5 years.[17] The BCCSS cohort was ascertained through the population-based National Registry of Childhood Tumors. Limited treatment information was obtained from clinical records to the level of detail given in Table 1.

Ascertainment of Deaths and SPNs

Ascertainment of deaths, including the underlying cause of death, and SPNs in the BCCSS was achieved by flagging the entire cohort of survivors of childhood cancer at the National Health Service Information Centre. Flagging informs the BCCSS when a survivor dies or develops an SPN by linking the population-based cohort with the national population-based death and cancer registration systems. Confirmation of all SPNs was undertaken by writing to relevant clinician(s) to obtain all diagnostic information, in particular, pathology reports.[4] Validation of causes of deaths was undertaken by two clinicians (E.S. and G.L.) by reviewing all available clinical records, including death certificates, to ascertain the underlying cause of death. Consequently, all SPNs and causes of death were validated.

BCCSS Questionnaire

Between 2001 and 2007, all survivors who were alive and age > 16 years were sent a 40-page questionnaire by their primary care physician on behalf of the BCCSS.[18] In total, 947 of all eligible survivors of WT (70.5%) completed and returned the questionnaire.[17] The BCCSS questionnaire inquired about potential adverse health and social outcomes of childhood cancer and its treatment, including questions regarding health status (Short Form 36 [SF-36]), health services use, medical conditions, medical procedures, marriage, adverse pregnancy outcomes (eg, miscarriage, stillbirth, preterm birth), smoking and alcohol consumption, and educational achievements.

Ethical approval for the BCCSS was obtained from the relevant multicenter research ethics committee and every local research ethics committee in Great Britain (212 total).

Statistical Analysis

Cause-specific mortality. Numbers of observed deaths among survivors of WT were compared with the number of expected deaths on the basis of the population of England and Wales. The at-risk period began 5 years after the initial diagnosis of childhood WT and continued until the first occurrence of emigration, death, or exit (December 31, 2010). Standardized mortality ratios (SMR) for specific causes of death were calculated as the ratio of observed deaths versus the expected number of deaths. Absolute excess risks (AERs) were calculated from observed deaths minus the expected number of deaths and divided by the number of person-years at risk multiplied by 10,000. The cumulative mortality for specific causes of death was estimated by treating other causes of death as competing risks.[19]

SPNs. The at-risk period for developing an SPN began 5 years after the diagnosis of WT and continued until the first occurrence of SPN, emigration, death, or exit (December 31, 2006). Multiple observed SPNs per survivor were permitted for comparison with those expected from the general population to avoid bias, but only the first SPN was considered in measures of cumulative risk. Standardized incidence ratios, AERs, and cumulative risk of developing an SPN were calculated as described in "Cause-specific mortality" in relation to death.

Health status: SF-36. Health status was measured by using the SF-36 questionnaire.[20] To compare SF-36 scale scores observed among survivors of WT with the general population, we used normative data from the Oxford Healthy Life Survey (OHLS).[21] For each SF-36 scale, the difference in mean scores between survivors of WT and OHLS was calculated by using linear regression, which adjusted for age and sex. In addition, we examined

Table 1. Characteristics of All Survivors of WT in the BCCSS and of All Those Who Completed a Questionnaire (N = 1,441)

Characteristic	All WT Survivors (N = 1,441)	Completed Questionnaire Returned (n = 947)	No Completed Questionnaire Returned (n = 494)
Sex			
Male	733 (51)	436 (46)	297 (60)
Female	708 (49)	511 (54)	197 (40)
Age at diagnosis, years			
Mean	3.3	3.3	3.3
Median	2.8	2.9	2.7
0-4	1,156 (80.2)	760 (80.3)	396 (80.2)
5-9	252 (17.5)	166 (17.5)	86 (17.4)
10-14	33 (2.3)	21 (2.2)	12 (2.4)
Age at questionnaire completion, years*			
Mean	N/A	28.3	N/A
5-9	N/A	0 (0.0)	N/A
10-19	N/A	221 (23.3)	N/A
20-29	N/A	350 (37.0)	N/A
30-39	N/A	261 (27.6)	N/A
40-49	N/A	90 (9.5)	N/A
50-59	N/A	22 (2.3)	N/A
≥ 60	N/A	3 (0.3)	N/A
Years from WT diagnosis†			
5-9	30 (2.1)	0 (0.0)	30 (6.1)
10-19	94 (6.5)	27 (2.9)	67 (13.6)
20-29	349 (24.2)	234 (24.7)	115 (23.3)
30-39	652 (45.2)	455 (48.0)	197 (39.9)
≥ 40	316 (21.9)	231 (24.4)	85 (17.2)
On long-term hospital follow-up‡			
Yes	N/A	360 (38.3)	N/A
No	N/A	546 (58.0)	N/A
Missing	N/A	35 (3.7)	N/A
Treated with abdominal radiotherapy			
Yes	756 (52.5)	489 (51.7)	267 (54.1)
No	164 (11.4)	111 (11.7)	53 (10.7)
Missing	521 (36.1)	347 (36.6)	174 (35.2)
Treated with chemotherapy			
Yes	701 (48.6)	460 (48.6)	241 (48.8)
No	203 (14.1)	125 (13.2)	78 (15.8)
Missing	537 (37.3)	362 (38.2)	175 (35.4)
Surgery			
Yes	921 (63.9)	598 (63.2)	323 (65.4)
No	13 (0.9)	9 (0.9)	4 (0.8)
Missing	507 (35.2)	340 (35.9)	167 (33.8)

NOTE. All data are given as No. (%) unless otherwise noted.
Abbreviations: BCCSS, British Childhood Cancer Survivor Study; N/A, not applicable; WT, Wilms tumor.
*The BCCSS questionnaire was sent out to survivors age ≥ 16 years.
†Years of follow-up after initial diagnosis. Percentages correspond to the total number in cohort or the number of those who completed questionnaire.
‡Regular hospital follow-up appointments in relation to the childhood cancer or its treatment.

responses to the individual questions (items) underlying the specific SF-36 scales by comparing the directly standardized percentage (for age and sex) of survivors of WT who reported a limitation or other problem with that reported by the general population.

Adverse pregnancy outcomes. To investigate the risks of adverse pregnancy outcomes, logistic regression models were used to calculate odds ratios (ORs) to compare the likelihood of low birth weight, preterm births, and miscarriage between pregnancy outcomes among female survivors of WT who were treated with abdominal radiotherapy with female survivors of non-WT childhood cancers who did not receive abdominal radiotherapy. Most female survivors of WT (87%) who reported being pregnant at least once had been treated with abdominal irradiation.

Smoking status, alcohol consumption, and education level. Among those survivors of WT who completed the BCCSS questionnaire, smoking, alcohol consumption, and educational attainment were compared with the general population by using data from the nationwide General Household Survey (GHS).[22] Adjustment for confounders and classification of current regular smokers, alcohol consumption, and educational attainment have been defined in previous BCCSS studies.[23-25] For each outcome, ORs that compared survivors of WT with the GHS were calculated by using multivariable logistic regression with a generalized estimating equation modification that took into account clustering within the GHS; these ORs were adjusted for attained age and sex.

Marital status. To investigate marital status among survivors of WT, ORs of ever being married, stratified by sex and attained age, were calculated by using data from the National Marriage Registry as the reference population.[26] Age-specific ORs were then pooled into one overall OR by using the Mantel-Haenszel method for combining ORs.[27]

Health services use. The frequency of doctor consultations, hospital outpatient visits, day patient hospitalizations, and inpatient hospitalizations were evaluated by calculating ORs to compare survivors of WT with the GHS by using a multivariable logistic regression model. ORs were adjusted for attained age, sex, educational attainment and were stratified by whether survivors were on regular long-term hospital follow-up stemming from their childhood cancer and its treatment.[28]

Statistical significance for all analyses was defined as a two-sided $P < .05$. All analyses were carried out with STATA software (version 12; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA).

RESULTS

Cohort Characteristics

Of the 1,441 survivors of WT in the cohort, 10% (n = 146) had died, 2% (n = 31) emigrated, and 88% (n = 1,264) were alive at the exit date (December 31, 2010). Characteristics of survivors of WT who completed the questionnaire were similar to all survivors of WT in the BCCSS cohort (Table 1). Regarding mortality, there were 38,803 person-years from 5-year survival, with mean and median follow-up of 26.9 years and 26.0 years, respectively. Table 1 indicates that 756 (82%) of 920 survivors were exposed to direct abdominal radiotherapy, and only 164 were known to be unexposed. Consequently, the analysis of the entire cohort, used for analysis of deaths and SPNs, corresponds to a group overwhelmingly exposed to direct abdominal radiotherapy.

Cause-Specific Mortality

Survivors experienced greater than five times the number of deaths expected (SMR, 5.4; 95% CI, 4.6 to 6.4 deaths), with 30.7 additional deaths (95% CI, 24.6 to 36.8) per 10,000 person-years in excess of that expected (Table 2). For specific causes of death, with $\geq$ 20 observed deaths, results are reported separately. In multiplicative terms, cause-specific mortality was greatest for SPNs (SMR, 7.3; 95% CI, 5.3 to 9.8) and for cardiac disease (SMR, 10.1; 95% CI, 6.5 to 14.9). Regarding AER, the greatest excess risk resulted from SPNs, which accounted for 32% of all excess deaths. This was followed by deaths as a result of recurrence and cardiac causes, which accounted for 21% and 19% of the excess deaths, respectively. Deaths from recurrence mostly occurred relatively early, with 22 of 25 such deaths between 5 and 14 years, three of 25 between 15 and 24 years, and none from 25 years after diagnosis (not shown in tables). The AER as a result of all causes of death except recurrence was 14 excess deaths (per 10,000 person-years) between 5 and 29 years after WT diagnosis; however, this increased eight-fold to 108.4 excess deaths beyond 30 years, which is equivalent to one additional death per 100 survivors each year (Table 3). From 30 years after WT diagnosis, deaths from SPNs and cardiac disease accounted for 50% and 25% of the total number of excess deaths, respectively.

Cumulative mortality from recurrence was 1.8% by 30 years after WT diagnosis, and it remained the same by 50 years as there were no more deaths as a result of recurrence. Cumulative mortality from all causes except recurrence was 5.4% by 30 years after WT diagnosis, but this increased substantially to 22.7% by 50 years. By 50 years from WT diagnosis, the cumulative mortality from SPNs and cardiac diseases were 8.2% and 6.3%, respectively (Fig 1).

There were 25 cardiac deaths according to the underlying cause of death on the death certificate, and we summarize the results of a comprehensive review of these causes of death, taking account of all hospital records and autopsy reports still available (Appendix Table A1, online only). This comprehensive review ascertained that four deaths were because of renal failure; nine from myocardial infarction (four with chest irradiation and/or lung metastases); seven from cardiomyopathy and/or heart failure (six with chest irradiation); three from pulmonary embolism; and two from other causes.

SPNs

The cumulative risk of developing an SPN was 3.7% (95% CI, 2.7% to 5.0%) by 30 years after WT diagnosis, which increased to 16.4% (95% CI, 10.7% to 23.2%) by 50 years (Fig 2). The most common SPNs were those of digestive sites, which occurred in 17 survivors of WT; seven were bowel cancers, and the other affected sites are specified in Table 4—all 17 survivors had previously received abdominal radiotherapy. Of SPNs $>$ 40% developed beyond 30 years after diagnosis of WT, and 10 of 17 digestive SPNs developed in this period, which accounted for 41% of the excess number of cancers in this follow-up period. All survivors of WT who developed breast cancer had previously received either abdominal or chest radiotherapy.

Health Status: SF-36

Survivors of WT scored significantly lower than did the general population on two of the eight SF-36 scales: physical functioning (difference in means [D], −1.8; 95% CI, −3.3

Table 2. Cause-Specific SMRs and AERs for Survivors of WT (N = 1,441)

Cause of Death	Obs/Exp	SMR (95% CI)	AER (95% CI)*	% of Total AER
All causes overall	146/26.8	5.4 (4.6 to 6.4)	30.7 (24.6 to 36.8)	100
Years from diagnosis				
5-9	25/1.6	15.7 (10.2 to 23.2)	36.2 (21.0 to 51.3)	
10-19	29/6.1	4.8 (3.2 to 6.9)	16.5 (8.9 to 24.0)	
20-29	37/6.8	5.5 (3.8 to 7.5)	21.1 (11.1 to 31.1)	
30-39	27/5.9	4.6 (3.0 to 6.6)	38.2 (19.8 to 56.7)	
≥ 40	28/6.5	4.3 (2.9 to 6.3)	92.7 (48.1 to 137.4)	
Infection	5/0.6	8.7 (2.8 to 20.2)	1.1 (0.0 to 2.3)	4
Recurrence	25/0	—	6.4 (3.9 to 9.0)	21
SPN	44/6.0	7.3 (5.3 to 9.8)	9.8 (6.4 to 13.1)	32
Blood	0/0.1	N/A	0.0 (N/A)	0
Endocrine	0/0.6	N/A	−0.1 (−0.1 to −0.1)	0
Mental	1/0.9	1.1 (0.0 to 6.2)	0.0 (−0.5 to 0.5)	0
Nervous	3/1.3	2.2 (0.5 to 6.6)	0.4 (−0.4 to 1.3)	1
Cardiac	25/2.5	10.1 (6.5 to 14.9)	5.8 (3.3 to 8.3)	19
Respiratory	6/1.2	4.9 (1.8 to 10.7)	1.2 (0.0 to 2.5)	4
Digestive	6/1.5	3.9 (1.4 to 8.5)	1.2 (−0.1 to 2.4)	4
Muscoskeletal	0/0.2	N/A	0.0 (N/A)	0
Genitourinary	6/0.2	33.1 (12.2 to 72.1)	1.5 (0.3 to 2.7)	5
Perinatal	2/0.7	3.0 (0.4 to 10.8)	0.3 (−0.4 to 1.1)	1
External	19/9.6	2.0 (1.2 to 3.1)	2.1 (0.2 to 4.6)	7
Other	4/1.4	2.9 (0.8 to 7.3)	0.7 (−0.3 to 1.8)	2

NOTE. Calculation of SMR for deaths from recurrence of WT would not be appropriate because the expected mortality rate in the general population would be zero. AER for recurrence was calculated as the incidence rate per 10,000 person-years. CIs for SMR were calculated by using the approximate method if number of deaths ≥ 100 and the Poisson exact method if number of deaths < 100.[29] Perinatal deaths refer to causes resulting from congenital abnormalities (two). External causes of death comprise accidents (seven motor accidents and five accidental poisonings), suicides (two) and other (one death could not be determined as accident or suicide and one death was from a medical procedure). Other causes of death were either unknown or ill-defined (two) or from general symptoms (one) and stroke (one).

Abbreviations: AER absolute excess risk; Exp, expected; N/A, not applicable; Obs, observed; SMR, standardized mortality ratio; SPN, second primary neoplasm; WT, Wilms tumor.

*Overall AER for all causes of death was 30.7 per 10,000 person-years but because of rounding, the specific causes of death sum to 30.4.

to −0.9) and general health perception (D, −6.7; 95% CI, −8.1 to −5.2; Appendix Table A2, online only). However, survivors of WT reported significantly better role–emotional functioning (D, 3.4; 95% CI, 1.2 to 5.6) than did the general population. When examining the responses to individual questions which comprise the physical functioning scale, survivors of WT reported significantly greater limitations on most items compared with the general population (Appendix Fig A1, online only). When examining responses to the individual questions which comprise the general health perception scale, survivors of WT reported greater agreement that their health was worse in relation to each question compared with the general population (Appendix Fig A2, online only).

Pregnancy Outcomes

Of the 511 female survivors of WT who completed the BCCSS questionnaire, 412 pregnancies were reported by 184 women, of which 32% resulted in low birth weight, 35% in a preterm delivery, and 22% in a miscarriage for those who responded to the relevant questions and had received abdominal irradiation. Female survivors of WT who were treated with abdominal radiotherapy were at an increased risk of giving birth to a low-birth-weight baby (OR, 3.3; 95% CI, 2.2 to 4.9) and of giving birth preterm (OR, 3.1; 95% CI, 2.1 to 4.7) compared with survivors of non-WT childhood cancer who were not treated with abdominal radiotherapy. Pregnancy analyses were stratified by eras of treatment (< 1970 and ≥ 1970); however, no statistical differences were found ($P \geq .386$; Appendix Table A3, online only).

Smoking, Alcohol, Education, and Marriage

Compared with the general population, survivors of WT were less likely to be regular smokers (OR, 0.7; 95% CI, 0.6 to 0.8), to consume alcohol (OR, 0.7; 95% CI, 0.6 to 0.9), or to consume harmful amounts of alcohol (OR, 0.5; 95% CI, 0.3 to 0.7). Survivors of WT did not significantly differ from the general population in achieving specific levels of education (all P values > .05). Male survivors were significantly less likely to be married (OR, 0.7; 95% CI, 0.5 to 0.9) compared with the general population.

Health Services Use

Compared with the general population, survivors of WT were significantly more likely to attend hospital outpatients (OR, 2.6; 95% CI, 2.2 to 3.1) at least once in the last 3 months, be hospitalized as a day patient (OR, 1.7; 95% CI, 1.3 to 2.1) at least once in the last year, and be hospitalized as an inpatient (OR, 2.0; 95% CI, 1.6 to 2.6) at least once in the last year. When stratified by whether survivors of WT were on long-term hospital follow-up for their childhood cancer or its treatment, survivors not on long-term hospital follow-up (n = 546) were still significantly more likely to be hospitalized as an outpatient (OR, 2.1; 95% CI, 1.7 to 2.6), day patient (OR, 1.5; 95% CI, 1.1 to 2.0), and inpatient (OR, 1.9; 95% CI, 1.4 to 2.6) compared with the general population. Survivors of WT who were on such long-term hospital follow-up (n = 360) were even more likely to be hospitalized as an outpatient (OR, 3.5; 95% CI, 2.7 to 4.6), day patient (OR, 1.9; 95% CI, 1.3 to 2.7), and inpatient (OR, 2.3; 95% CI, 1.6 to 3.5).

Table 3. AER of Specific Causes of Death by Years of Follow-Up as a Proportion of Total AER

	AER < 30 Years From Diagnosis			AER ≥ 30 Years From Diagnosis		
Cause of Death	Obs/Exp	AER (95% CI)	% of Total AER	Obs/Exp	AER (95% CI)	% of Total AER
Recurrence	25/0	7.2 (4.4 to 10.0)	34	0/0	0.0 (N/A)	0
SPN	18/2.8	4.4 (2.0 to 6.8)	21	26/3.2	53.8 (30.2 to 77.4)	50
Cardiac	12/0.9	3.2 (1.2 to 5.2)	15	13/1.5	27.0 (10.3 to 43.7)	25
External	14/8.3	1.6 (−0.5 to 3.7)	7	5/1.2	8.9 (−1.4 to 19.2)	8
All other causes	22/5.5	5.0 (2.3 to 7.7)	23	11/2.9	19.1 (3.8 to 34.4)	17
All deaths*	91/17.8	21.2 (15.8 to 26.6)	100	55/9.0	108.4 (74.1 to 142.7)	100

NOTE. AER presented per 10,000 person-years.
Abbreviations: AER, absolute excess risk; Exp, expected; N/A, not applicable; Obs, observed; SPN, second primary neoplasm.
*AER for all causes of death was 21.2 per 10,000 person-years < 30 years from diagnosis and 108.4 per 10,000 person-years ≥ 30 years from diagnosis, but because of rounding, the specific causes of death sum to 21.4 and 108.8, respectively.

DISCUSSION

New findings include the identification of a substantial increase in cumulative mortality as a result of causes of death other than recurrence in the period from 30 to 50 years after WT diagnosis—increasing from 5.4% to 22.7%, which corresponds to one extra death per 100 survivors per year. Consistent with our study, a previous US-based, large-scale study[3] found that cumulative mortality at 30 years from WT diagnosis was approximately 3%, but thus far, to our knowledge, no study has demonstrated the substantial increase in mortality from 30 to 50 years from WT diagnosis. The excess of deaths after 30 years was mainly attributable to SPNs (50%) and cardiac-related deaths (25%), which together accounted for 75% of all excess deaths. The AER for the first 30 years after diagnosis is consistent with that found in the National Wilms Tumor Study[30], but this study also did not have sufficient follow-up to demonstrate a substantial increase in the AER beyond 30 years from diagnosis as observed in the current study.

The excess of SPNs during the initial 30 years from WT diagnosis was comparable to that reported in previous studies.[6,31] Beyond 30 years from WT diagnosis, previous studies had insufficient follow-up to satisfactorily assess evidence for an excess. Our cumulative risk increased from 3.7% at 30 years to 16.4% at 50 years. Beyond 30 years from WT diagnosis, there were 4.5 excess cancers observed per 1,000 survivors per year. This excess was mainly attributable to digestive cancers (41%) and breast cancers (7%), together accounting for 48% of the total excess of cancers. All survivors of WT who developed a digestive SPN had received abdominal radiotherapy, and all survivors who developed breast cancer received either abdominal or chest radiotherapy. We have previously reported the strong link between abdominopelvic irradiation and subsequent bowel cancer.[32] Specifically, the risk of developing bowel cancer among survivors of childhood cancer who were treated with direct abdominopelvic irradiation is at least

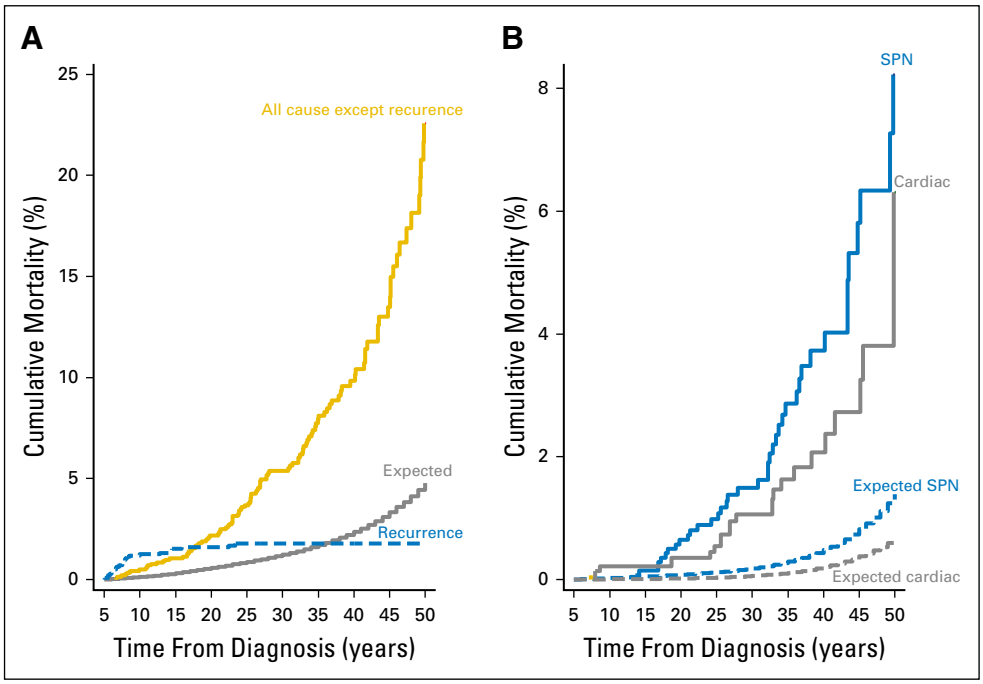

Fig 1. Observed and expected cumulative mortality among 1,441 survivors of Wilms tumor. SPN, second primary neoplasm.

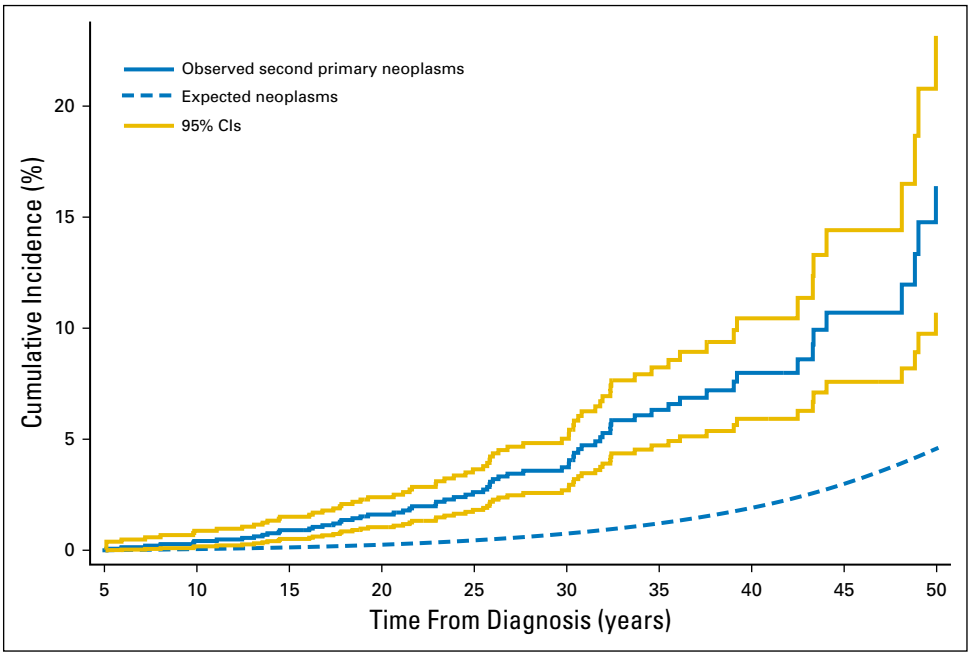

Fig 2. Observed and expected cumulative incidence of developing a second primary neoplasm among 1,441 survivors of Wilms tumor, with 95% CIs.

the same as that observed among individuals who have at least two first-degree relatives diagnosed with bowel cancer, and for whom colonoscopy is currently recommended, from age 35 to 45 years[33] or from age 50 years.[34] This raises the serious question of whether irradiated survivors of WT, who comprise the majority of survivors of childhood cancer who were treated with direct abdominopelvic irradiation, should be similarly recommended for colonoscopy.

Previous studies have shown that survivors of WT reported adverse health status outcomes comparable to our study,[3,35] that is, lower general health perception and physical function. In addition, survivors of WT also reported lower overall health status in previous studies.[15,36-38] Survivors of WT in our study reported that role–emotional was significantly higher than OHLS; however, this is likely a result of ceiling effects because role–emotional was measured by three categories, which caused a clustering of scores at the maximum level.[39]

Consistent with previous studies,[7-9,14,40] completed pregnancies were more likely to be premature and to result in low birth weight. The results of the current and previous studies suggest that female survivors who were treated with abdominal radiation should be carefully monitored during pregnancy.

With respect to social outcomes, and consistent with previous studies, survivors of WT seem to have a healthier life style, being less likely to be regular smokers[41,42] and consuming lower amounts of alcohol than the general population. Similar to a previous study, male survivors were less likely to be married than the general population.[43]

Survivors of WT were more likely to visit the hospital and to be hospitalized, regardless of whether they were on regular long-term hospital follow-up as a result of their childhood cancer or its treatment, a finding that is similar to previous studies.[3,44]

A limitation of our study was the lack of detailed information on radiotherapy and chemotherapy treatment administered to survivors of WT. It is also important to acknowledge that survivors included in the cohort were treated between 1940 and 1991; therefore, our findings are unlikely to be generalizable to survivors treated in more recent years because of changes in exposure to different treatments. For example, the vast majority (82%) of survivors presented here had received radiotherapy as part of their

Table 4. SIRs and AERs for Developing Specific SPNs After Diagnosis With WT

Outcome	Obs/Exp	SIR (95% CI)	AER (95% CI)	AER (95% CI; No.) < 30 Years From Diagnosis	AER (95% CI; No.) ≥ 30 Years From Diagnosis
All	71/15.1	4.7 (3.7 to 5.9)	16.6 (11.7 to 21.5)	11.8 (7.4 to 16.1; 41)	44.6 (23.0 to 66.3; 30)
Digestive*	17/1.3	13.0 (7.6 to 20.9)	4.7 (2.3 to 7.1)	2.3 (0.5 to 4.1; 7)	18.2 (5.7 to 30.7; 10)
Genitourinary	9/3.5	2.6 (1.2 to 4.9)	1.6 (−0.1 to 3.4)	1.8 (0.0 to 3.6; 7)	0.5 (−5.1 to 6.1; 2)
Breast	9/2.9	3.1 (1.4 to 5.8)	1.8 (0.1 to 3.5)	1.5 (−0.4 to 1.8; 5)	3.3 (−4.6 to 11.2; 4)
Bone	6/0.3	20.6 (7.5 to 44.8)	1.7 (0.3 to 3.1)	1.6 (0.1 to 3.2; 5)	2.0 (−2.0 to 5.9; 1)

NOTE. AER is shown per 10,000 person-years. Thirty other SPNs include soft tissue sarcoma (six), unknown primary site (five), glioma (three), leukemia (three), non-Hodgkin lymphoma (three), thyroid (three), melanoma (two), adrenal (one), Hodgkin's lymphoma (one), mesothelioma (one), leiomyosarcoma (one), and oral (one).
Abbreviations: AER, absolute excess risk; Exp, expected; Obs, observed; SIR, standardized incidence ratio; SPN, second primary neoplasm; WT, Wilms tumor.
*The 17 digestive SPNs comprise bowel (seven), retroperitoneum/peritoneum (four), liver (two), pancreas (one), small intestine (one), pyloric antrum (one), and unknown digestive site (one).

initial treatment. In contrast, only 27% of nonanaplastic patients with WT who were included within a relatively recent randomized clinical trial (UKW3),[45] which recruited between 1991 and 2001, received radiotherapy as part of their initial treatment. Nevertheless, there are still an entire cohort of survivors being seen in follow-up clinics or discharged into the community who were treated before 1991 and our evidence relates directly to them.

In conclusion, between 30 and 50 years from diagnosis, survivors of WT are at a substantially increased risk of premature mortality, and 75% of excess deaths were accounted for by SPNs and cardiac diseases. Radiotherapy exposure was a risk factor for both outcomes. The proportion of patients with WT who were exposed to radiotherapy has reduced substantially in recent decades because of initiatives such as the SIOP WT 2001 clinical trial, which sought to reduce late effects.[45] However, the majority of current survivors, $\geq$ 30 years from diagnosis, received radiotherapy. Surveillance of this group should focus on SPNs, in particular, bowel and breast cancers, and cardiac conditions as these account for 50% and 25% of total excess deaths observed, respectively.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk of Adverse Health and Social Outcomes Up to 50 Years After Wilms Tumor: The British Childhood Cancer Survivor Study

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Appendix

The British Childhood Cancer Survivor Study (BCCSS) is a national collaborative undertaking guided by a steering group comprised of Douglas Easton (chair), Michael Hawkins, Helen Jenkinson, Meriel Jenney, Raoul Reulen, Kathryn Pritchard-Jones, Michael Stevens, Elaine Sugden, Andrew Toogood, and Hamish Wallace.

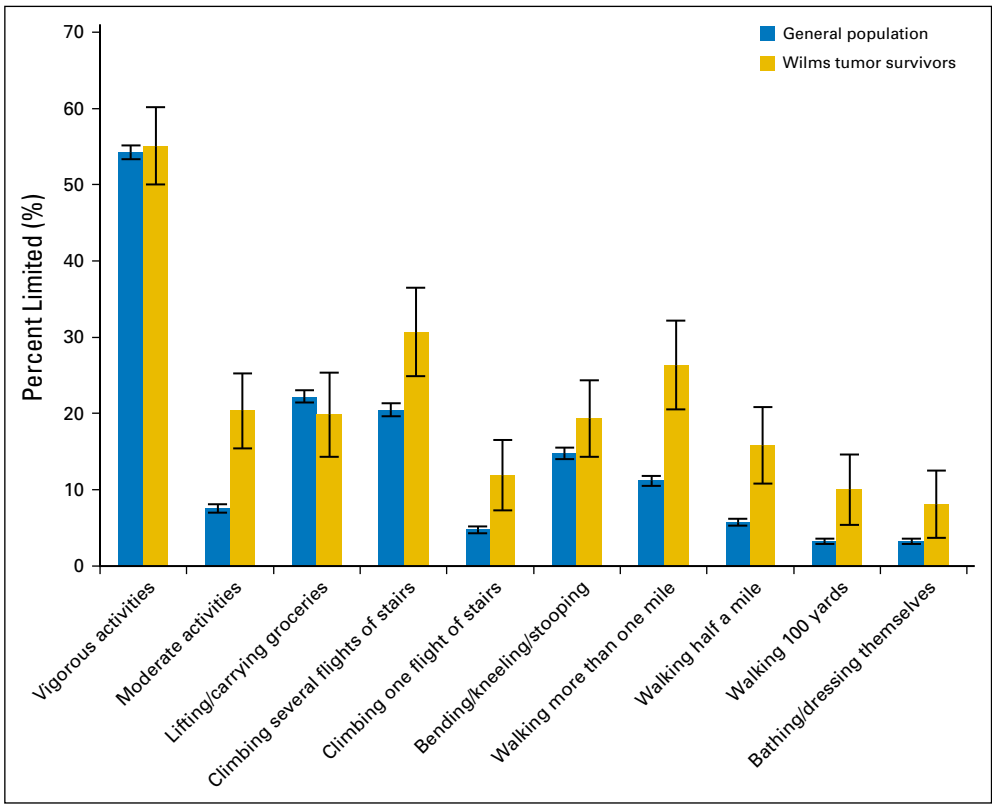

Fig A1. Specific questions underlying the Short Form 36 Physical Function scale; directly standardized proportions with limitation in specific activities.

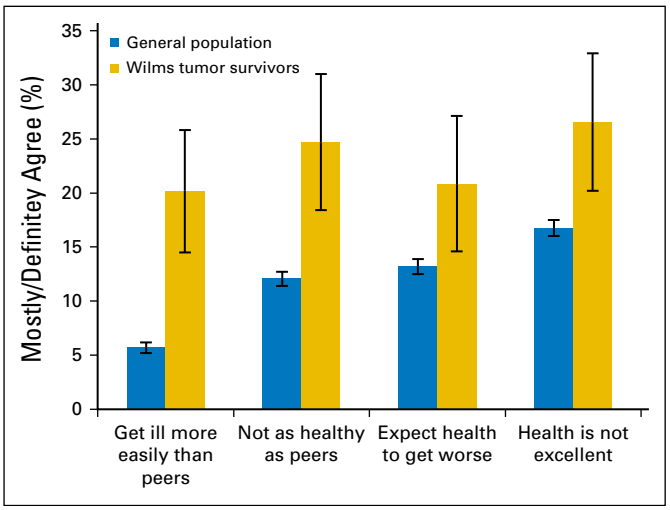

Fig A2. Specific questions underlying the Short Form 36 General Health Perception scale; directly standardized proportions with specified level of agreement in relation to each question.

Table A1. Results of a Comprehensive Review by Using Hospital Records and Autopsy Reports of 25 Causes of Death Relating to the 25 Deaths Coded as Cardiac on the Death Certificate

Type of Circulatory Death	Frequency	Comments
Myocardial infarction	9	Four had chest radiotherapy and/or lung metastasis documented
Cardiomyopathy/heart failure	7	Six had chest radiotherapy documented, two also had renal failure; myocardial, lung, and liver fibrosis at autopsy in two
Pulmonary embolism	3	
Other	2	Comprised of one atrial myxoma and one alcoholic cardiomyopathy

NOTE. Of the 25 deaths, four were considered deaths from renal failure. The age of death was > 50 years in only four persons.

Table A2. Differences in Mean SF-36 Scores Between Survivors of Wilms Tumor (n = 947) and OHLS Reference Population

SF-36 Scale	D (95% CI)*
Reported health change	0.0 (–1.1 to 1.1)
Physical function	−1.8 (– 3.3 to –0.9)
Role–physical	−1.2 (–3.3 to 0.9)
Role–emotional	3.4 (1.2 to 5.6)
Social functioning	−0.1 (–1.4 to 1.3)
Mental health	0.6 (–0.6 to 1.8)
Vitality	0.0 (–1.4 to 1.4)
Bodily pain	0.3 (–1.2 to 1.9)
General health perception	−6.7 (–8.1 to –5.2)

Abbreviations: D, differences in mean; OHLS, Oxford Healthy Life Survey; SF-36, Short Form 36.
*Calculated scores were adjusted for age and sex.

Table A3. ORs of Pregnancy Outcomes, Smoking Status, Alcohol Consumption, Education Level, Marriage Status, and Medical Care of Survivors of Wilms Tumor (n = 947)

Variable	Proportion of Affected Outcomes (%)	OR (95% CI)
Pregnancy outcome*		
Females survivor		
Low birth weight	61/192 (31.8)	3.3 (2.2 to 4.9)
Premature	66/187 (35.3)	3.1 (2.1 to 4.7)
Miscarriage	67/303 (22.1)	1.4 (0.9 to 2.1)
Partners of males survivors		
Low birth weight	8/134 (6.0)	0.6 (0.3 to 1.2)
Premature	12/136 (8.8)	0.6 (0.3 to 1.3)
Miscarriage	30/202 (14.9)	1.2 (0.7 to 1.9)
Smoking†		
Current regular smoker	220/934 (23.6)	0.7 (0.6 to 0.8)
Alcohol‡		
Alcohol consumption	766/942 (81.3)	0.7 (0.6 to 0.9)
Consumption over recommendation	210/766 (27.4)	0.8 (0.7 to 1.0)
Consuming harmful doses	34/766 (4.4)	0.5 (0.3 to 0.7)
Education achievement§		
Degree	133/672 (19.8)	0.9 (0.7 to 1.1)
Teaching qualification	204/672 (30.4)	0.9 (0.7 to 1.1)
A-level	385/774 (49.8)	0.9 (0.8 to 1.1)
O-level	690/924 (74.7)	1.0 (0.8 to 1.1)
Marital status‖		
Male	123/426 (28.9)	0.7 (0.5 to 0.9)
Female	197/505 (39.0)	1.0 (0.8 to 1.3)
Hospitalization¶		
Talked to a doctor in the last 2 weeks	152/900 (16.9)	1.2 (1.0 to 1.5)
Not on long-term follow-up	88/549 (16.0)	1.1 (0.9 to 1.4)
On long-term follow-up	57/329 (17.3)	1.3 (1.0 to 1.8)
Attended hospital outpatient	229/897 (25.5)	2.6 (2.2 to 3.1)
Not on long-term follow-up	123/546 (22.5)	2.1 (1.7 to 2.6)
On long-term follow-up	101/329 (30.7)	3.5 (2.7 to 4.6)
Hospitalized as a day patient	118/904 (13.1)	1.7 (1.3 to 2.1)
Not on long-term follow-up	71/552 (12.9)	1.5 (1.1 to 2.0)
On long-term follow-up	43/330 (13.0)	1.9 (1.3 to 2.7)
Hospitalized as an inpatient	93/904 (10.3)	2.0 (1.6 to 2.6)
Not on long-term follow-up	55/553 (10.0)	1.9 (1.4 to 2.6)
On long-term follow-up	36/329 (10.9)	2.3 (1.6 to 3.5)

NOTE. Total numbers represent the number of survivors of Wilms tumor that answered a question relating to the specific outcome on the British Childhood Cancer Survivors Study questionnaire or, in the case of pregnancies, the total number of pregnancies in irradiated female survivors of Wilms tumor.

Abbreviation: OR, odds ratio.

*Modeled as pregnancies of female survivors of Wilms tumor who received abdominal radiotherapy versus pregnancies of female survivors of any other childhood cancer who did not receive abdominal radiotherapy. There were 412 pregnancies from female survivors and 235 pregnancies from partners of male survivors. Models were adjusted for maternal age and pregnancy order. Low birth weight was defined as any birth weight $< 2{,}500$ g. Preterm birth was defined as gestational age < 37 weeks.

†Adjusted for sex, attained age, marital status, socioeconomic classification, and educational attainment.

‡Controlled for attained age, sex, legal marital status, socioeconomic classifications, educational attainment, and region, and took into account the General Household Survey weighting factor for the likelihood of consuming over the recommendations for weekly alcohol units or consuming harmful weekly amounts of alcohol.

§Adjusted for, sex, and attained age.

‖Compared with the British population marriage statistics from ONS 2002.

¶Versus no compared with the general British population.