Radiotherapy, Alkylating Agents, and Risk of Bone Cancer After Childhood Cancer

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Background: **Individuals who had cancer in childhood are at higher risk of developing bone cancer than any other type of second primary cancer.** ***Purpose:*** **Using the population-based National Registry of Childhood Tumours in Britain, we investigated the incidence and etiology of second primary bone cancer after childhood cancer in a cohort study and in a case–control study.** ***Methods:*** **A cohort study of 13 175 3-year survivors of childhood cancer diagnosed in Britain between 1940 and 1983 revealed 55 subsequent bone cancers. A largely nested case–control study comprised 59 case subjects developing second primary bone cancer, and 220 control subjects were selected and matched for sex, type of first cancer, age at first cancer, and interval between diagnosis of first cancer and subsequent bone cancer. Outcome measures were the incidence of bone cancer after childhood cancer, the cumulative dose of radiation received at the site of the second bone cancer in the case subject and at the corresponding anatomic site in the matched control subjects, and the cumulative dose of alkylating agents and vinca alkaloids received by case and control subjects.** ***Results:*** **The percentage of 3-year survivors developing bone cancer within 20 years did not exceed 0.9%, except following heritable retinoblastoma (7.2%), Ewing's sarcoma (5.4%), and other malignant bone tumors (2.4%). The risk of bone cancer increased substantially with increased cumulative dose of radiation to the bone ($P<.001$, linear trend). At the highest levels of exposure, however, the risk appeared to decline somewhat ($P = .065$, nonlinearity). Exposure to less than 10 Gy was, at worst, associated with only a small increased relative risk (RR) of bone cancer (RR = 0.7; 95% confidence interval = 0.2-2.2). The risk of bone cancer increased linearly ($P = .04$, one-tailed test) with increased cumulative dose of alkylating agents.** ***Implications:*** **This population-based study provides grounds for reassurance of the majority of survivors in that their risk of developing bone cancer within 20 years of 3-year survival did not exceed 0.9%. The higher risks found for bone cancer following the other specific rare types of childhood cancer provide a rational basis for surveillance. The RRs reported for bone cancer after specified levels of exposure to radiation should help in making decisions concerning future treatment protocols. [J Natl Cancer Inst 1996;88:270-8]**

Bone cancer accounts for the highest risk of any specific type of second primary cancer to develop after both heritable retinoblastoma and all other types of childhood cancer (*1*). It is therefore important to quantify the risks of occurrence and to investigate the relationship between the risk of occurrence and elements of therapy and genetic makeup. The identification of specific aspects of therapy or genetic makeup associated with a particularly high risk of subsequent second bone cancer would provide a rational basis for counseling survivors and their families, planning surveillance of groups of survivors at particular risk, and planning future treatment protocols. More generally, such studies further clarify mechanisms underlying the development of bone cancer and the consequences of exposure when young to radiation and cytotoxic drugs.

Using the population-based National Registry of Childhood Tumours in Britain, we investigated the incidence and etiology of second primary bone cancer after childhood cancer in a cohort study and in a case–control study.

Subjects and Methods

Criteria for Inclusion of Neoplasms

For each patient developing a second primary bone cancer, whether included in the cohort or the case–control study, diagnosis of both the first and second primary neoplasms included histologic confirmation, with the exception of three cases of retinoblastoma. Representative sections of both the first and second neoplasms, when still available, were centrally reviewed by a pediatric histopathologist (H. B. Marsden). Sections were available for all but three second primary bone cancers and all but two first primary neoplasms other than retinoblastoma. For each control subject, we obtained the definitive diagnostic report(s) confirming the type of childhood cancer diagnosed. For those patients included in the cohort who did not develop a subsequent bone cancer, almost all diagnoses were histologically verified except for 4% of leukemias, 13% of central nervous system tumors, and 7% of retinoblastomas, which were based on blood cell counts, radiology or scans, and examination of the patient under anesthesia, respectively. Because of recent evidence of clonality in Langerhans' cell histiocytosis (*2*), the possibility that this disease arises from somatic mutation of DNA in a normal Langerhans' cell, or precursor cell, leading to a neoplastic phenotype, must now be seriously considered. Therefore, for the purposes of this article, Langerhans' cell histiocytosis of bone was considered as a possible

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See "Notes" section following "References."

second primary "cancer." We regard patients with heritable retinoblastoma as comprising all patients who were either bilaterally or unilaterally affected but with a family history of the disease; those with nonheritable retinoblastoma comprised all patients who were unilaterally affected and without a family history of the disease. We always refer explicitly to the heritable and nonheritable types of retinoblastoma; both types combined are often referred to as "retinoblastoma."

Cohort Study

The cohort study population was assembled from all patients known to have been diagnosed with childhood cancer in Britain between 1940 and 1983 inclusive and who survived at least 3 years from the date of diagnosis. For the period of diagnosis 1962-1983, the patients were ascertained by use of the National Registry of Childhood Tumours, which is based on the resident population of Britain. For the period of diagnosis 1940-1961, we approached the main medical centers treating childhood cancer in Britain and included records relating to patients for all diagnosis years for which we could identify all patients diagnosed in a particular center; this procedure resulted in the inclusion of nearly 2000 patients. Entry to the study occurred 3 years after diagnosis. Patients exited the study when one of the following occurred: A second bone cancer was diagnosed, the patient died, the patient emigrated, or the date of last follow-up was reached. We conducted a specifically designed follow-up study by writing to general practitioners of all eligible patients who were not known to have died or to have emigrated; we asked them about the possible development of a second primary neoplasm in their patient. To ensure that our ascertainment of second bone cancer was as complete as possible, all patients not known to have died were flagged at the National Health Service Central Registers, which should ensure the automatic notification of any deaths or cancers registered for those patients (*3*). For patients known to have died, we routinely obtained general practitioners' notes, which were inspected for any evidence that a second cancer had been diagnosed. In addition, through our close links with the U.K. Children's Cancer Study Group, clinicians at the main centers treating childhood cancer in Britain directly informed us of a diagnosis of a second cancer in their patients. We are confident that these overlapping systems of ascertainment of second bone cancer provide as near to complete ascertainment as is practically achievable.

For patients who were alive and not diagnosed with second bone cancer, the study end date, assuming that they had not emigrated, was the date the general practitioner completed the questionnaire indicating the patient was alive and had never been diagnosed with a second bone cancer. The study end date for the few patients for whom no completed questionnaire was returned was the latest date up to which the National Health Service Central Registers would have informed us of all registered cancers occurring in flagged patients (*3*). Expected numbers of bone cancers were calculated on the basis of rates of occurrence of these diseases in the general population of England and Wales; the Office of Population Censuses and Surveys, Titchfield, U.K., supplied a magnetic tape with the relevant information. Sex-, age-, and calendar period-specific rates were applied to corresponding person-years of observation. We assumed that the observed numbers of second bone cancers approximated a Poisson distribution and had a mean equal to that of the corresponding expected number from England and Wales rates. Tests of statistical significance and confidence intervals for relative risks (RRs) were based on exact or approximate Poisson methods, as appropriate (*4*). Unless stated to the contrary, all statistical tests of significance were two-tailed. The cumulative risks of second bone cancer were estimated by standard life-table methods (*5*).

Case–Control Study

All 55 patients included in the cohort study who developed a second primary bone cancer were included in the case–control study as case subjects, except for one patient who developed a second osteosarcoma for whom no control subjects satisfied the matching criteria. A further five patients who were known to have developed a second primary bone cancer but who were not eligible for the cohort study were included in the case–control study. Three of these additional patients were ascertained only as a result of the second bone cancer being diagnosed. Two second bone cancers were diagnosed 7 months after the study end date; for these two case subjects, eligible control subjects who had neither died nor emigrated were selected by extending the study end dates by a similar period. Hence, ultimately, the total number of case subjects in the case–control study was 59, and the type of bone cancer developing in each of the five additional patients was osteosarcoma. The case–control study was therefore almost completely nested within the cohort study.

Corresponding to each case subject, we attempted to select four control subjects matched for sex, histologic type of first cancer, and age at first cancer (within 3 years). In addition, control subjects were required to have survived free of any second primary neoplasm at least as long as the interval between the diagnosis of the first primary neoplasm and the diagnosis of the second bone cancer in the corresponding case subject. In selecting control subjects, we matched for whether retinoblastoma was heritable or nonheritable. We did not match for calendar year of diagnosis because there was no evidence of substantial time trends in the incidence of bone cancer in the general population. The cumulative doses of radiotherapy and chemotherapy were based on the period from the diagnosis of the original childhood cancer to the diagnosis of bone cancer in each case subject and a corresponding period from diagnosis in the 220 matched control subjects. Study outcome measures were the following: 1) the incidence of bone cancer after childhood cancer, 2) the cumulative dose of radiation received at the site of the second bone cancer in the case subject and at the corresponding anatomic site in the matched control subjects, and 3) the cumulative dose of alkylating agents and vinca alkaloids received by case and control subjects.

Standard conditional logistic regression methods (*6*) were used to compare case and control subjects. The EGRET epidemiologic software was used for analysis (*7*). Unless otherwise specified, all statistical tests of significance were two-tailed.

Radiation Dosimetry

Radiation-absorbed dose was estimated for each patient on the basis of measurements in a water phantom and an anthropomorphic phantom (Humanoid); these measurements included all contributions to dose, such as collimator scatter, head leakage, and scatter within the patient. Dose estimates were corrected for differential absorption in bone on the basis of radiation energy. Details on each patient's treatment were abstracted from the patient's radiotherapy record. Factors included in dose estimates were patient age and size, as well as treatment parameters such as field or implant location, field size, energy of radiation, and radiation dose to the tumor. For each case subject, the bone tumor was located as specifically as possible; this site was used for dose estimation in the case subject and his or her control subjects.

Quantifying Exposure to Chemotherapy

For those patients who received cytotoxic drug therapy, we subdivided the treatment into cycles or courses. We obtained chemotherapy records for individual patients; for each drug received within each cycle, we recorded the dates of start and end of administration, total dose received per unit surface area, and route of administration. For the analysis, we simply summed across cycles the total dose received per unit surface area for each drug received. Because of the relatively small number of case subjects and the heterogeneity of multiple-agent therapy used to treat patients included in the study, it was necessary to consider drugs in terms of exposure groups rather than to analyze single agents. Alkylating agents were the group of drugs used most frequently to treat patients included in the study.

There is uncertainty concerning the relative carcinogenicity of different drugs within a specific exposure group, and it was considered wise to use more than one method of combining exposures. Tucker et al. (*8*) proposed one method of combining exposures to drugs within a particular exposure group. For example, the "alkylating score" of Tucker et al. was obtained by assigning to patients a score of 0, 1, 2, or 3 for each alkylating agent, depending on whether they received none or the lower, middle, or upper third of the distribution of total doses per unit of surface area for that agent, respectively. The alkylating score for each patient was the sum of the scores for each alkylating agent given to that patient. We used the approach of Tucker et al. as well as an approach based on the simple assumption that all drugs within a particular exposure group are equally carcinogenic for a specified amount of drug given per unit of surface area. For ease of communication, we term these two methods of measuring exposure to particular groups of drugs the "scores" and "equivalent mg/m^2" methods, respectively.

Results

Cohort Study

The cohort study consisted of 13 175 patients surviving at least 3 years after diagnosis of childhood cancer in Britain between 1940 and 1983; 55 of these patients developed a second primary bone cancer that was ascertained without any known potential source of bias (*see* "Subjects and Methods" section). The types of second bone cancer developing in patients included in the cohort study were osteosarcoma (45 patients), fibrosarcoma (three patients), chondrosarcoma (two patients), angiosarcoma (one patient), round-cell sarcoma (one patient), sarcoma not otherwise specified (one patient), malignant fibrous histiocytoma (one patient), and Langerhans' cell histiocytosis (one patient). The patient who developed Langerhans' cell histiocytosis after Ewing's sarcoma was excluded from comparisons of observed and expected numbers because Langerhans' cell histiocytosis would not have been regarded as a malignant disease in the past and therefore would not contribute to the expected numbers. However, this patient was included in estimates of cumulative risk as well as in the case–control study.

Table 1 gives the absolute risks and RRs of second primary bone cancer after all types of first cancer, after retinoblastoma, and after all types of first cancer except retinoblastoma. It also provides the corresponding risks after each main specific type of childhood cancer; in particular, risks are provided separately for survivors of heritable and nonheritable retinoblastomas. There was no evidence of a difference between the RRs of second bone cancer for male and female survivors following each category of first tumors given in Table 1.

There was also no evidence of either heterogeneity or a trend in the RRs of second bone cancer across different follow-up intervals beyond 3-year survival (subdivided into 0-4, 5-9, 10-14, 15-19, and ≥20 years) after all first neoplasms, all retinoblastomas, and all first neoplasms except retinoblastoma (Table 2). In Fig. 1, we illustrate the cumulative risks of bone cancer developing after each of these groups of childhood neoplasms.

Within both the cohort and case–control studies, there were eight second primary bone cancers diagnosed after a first primary bone cancer. There were four osteosarcomas and one Langerhans' cell histiocytosis after Ewing's sarcoma, a fibrosarcoma and a malignant fibrous histiocytoma that developed after osteosarcoma, and an osteosarcoma that developed after fibrosarcoma. Comparison of the cumulative risk of second bone cancer developing after Ewing's sarcoma with that after bone cancers other than Ewing's sarcoma revealed evidence of a difference (logrank $P = .074$). Each of the five patients who developed second bone cancer after Ewing's sarcoma had previously received radiotherapy; four of these patients had second cancers that developed inside or on the edge of tissue directly irradiated to treat the Ewing's sarcoma (three of these four patients had also received cyclophosphamide and doxorubicin for their Ewing's sarcoma), and the fifth patient had a second cancer that developed outside such tissue. Of the three patients who developed second primary bone cancer after an initial bone cancer other than Ewing's sarcoma, only one had received radiotherapy and none had received chemotherapy for the initial primary cancer.

Treatment information was missing or incomplete for an indeterminable but substantial fraction of the cohort. Therefore, comparisons based on treatment were confined to the case–control study.

Case–Control Study

Table 3 gives the variation in the RRs of second primary bone cancer in relation to the different types of treatment given for

Table 1. Absolute and relative risks of second bone cancer by type of first cancer: cohort study

First cancer	No. of 3-y survivors	Mean follow-up, y	% with bone cancer by 20 y from 3-y survival (standard error)	Observed No. of second bone cancers (O)	Expected No. of second bone cancers (E)	Relative risk (O/E)*	95% confidence interval on relative risk
Retinoblastoma	948	17.7	3.5 (0.7)	24	0.135	178	114-263
Heritable	439†	17.6	7.2 (1.5)	23	0.060	381	242-571
Nonheritable	504†	17.8	0.3 (0.3)	1	0.074	14	0.3-75
All childhood cancers except retinoblastoma	12 227	10.1	0.5‡ (0.1)	30	1.134	26	18-38
Leukemia	3297	6.5	0.1 (0.1)	1	0.216	5	0.1-26
Hodgkin's disease	1078	9.8	0.5 (0.2)	4	0.105	38	10-98
Non-Hodgkin's lymphoma	598	11.7	0.4 (0.3)	2	0.065	31	4-111
Central nervous system tumors	3320	11.4	0.2 (0.1)	4	0.340	12	3-30
Wilms' tumor	1043	12.8	0.9 (0.6)	3	0.120	25	5-73
Ewing's sarcoma of bone	207	7.1	5.4§ (2.6)	4	0.015	267	72-683
Other malignant bone cancers	303	11.2	2.4 (1.5)	3	0.029	104	21-304
Soft-tissue sarcoma	872	12.3	0.9 (0.4)	5	0.094	53	17-124
Other nonretinoblastoma cancers	1509	12.2	0.4 (0.2)	4	0.152	26	7-67
All childhood cancers	13 175	10.7	0.9‖ (0.1)	54	1.269	43	32-56

*Although not shown, expected values (E) with seven decimal places were used to calculate each O/E value (e.g., 24 [O]/0.1348239 [E] = 178).
†There was insufficient information to classify five retinoblastoma survivors as having heritable or nonheritable retinoblastoma.
‡Based on 31 observed second bone cancers including the Langerhans' cell histiocytosis.
§Based on five observed second bone cancers including the Langerhans' cell histiocytosis.
‖Based on 55 observed second bone cancers including the Langerhans' cell histiocytosis.

Table 2. Observed and expected second primary bone cancers in relation to follow-up

	Years from entry*				
	0-4	5-9	10-14	15-19	≥20
After all childhood cancers					
No. still at risk at start of risk interval	13 175	9128	5836	3400	1951
Observed No. (O)	18	20	9	7	0
Expected No. (E)	0.513	0.398	0.217	0.086	0.056
O/E†	35	50	41	81	0
95% confidence interval	21-55	31-77	19-79	33-167	
After retinoblastoma					
No. still at risk at start of risk interval	948	857	714	538	356
Observed No. (O)	4	9	7	4	0
Expected No. (E)	0.022	0.042	0.038	0.018	0.014
O/E†	182	215	184	216	0
95% confidence interval	50-467	98-408	74-378	59-554	
After all childhood cancers except retinoblastoma					
No. still at risk at start of risk interval	12 227	8271	5122	2862	1595
Observed No. (O)	14	11	2	3	0
Expected No. (E)	0.491	0.356	0.178	0.068	0.042
O/E†	29	31	11	44	0
95% confidence interval	16-48	15-55	1.4-41	9-130	

*Entry = 3-y survival.
†Although not shown, expected values (E) with seven decimal places were used to calculate each O/E value.

childhood cancer. Those patients receiving neither radiotherapy nor chemotherapy were used as the base-line or reference group (i.e., corresponding to an RR of unity) for determining RRs for other groups. There was evidence of heterogeneity (P = .066) in the RRs associated with the different types of treatment. In particular, patients receiving radiotherapy and chemotherapy experienced a risk 3.6 times that experienced by patients receiving neither of these forms of treatment (P = .018). Table 3 is useful in providing a crude overall summary of the relationship between different treatments for childhood cancer and the risk of subsequent bone cancer. However, a more detailed understanding of the relationship between particular elements of therapy and the risk of second bone cancer may be obtained by investigating for evidence of dose–response.

Table 4 summarizes the relationship between the RR of bone cancer and the cumulative dose of radiation that patients received as a consequence of radiotherapy. If we adjusted for other elements of treatment that were related to the RR of bone

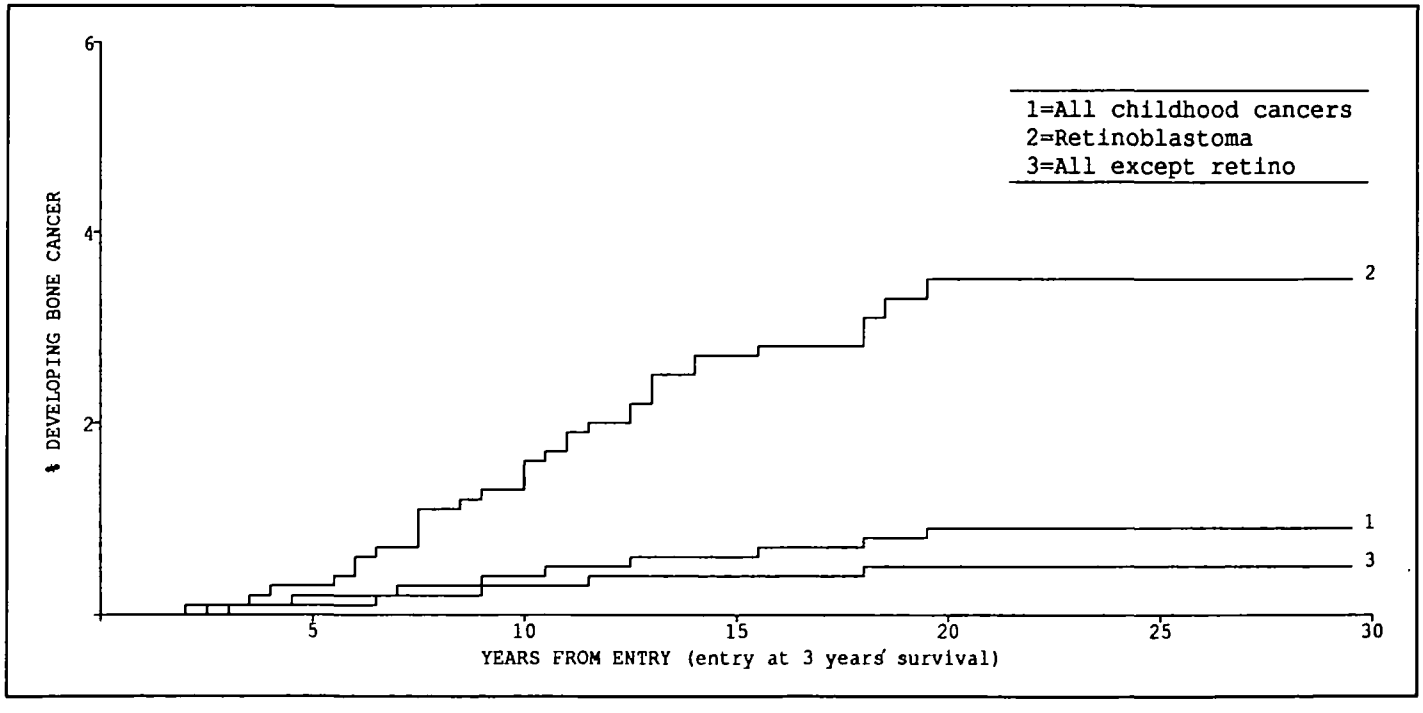

Fig. 1. Cumulative risk of bone cancer among 3-year survivors of childhood cancers. Numbers at risk within different follow-up intervals may be obtained from Table 2. retino = retinoblastoma.

Table 3. Relative risks (RRs) of second primary bone cancer in relation to type of treatment*

Treatment	No. of patients		RR (95% confidence interval); *P* value
	Control	Case	
Information missing	1	0	
Neither radiotherapy nor chemotherapy	50	8	1.0†
Radiotherapy only	106	26	1.7 (0.6-4.7); *P* = .272
Chemotherapy only	11	2	1.6 (0.3-10.0); *P* = .607
Both radiotherapy and chemotherapy	52	23	3.6 (1.2-10.4); *P* = .018
Total	220	59	

*Likelihood ratio test for evidence of heterogeneity in RRs across different treatments; *P* = .066.
†Reference category.

cancer (specifically, alkylating agents—*see below*), there was evidence of heterogeneity (*P*<.001) as well as a linear trend (*P*<.001) in the RRs of bone cancer across the different levels of exposure to radiation. In addition, there was evidence of nonlinearity in the variation of the RRs across different levels of radiation exposure (*P* = .065). Table 4 shows evidence that the RR of bone cancer appears to decrease at the highest levels of exposure to radiation. These results were unaffected by the methodology used to quantify exposure to alkylating agents (i.e., equivalent mg/m^2 or scores). In fact, all results from the case–control study were similar, irrespective of the method used to quantify exposure to alkylating agents; therefore, we report only the results relating to equivalent mg/m^2. A majority of patients receiving alkylating agents received cyclophosphamide (Table 5), including all but two patients treated with alkylating agents for retinoblastoma; therefore, the equivalent mg/m^2 methodology was considered most appropriate for reporting. Despite exhaustive searches, it was unfortunate that 49 (35%) of 140 patients originally diagnosed with retinoblastoma did not have sufficient radiotherapy details available for satisfactory radiation dosimetry to be carried out. This situation arose primarily because of very incomplete information in the clinical notes documenting the implants, or brachytherapy, that these patients had received. Most of these patients with insufficient detail for radiation dosimetry were either case subjects, or control subjects matched to case subjects, in whom the second primary bone cancer arose in the skull bones; therefore, given the proximity to the orbit, they were exposed to a level of radiation that was high but that could not be estimated. An important consequence of this is that it was impossible to estimate the RRs associated with different levels of exposure to radiation for survivors of retinoblastoma. The magnitude of, and variation in, RRs of second primary bone cancer in relation to radiation exposure for patients originally diagnosed with childhood cancer other than retinoblastoma were broadly similar to those seen after all types of childhood cancer.

Of the 29 second bone cancers after retinoblastoma, 12 developed inside or on the edge of tissue directly irradiated to treat the original retinoblastoma, 11 developed outside such tissue, and six developed in patients who had not received

Table 4. Relative risks (RRs) of second primary bone cancer in relation to cumulative dose of radiation

Radiation dose, cGy	No. of patients (median dose, cGy)		RR (95% confidence interval); *P* value	
	Control	Case	Unadjusted	Adjusted* for alkylating agent exposure
Incomplete information	52	9		
0	61	10	1.0†	1.0†
1-999	79 (10)	13 (8)	0.8‡ (0.3-2.4); *P* = .700§	0.7 (0.2-2.2); *P* = .537
1000-2999	15 (1740)	7 (2160)	14.8‡ (1.5-149.8); *P* = .022§	12.4 (0.9-163.3); *P* = .055
3000-4999	7 (3750)	15 (4150)	131.3‡ (9.4-1825.4); *P*<.001§	93.4 (6.8-1285.4); *P*<.001
≥5000	6 (5525)	5 (7570)	59.2‡ (3.5-1009.4); *P* = .005§	64.7 (3.8-1103.4); *P* = .004
Total	220	59		
Likelihood ratio test for evidence of heterogeneity in RRs across different levels of exposure to radiation			*P*<.001	*P*<.001
Likelihood ratio test for evidence of a linear trend in RRs across different levels of exposure to radiation			*P*<.001	*P*<.001
Likelihood ratio test for evidence of nonlinear variation in RRs across different levels of exposure to radiation			*P* = .019	*P* = .065

*Adjusted RRs and their corresponding *P* values were derived in a similar way as unadjusted values, except we also simultaneously fitted a factor for alkylating agent exposure with four levels; *see* Table 6 for a definition of levels of alkylating agent exposure.
†Reference category.
‡Estimates of RR obtained by fitting radiation dose as a factor with five levels.
§Wald-based *P* values and confidence intervals.

Table 5. Numbers of cytotoxic drugs received by patients in the case–control study classified by type of first cancer

	No. of patients with retinoblastoma receiving specified drug (No. of case subjects/ control subjects)	No. of patients with nonretinoblastoma receiving specified drug (No. of case subjects/ control subjects)	Total No. of patients receiving specified drug (No. of case subjects/ control subjects)
Alkylating agents			
Cyclophosphamide	27 (11/16)	37 (9/28)	64 (20/44)
Chlorambucil		6	6 (0/6)
Lomustine		2	2 (0/2)
Mustine		3	3 (1/2)
Nitrogen mustard		2	2 (0/2)
Cisplatin		2	2 (0/2)
Triethylenemelamine	2		2 (1/1)
Dacarbazine		2	2 (0/2)
Procarbazine		9	9 (1/8)
Vinca alkaloids			
Vincristine		40	40 (10/30)
Vinblastine		9	9 (1/8)
Anticancer antibiotics			
Doxorubicin		26	26 (5/21)
Dactinomycin		29	29 (7/22)
Bleomycin		2	2 (0/2)
Mithramycin		1	1 (0/1)
Antimetabolites		26	26 (3/23)
Epipodophyllotoxins		4	4 (0/4)
Asparaginase		4	4 (1/3)

radiotherapy. Of the 30 second bone cancers after childhood cancers other than retinoblastoma, the corresponding numbers were 23, four, and three, respectively. Thus, it appears that prior radiotherapy is involved in the development of most second primary bone cancers, with the exception of those developing after retinoblastoma.

Table 6 gives the variation in RRs of bone cancer in relation to exposure to alkylating agents. After adjustment for exposure to radiation, there was evidence ($P = .080$) of a linear trend in the RR of bone cancer across different levels of exposure to alkylating agents. A one-tailed test (which seems justified given previous work; *see* "Discussion" section) yields $P = .040$. There was no evidence of nonlinear variation in the RRs across different levels of exposure to alkylating agents. Again, the magnitude and pattern of RRs after all types of childhood cancers other than retinoblastoma were broadly similar to those seen after all types of childhood cancer.

There was no evidence of an association between the cumulative dose of vinca alkaloids and the RR of second primary bone cancer, irrespective of the methodology used to quantify exposure to these drugs. We could not satisfactorily assess the relation between cumulative exposure and the risk of second

Table 6. Relative risks (RRs) of second primary bone cancer in relation to exposure to alkylating agents

Total cumulative exposure to alkylating agents, mg/m^2	No. of patients (median dose, mg/m^2)		RR (95% confidence interval); *P* value	
	Control	Case	Unadjusted	Adjusted* for radiation exposure
Incomplete information	7	2		
0	164	37	1.0†	1.0†
1-9999	21 (4653)	6 (2552)	1.5‡ (0.5-4.4); $P = .499$§	1.3 (0.3-6.0); $P = .698$
10 000-19 999	20 (14 313)	7 (16 389)	2.0‡ (0.6-6.2); $P = .251$§	3.0 (0.4-21.7); $P = .278$
≥20 000	8 (24 232)	7 (29 291)	3.9‡ (1.3-11.6); $P = 0.016$§	3.3 (0.8-13.8); $P = .107$
Total	220	59		
Likelihood ratio test for evidence of a linear trend in RRs across different levels of exposure to alkylating agents			$P = .014$	$P = .080$
Likelihood ratio test for evidence of nonlinear variation in RRs across different levels of exposure to alkylating agents			$P = .923$	$P = .904$

*Adjusted RRs and their corresponding *P* values were derived in a similar way as unadjusted values, except we also simultaneously fitted a factor for radiation exposure with five levels; *see* Table 4 for a definition of levels of radiation exposure.

†Reference category.

‡Estimates of RR obtained by fitting alkylating agent exposure as a factor with four levels.

§Wald-based *P* values and confidence intervals.

bone cancer because insufficient numbers of patients were exposed to each of the following groups of drugs: anthracyclines (doxorubicin), dactinomycin, antimetabolites, and epipodophyllotoxins.

Exclusion of the five additional cases of second bone cancer not included in the cohort study did not have any important effect on the case–control study results.

Discussion

Cohort Studies of Bone Cancer After All Types of Childhood Cancer

Our present cohort study indicated that 0.9% of patients surviving at least 3 years after diagnosis of all types of childhood cancer developed bone cancer within 20 years. This was 43 times the expected number of bone cancers and confirms the importance of investigating etiology. From our previous cohort study (*1*), a comparison of the RRs associated with each of the main types of second cancer developing after childhood cancer revealed that the highest RR was associated with second bone cancer, 43 times that expected, almost identical to the estimate from our present study. The Late Effects Study Group (*9*) has reported on a cohort study that again indicated that bone cancer was associated with the highest RR of any specific type of second cancer, 133 times that expected; they (*10*) also reported that the cumulative risk by 18 years from 2-year survival was 2.8%. A large Nordic population-based cohort study (*11*) indicated that 7.5 times the expected number of second bone cancers were observed. A cohort study from the Institute Gustave Roussy, Paris (*12*), reported a cumulative risk of bone cancer of 0.9% at 25 years from diagnosis of childhood cancer, which corresponded to 77 times the expected number of bone cancers. From the cohort study of the Late Effects Study Group (*10*), there was evidence that the RR of bone cancer increased with increased follow-up. The present cohort study, in common with the Nordic cohort study (*11*), provided no evidence of systematic variation in the RR of bone cancer with increased follow-up. There was no evidence of a difference between the RR of second bone cancer according to sex of survivor from our study or that of the Late Effects Study Group.

Cohort Studies of Bone Cancer After Heritable Retinoblastoma

In our previous cohort study of heritable retinoblastomas (*1*), the estimated cumulative risk of second bone cancer by 20 years from 3-year survival was 6.0%, corresponding to 415 times the expected number of bone cancers, based on a mean follow-up period of 13.7 years. The corresponding values from the present study were 7.2% and 381 times expected, based on a mean follow-up period of 17.6 years. A review of the literature (*13*) identified eight studies with 50 or more retinoblastoma patients who were followed for second cancers; the cumulative risk of second cancer within 20 years of bilateral or heritable retinoblastoma clustered around 10%, and the predominant types of tumors observed were bone and soft-tissue sarcomas. In addition to reviewing the literature, these authors (*13*) also produced the first report on the largest cohort of retinoblastoma patients to have been established. Their initial analysis was confined to mortality and included evidence of an excess (threefold expected) of deaths from second cancers among 684 patients with unilateral retinoblastoma, based on five observed deaths. However, as these authors acknowledge (*13*), a proportion of unilateral patients have heritable disease (*14*). In our study of unilaterally affected patients with no family history of retinoblastoma, there was no evidence of an excess of bone cancer. The authors of this same study (*13*) reported that the excess of deaths from second cancers was greater among females than among males, although they indicated that the difference was accounted for mainly by cancers other than those of bone and connective tissue. In our study, there was no evidence of the excess of second bone cancers differing between males and females.

Cohort Studies of Bone Cancer After Ewing's Sarcoma

A review of the literature (*15*) identified a number of small series (<50 patients) of Ewing's sarcoma survivors who were followed up to investigate the occurrence of second cancer. There were only two larger series. One was part of the cohort study of the Late Effects Study Group (*10*), who reported a cumulative risk of 22% of developing bone cancer by 20 years from diagnosis of Ewing's sarcoma; this risk was estimated to be 649 times the expected number of bone cancers. The other larger series (*15*), the only previous population-based cohort study, indicated an observed risk of bone cancer 100 times expected. In our study, 5% of 3-year survivors of Ewing's sarcoma developed second bone cancer within 20 years, and this was 267 times the expected risk. Both from our study and the Late Effects Study Group cohort study (*10*), it appears that alkylating agents and, more importantly, relatively high doses of radiation were involved in the development of most of the second primary bone cancers that occurred after Ewing's sarcoma. However, since few patients survived Ewing's sarcoma in the absence of at least one of these therapies, inherent genetic predisposition cannot be reliably estimated at present.

Case–Control Studies of Etiology of Second Bone Cancer

There has been only one previous case–control study concerned specifically with the etiology of second bone cancer after childhood cancer (*10*). The conclusions from that investigation by the Late Effects Study Group were broadly similar to those from our case–control study. In both studies, the risk of second bone cancer increased substantially with the increased exposure to radiation that bone had received during radiotherapy for the initial childhood cancer. There was also agreement concerning evidence that the risk of bone cancer declined at the highest levels of exposure, and it is possible that the phenomenon of "cell killing" may underlie this observation (*10*). The estimates of RR associated with specific levels of radiation exposure appear to be higher in our study than in the investigation conducted by the Late Effects Study Group. Both studies, however, were small, and no firm conclusion of a difference is possible.

There was firm agreement from both studies that children whose bone was exposed to less than 10 Gy had, at worst, only a small increased risk of bone cancer and possibly no increased risk—taking the upper 95% confidence bound as the worst case.

Both studies showed evidence of an association between exposure to alkylating agents and a subsequent risk of bone cancer; this association was independent of radiation exposure. There was also agreement that this association was considerably weaker than that with radiation exposure. In our case–control study, the association between exposure to alkylating agents, mostly cyclophosphamide, and the risk of second bone cancer appeared to be linear.

The case–control study conducted by the Late Effects Study Group produced values of RR of second bone cancer for specified levels of radiation exposure that were similar for children originally diagnosed with retinoblastoma and other types of childhood cancer. Unfortunately, we were unable to investigate this suggested similarity of RRs because of the incompleteness of information relating to radioactive implants used to treat retinoblastoma patients.

There were insufficient numbers of patients exposed to orthovoltage radiotherapy in our study to assess satisfactorily the extent to which this form of radiation may be associated with an increased risk of second bone cancer. There was no evidence in the study by the Late Effects Study Group to indicate that orthovoltage radiotherapy was associated with an enhanced risk of second bone cancer.

Clinical Implications

In conclusion, it is important to assess the clinical implications of our mainly population-based studies. With regard to counseling survivors of childhood cancer and their families, there are grounds for reassurance for the majority of survivors. The percentage of 3-year survivors developing bone cancer within the subsequent 20 years did not exceed 0.9%, except for patients diagnosed with heritable retinoblastoma, Ewing's sarcoma, and other malignant bone tumors; for those patients, the corresponding risks were 7.2%, 5.4%, and 2.4%, respectively. The higher risks for bone cancer following these three rare types of childhood cancer, which accounted for only 11% of the cohort population, provide a rational basis for closer surveillance of these particular survivors in long-term follow-up clinics. However, the risks among patients with these rare cancers treated more recently may be different as a result of changes in therapeutic practice. The evidence of a greatly increased risk of second bone cancer with increased exposure to radiation has important implications for those deciding the composition of future treatment protocols. The present study provides information relevant to the likely risk of bone cancer after a specified level of exposure to radiation and should help in making decisions as to whether to include radiotherapy in a particular protocol. Radiation doses of less than 10 Gy appear to carry, at worst, only a small increased risk of subsequent bone cancer. If the use of radiotherapy is considered to provide the best option after balancing the likelihood of care and the likely adverse effects of treatment, then radiation exposure should be as sharply focused as possible with the decline in dose with distance from the tumor being maximized. In contrast to radiotherapy given at doses of 10 Gy or more, regimens of chemotherapy to which the present cohort was exposed do not appear to be as important in the development of subsequent bone cancer. However, there were insufficient numbers of patients exposed to anthracyclines, epipodophyllotoxins, and some other types of drugs to assess satisfactorily possible relations between cumulative exposure and the risk of subsequent bone cancer. The tendency for an increased risk of bone cancer with increased exposure to alkylating agents taken together with the known leukemogenicity of these drugs indicates that doses should be kept as low as possible without compromising the prospects of cure. Finally, although there is some knowledge of the extent to which heritable retinoblastoma, in the absence of radiotherapy or chemotherapy, increases the risk of second bone cancer, very little is known about the possible involvement of genetic predisposition in the development of bone cancer after other types of childhood cancer. We are carrying out a study to investigate this issue.

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Notes

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