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ORIGINAL REPORT

Malignant Breast Tumors After Radiotherapy for a First Cancer During Childhood

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A B S T R A C T

Purpose
To assess the specific role of treatment and type of first cancer (FC) in the risk of long-term subsequent breast cancer (BC) among childhood cancer survivors.

Patients and Methods
In a cohort of 1,814 3-year female survivors treated between 1946 and 1986 in eight French and English centers, data on chemotherapy and radiotherapy were collected. Individual estimation of radiation dose to each breast was performed for the 1,258 patients treated by external radiotherapy; mean dose to breast was 5.06 Gy (range, 0.0 to 88.0 Gy) delivered in 20 fractions (mean).

Results
Mean follow-up was 16 years; 16 patients developed a clinical BC, 13 after radiotherapy. The cumulative incidence of BC was 2.8% (95% CI, 1.0% to 4.5%) 30 years after the FC and 5.1% (95% CI, 2.1% to 8.2%) at the age of 40 years. The annual excess incidence increased as age increased, whereas the standardized incidence ratio decreased. On average, each Gray unit received by any breast increased the excess relative risk of BC by 0.13 ($<$ 0.0 to 0.75). After stratification on castration and attained age, and adjusting for radiation dose, FC type, and chemotherapy, a higher risk of a subsequent BC was associated with Hodgkin's disease (relative risk, 7.0; 95% CI, 1.4 to 30.9).

Conclusion
The reported high risk of BC after childhood Hodgkin's disease treatment seems to be due not only to a higher radiation dose to the breasts, but also to a specific susceptibility.

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INTRODUCTION

Together with the thyroid and bone marrow, breast tissue is known to be one of the most radiosensitive organs of the human body,[1] especially in children. With notable improvement in therapies, children treated for a cancer have become long-term survivors, 70% of them survive at least 5 years,[2] and 94% survive at least 5 years among pediatric Hodgkin's patients.[3] Consequently, patients exposed to these therapies have considerable opportunity to develop late sequelae. Among these, the occurrence of a

second primary tumor in childhood survivors has been particularly analyzed. Since the first publications[4-6] on the risk of developing a radiation-induced cancer after treatment for a childhood cancer, many articles have dealt with the risk of secondary breast cancer (BC) after all types of childhood cancer[7-10]; others have considered the risk specifically after Hodgkin's disease.[11-17] In these studies, the estimates of the standardized incidence ratio (SIR) range from 1.4 to 75 when the first cancer (FC) occurred before the age of 20 years. However, none of the articles analyzed the risk of a secondary

197

breast malignancy according to the estimated dose received by the breasts during radiotherapy.

We report here the results of a subcohort study designed to evaluate the long-term risk of a subsequent BC after fractionated high doses of external-beam radiotherapy. Radiation doses to each breast were separately estimated for every child with specialized software. An attempt was made to assess the role of the FC type in determining the risk of subsequent BC, controlling for treatment and particularly for the radiation dose to the breasts.

PATIENTS AND METHODS

Patients

A retrospective cohort of 4,400 children treated in eight large cancer treatment centers in France and the United Kingdom was constructed from 3-year survivors of all types of cancer (with the exception of leukemia) diagnosed before the age of 17 and before 1986. The study was initiated in the Gustave Roussy Institute (Villejuif, France), where no childhood leukemias are treated. All patients fulfilling these criteria in each participating center were included, except patients treated for retinoblastoma in the United Kingdom centers. A description of the initial cohort has been published[18-21] and general characteristics of this subcohort are described in Table 1.

From these 4,400 children, only the female patients were selected because among males, no BC was observed. One hundred fifty-one patients were excluded because they had received brachytherapy or information on radiation doses was not available. Among the 1,814 remaining women, 1,258 had received external-beam radiotherapy. The end of the period at risk was the date of the last contact, death, or the last time the patient was known to be alive; for those with a BC, this was the date of the diagnosis. The follow-up data were obtained using registries for the English patients or, for the French patients, from hospital clinical files actualized by physicians who performed an active follow-up by writing to patients and linking their database with the national death certificate data. Twelve percent of the cohort (n = 210) was lost to follow-up.

Information on treatments was abstracted from the clinical notes and radiotherapy files in the participating centers and the diagnoses of the first and second malignant neoplasms were histologically confirmed. The International Classification of the Diseases for Oncology was used to classify the tumors.[22]

Radiation Dosimetry

The radiation doses were estimated in the middle of the right and left nipples for each of the 1,258 patients treated with ionizing radiation. The dose to 149 other anatomic sites including the thymus, spleen, gonads, and 91 skeletal sites was also estimated. A computer program called Dos_EG, described elsewhere,[23,24] was developed for these calculations.

In the estimation, all treatments delivered on the same day were considered as one fraction. This definition is considered acceptable, given that there was no hyperfractionated treatment in the cohort.

Among the 1,258 patients who received external radiotherapy, the mean number of fractions was 20 and the average radiation dose for the 1,258 patients was 5.06 Gy for a breast (Table 2). Figure 1 shows the distribution of the radiation dose to breast in Grays (median, 0.85 Gy). Because of variations in the radiotherapy instruments and in the treatment modalities of the FC, the mean dose to the breast varied according to the calendar period: 3.5 Gy before 1960, 4.4 Gy during the 1960s, 6.3 Gy during the 1970s, and 3.6 Gy during 1980 to 1985.

Measurement of Chemotherapy

Chemotherapy doses were not available for four of the 1,167 patients who received chemotherapy: 360 had chemotherapy alone with (n = 326) or without (n = 34) surgery. Drugs were grouped into five categories according to their known mechanism of action in the cell: electrophilic agents, spindle inhibitors, nucleotide synthesis inhibitors (NSI), topoisomerase II inhibitors, and other compounds. To quantify the total amount of each drug category administered, the dose of each cytotoxic agent was

	No. of Patients	Year of First Cancer Treatment				Age at First Cancer (years)				Follow-Up (years)				Type of First Cancer Treatment					
														RT, No CT		CT, No RT		RT and CT	
First Cancer		Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range	No. of Patients	%	No. of Patients	%	No. of Patients	%
Wilms' tumor	373	1973	8	1974	1950-1985	3	3	3	0-15	17	8	16	3-39	42	11	86	23	235	63
Neuroblastoma	276	1974	8	1976	1951-1986	2	3	1	0-16	16	8	14	3-38	50	18	88	32	102	37
Hodgkin's disease	123	1976	7	1978	1954-1985	11	4	12	2-16	14	6	13	3-34	28	23	9	7	86	70
NHL	127	1976	7	1978	1951-1985	8	4	8	0-16	14	7	12	3-41	15	12	33	26	78	61
Soft tissue sarcoma	209	1974	8	1977	1949-1985	6	5	5	0-15	15	9	13	3-40	32	15	50	24	92	44
Bone sarcoma	95	1977	7	1978	1950-1986	10	3	11	1-16	11	7	9	3-35	10	11	30	32	50	53
Brain tumor	352	1972	9	1973	1947-1985	7	4	6	0-16	17	9	15	3-43	213	61	3	0.9	73	21
Gonadal tumor	69	1974	9	1976	1946-1984	9	4	11	0-16	17	9	15	6-46	23	33	26	38	16	23
Thyroid carcinoma	24	1969	9	1969	1946-1984	11	3	11	2-15	22	9	22	8-45	5	21	1	4	1	4
Retinoblastoma	59	1978	6	1979	1956-1985	1	2	1	0-7	12	7	11	3-36	11	19	5	8	35	59
Other first cancers	107	1976	6	1978	1954-1985	6	8	6	0-15	13	7	11	3-35	22	21	29	27	39	36
Total	1,814	1974	8	1976	1946-1986	6	4	5	0-16	16	8	14	3-46	451	25	360	20	807	45

Table 1. General Characteristics of the 1,814 3-Year Female Survivors of a First Cancer in Childhood

Abbreviations: SD, standard deviation; RT, radiotherapy; CT, chemotherapy; NHL, non-Hodgkin's lymphoma.

Table 2. Radiation Dose Received by Breasts in 1,258 Females According to the Type of Instrument																	
Type of Instrument	No. of Patients	No. of Person-Years	Period of Treatment				Duration of Course (days)				No. of Fractions			
			Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range
Low-energy x-rays	198	5,278	1960	6	1961	1947-1978	45	28	38	0-153	20	9	20	0-45
Cobalt-60	805	11,638	1976	6	1976	1952-1986	39	23	35	0-198	19	8	20	1-57
High-energy x-rays	277	3,747	1977	7	1979	1960-1987	40	21	39	1-119	20	9	20	1-46
Electrons	139	1,800	1976	5	1977	1964-1985	32	15	30	0-105	15	7	15	1-34
All types*	1,258	20,323	1974	8	1975	1947-1987	40	23	36	0-198	20	9	20	0-57

			Dose (Gy) to:											
			Left Breast				Right Breast				Both Breasts			
Type of Instrument	No. of Patients	No. of Person-Years	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range
Low-energy x-rays	198	5,278	4.33	9.5	0.99	0-52.5	3.59	8.0	1.04	0-57.9	3.97	8.1	1.05	0-52.3
Cobalt-60	805	11,638	5.27	9.0	0.95	0-78.6	5.60	9.6	0.93	0-78.6	5.44	8.8	1.02	0-78.6
High-energy x-rays	277	3,747	5.22	8.6	1.15	0-53.4	5.15	9.5	0.95	0-87.9	5.19	8.3	1.16	0-48.3
Electrons	139	1,800	3.89	7	0.0	0-22.5	3.07	6.2	0.0	0-21.9	3.46	6.4	0.003	0-21.5
All types*	1,258	20,323	5.04	8.9	0.89	0-78.6	5.09	93	0.84	0-88.0	5.06	8.5	0.96	0-78.6

Abbreviation: SD, standard deviation.
*161 children were treated with more than one type of instrument.

converted into moles per square meter, rather than into milligrams per square meter. A detailed description of the chemotherapy administered to cohort patients has been published.[18] The median doses for each drug category and main drugs administered to the children were calculated (Web Table 1).
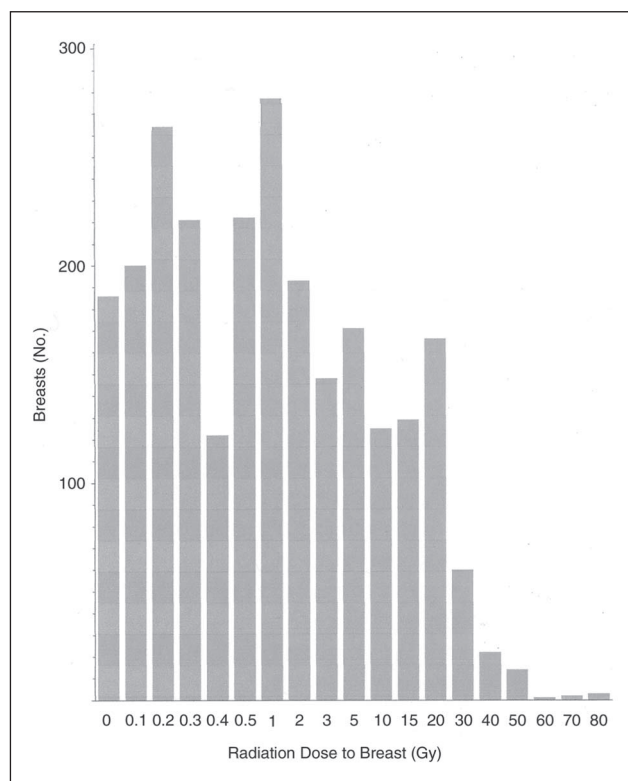
Fig 1. Distribution of the radiation dose to breasts by breast for the 1,258 female childhood cancer survivors treated by external-beam radiotherapy.

Statistical Methods

For analysis, the follow-up ended on January 1, 1993, for patients treated in the French centers and January 1, 1991, for those treated in United Kingdom. We used the competing method to estimate the cumulative incidence of breast tumors.[25] The expected numbers of BC (number of tumors) per 5-year calendar periods and per 5-year age classes were calculated from 1975 to 1995 Francim data (based on the French cancer registries) for the French patients[26] and on the England and Wales cancer registry data for the United Kingdom patients.[27] The SIR was defined as the ratio between the observed and expected number of breast tumors. The relative risk (RR) was defined in a similar manner: the expected number of breast tumors was estimated from a given reference category within the cohort; an individual breast was used as the statistical unit.

Both the SIR and RR of BC were modeled assuming that the number of BC (number of tumors) followed Poisson distribution. Statistical tests were carried out using deviance of nested models.[28]

The basic model for calculating the excess relative risk (ERR) of BC as a function of the radiation dose was that generally used in radiation epidemiology[29]: $ERR = Cst \ (\alpha \cdot dose + \beta \cdot dose^2) \ [exp(-\gamma \ dose)]$, where the constant (Cst) summarizes the role of dichotomous variables such as having had a given type of FC (yes or no) or chemotherapy; the negative exponential term models the cell sterilization for high doses.

We used an empirical approach to investigate the role of dose fractionation and introduced a threshold number of fractions to test the similarity of the coefficients for the doses delivered with a high ($dose_1$) and low ($dose_2$) number of fractions in a linear model, using the following equation: $ERR = Cst \ (\alpha_2 \cdot dose_2 + \alpha_1 \cdot dose_1)$.

The simple linear model of the risk as a function of the total dose is nested in this model: $ERR = Cst \ [\alpha_2(dose - dose_1) + \alpha_1 \cdot dose_1] = Cst \ (\alpha_2 \cdot dose - \alpha_2 \cdot dose_1 + \alpha_1 \cdot dose_1) = Cst \ [\alpha_2 \cdot dose + (\alpha_1 - \alpha_2) \ dose_1]$.

The effect of the dose rate was considered significant with this model if the decrease in deviance between model 2 fractionated dose and model 1 total dose limited to the linear term was greater than 3.84 (ie, the value of χ^2_1 for $P = .05$). The standard

deviation of the coefficient for doses delivered with fewer than 20 fractions (ie, $\alpha_1 - \alpha_2$) was estimated as follows: standard deviation $(\alpha_1 - \alpha_2) = \sqrt{[\text{var}(\alpha_1) + \text{var}(\alpha_2) + 2 \cdot \text{cov}(\alpha_1, \alpha_2)]}$.

These analyses were done using AMFIT Software.[29] The 95% CIs were estimated for parameters using the maximum likelihood method.[30]

RESULTS

The overall average follow-up after any FC was 16 years (range, 3 to 46 years), varying according to the type of FC (Table 1). A total of 457 persons (25%) were followed-up for 20 years or more, and 344 of them had received radiotherapy; 252 patients (14%) died during the follow-up. Mean age at diagnosis of the FC was 6 years (median, 5 years); 28% of the cohort was 2 years old or younger. The types of treatments administered to the patients are listed in Table 1.

During the follow-up, 16 patients had developed a clinical BC (0.95 expected), excluding carcinoma in situ: 11 cancers arose in the left breast and three in the right; in two patients, this information was not available. The histological type was invasive ductal carcinoma in 12 patients (nine of them had a grade II or III according to the Scarff, Bloom, and Richardson scale, a histoprognostic grading system of invasive breast tumors based on the degree of differentiation of the tumor, mitotic index, and anisonucleosis, grade I to III, where I is a good prognosis), malignant phyllodes

tumor in three patients, and tumor of an unknown type in one patient. Among the carcinomas, six patients presented with axillary involvement.

Thirteen patients developed a BC after radiotherapy, either with or without chemotherapy, with a follow-up between 13 and 37 years. One patient developed a BC (at 9 years of follow-up) for an FC treated by surgery alone; two patients developed a BC after chemotherapy (follow-up, 18 and 19 years, respectively). All but one cancer occurred in patients with a dose less than 20 Gy to the breast containing the tumor. The treatment characteristics of the children who developed a secondary breast tumor are listed in Table 3.

The cumulative incidence of BC after a 30-year follow-up was 2.8% (95% CI, 1.0% to 4.5%) and 10.7% (95% CI, 1.4% to 19.9%) after 40 years. Figure 2 depicts the cumulative incidence by attained age for the entire cohort. The annual incidence of BC increased dramatically to reach 537×10^{-5} person years (95% CI, 269 to 942) when women were 30 to 39 years old. The annual excess incidence increased considerably to 515×10^{-5} person years (95% CI, 246 to 919) for those aged 30 to 39 years, but the SIR declines from 185 (95% CI, 31 to 573) in the 10- to 19-year age group to 23.2 (95% CI, 12 to 41) for the 30- to 39-year age group (Table 4).

A total of 222 patients underwent a surgical or radiologic castration. None of them developed a secondary BC later ($P = .1$).

Radiotherapy, measured as ever versus never, was not associated with an increased risk of BC (RR, 1.3; 95% CI, 0.4

First Cancer Type	First Cancer Treatment					Radiation Dose at the Breast (Gy)		Breast Cancer Diagnosis	
	Year	Age (months)	Country	Chemotherapy	Radiotherapy	Right*	Left*	Year	Age (years)
Wilms' tumor	1956	177	France	0	Low-energy x-rays	0.64	**1.30**	1992	51
Wilms' tumor	1958	23	France	0	Low-energy x-rays	**57.94**	45.82	1992	35
Wilms' tumor	1967	42	France	Act	Linac photon	**0.63**	1.87	1985	21
Neuroblastoma	1954	19	France	0	Low-energy x-rays	0.59	**19.39**	1991	38
Neuroblastoma	1956	7	France	0	Low-energy x-rays	1.02	**0.99**	1983	27
Neuroblastoma	1961	29	France	0	Low-energy x-rays	23.72	**2.07**	1975	16
Hodgkin's disease	1961	78	France	Vlb	^{60}Co	5.33	**5.34**	1989	34
Hodgkin's disease	1966	172	France	Cary, Pcb, Vcr	^{60}Co	13.32	**8.34**	1984	32
Hodgkin's disease	1968	146	France	Cary, Clb, Pcb, Vlb, Vcr	^{60}Co	**12.37**	9.83	1990	33
Hodgkin's disease	1974	172	France	0	Linac photon	10.26	**16.22**	1990	30
Non-Hodgkin's lymphoma	1960	170	Great Britain	0	Low-energy x-rays	0.90	0.46	1977	31
Soft tissue sarcoma	1969	150	France	Act	Linac photon	1.79	**0.75**	1990	33
Soft tissue sarcoma	1958	35	Great Britain	0	0	—	0.00	1968	12
Brain	1964	123	France	Mtx	Low-energy x-rays	0.83	**0.49**	1991	37
Gonads	1969	134	France	Act, Cpm, Mtx, Vcr	0	—	**0.00**	1988	30
Others	1966	69	France	Doop	0	—	**0.00**	1984	24

Abbreviations: Act, actinomycin; Cary, caryolysine; Clb, chlorambucil; Cpm, cyclophosphamide; Mtx, methotrexate; Pcb, procarbazine; Vlb, vinblastine; Vcr, vincristine; Doop, mitotane.
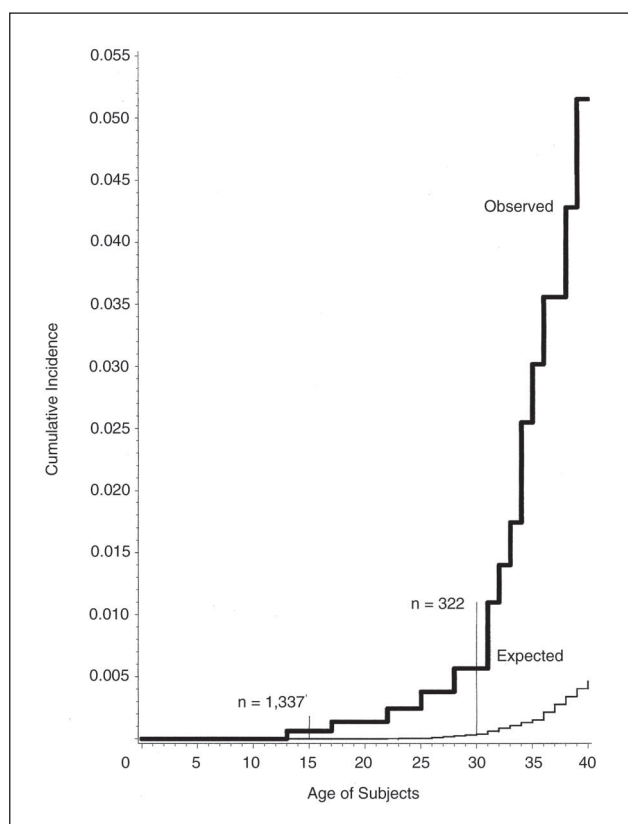*Breast cancer laterality is shown in bold.

Fig 2. True cumulative incidence of breast tumors according to the patients' attained age.

to 5.9). The ERR of occurrence of a BC was found to be nonsignificantly linearly linked to the total dose of radiation (ERR/Gy, 0.13; 95% CI, < 0.0 to 0.75; $P = .06$) received by the breast, after adjustment for castration, chemotherapy, and FC type. When model 2 with a threshold at 20 fractions was used, a significant effect of the dose fractionation was observed ($P = .05$): the radiation dose delivered in less than 20 fractions led to a higher risk (ERR/Gy = 0.12; 95% CI, −0.14 to 0.38) than when it was administered in 20 fractions or more (ERR/Gy = −0.02; 95% CI, −0.06 to 0.03).

Overall, chemotherapy was associated with a nearly significant RR of 2.7 (95% CI, 0.9 to 7.6; $P = .07$) when stratified on castration and attained age, and adjusted for radiation dose and FC type compared with no chemotherapy (Web Table 2). When we examined the role of the different classes of chemotherapeutic agents, we observed that electrophilic agents, spindle inhibitors, and topoisomerase II inhibitors had no significant effect on the risk of developing a BC in this cohort (Web Table 2). When stratification on castration and attained age plus adjustment on other drug categories, FC type, age at FC, and radiation dose to the breast were made, the RR for NSI (ie, for methotrexate) was found to be 4.6 (95% CI, 0.7 to 19.9; Table 5). Only 62 patients received mechlorethamine, vincristine, procarbazine, and prednisone, of whom two developed a BC. There was no evidence for a role of the number of moles per square meter for any of the drug categories or of the total number of moles per square meter administered.

Four of the 16 BCs occurred among the 123 patients treated for Hodgkin's disease (SIR, 71; 95% CI, 22 to 164), three occurred among the 276 treated for a neuroblastoma (SIR, 47; 95% CI, 12 to 122), three occurred among the 373 treated for a Wilms' tumor (SIR, 28; 95% CI, 7.0 to 73), two occurred among the 209 patients treated for soft tissue sarcoma (SIR, 16; 95% CI, 2.7 to 51), and one in each of the following FC types: brain, gonad, and non-Hodgkin's lymphoma (Table 3). A heterogeneity was evidenced in SIR between FC ($P = .02$).

After Hodgkin's disease, none of the four BCs occurred before 16 years after first diagnosis, and breasts of these patients received a mean dose of 11.84 Gy, whereas for all other patients, the mean dose was 4.39 Gy. The latent periods after neuroblastoma and Wilms' tumors were, respectively, 13 to 37 years and 18 to 36 years, and the mean doses received by the breasts were 5.85 Gy (v 4.95 Gy when excluding neuroblastoma patients) and 7.04 Gy (v 4.51 Gy for non-Wilms' tumor patients). When patients treated for these three types of malignancies were excluded, the mean dose administered to the breasts decreased to 3.06 Gy. When age at FC, attained age,

		Breast Cancers						
Attained Age (years)	Person-Years	Breast Cancer (No.)	Annual Incidence × 10⁻⁵	95% CI	Annual Excess Incidence × 10⁻⁵	95% CI	Standardized Incidence Ratio*	95% CI
3-9	5,582	0	—	—	—	—	—	—
10-19	11,229	2	18	3 to 55	18	3 to 55	185.0	30.8 to 572.6
20-29	6,272	3	47	12 to 124	47	9 to 123	18.8	4.7 to 48.9
30-39	1,862	10	537	269 to 942	515	246 to 919	23.2	11.6 to 40.6
≥ 40	308	1	325	186 to 1,431	208	68 to 1,314	2.9	0.2 to 12.8
Total	25,253	16	63	37 to 100	48	23 to 83	16.9	9.9 to 26.6

Table 4. Occurrence of Breast Cancers According to Attained Age in a Cohort of Women Treated for a First Pediatric Cancer

*Compared with the general population.

Table 5. Risk Factors for Breast Cancer in the Cohort of Women Treated for a First Pediatric Cancer

Risk Factor	Relative Risk of Breast Cancer*	95% CI	P†
First cancer type			
Hodgkin disease v others	7.0	1.4 to 30.9	.01
Neuroblastoma v others	2.9	0.6 to 11.6	.15
Nucleotide synthesis inhibitors			
Yes v no	4.6	0.6 to 19.9	.06
Age at first cancer, years			
Per year of age at first cancer	0.9	0.7 to 1.0	.10
Radiation dose to breasts, Gy			
> 0 to < 1	1.3	0.3 to 6.3	
1 to < 10	1.5	0.3 to 8.1	.06
10 to < 20	3.7	0.6 to 24.2	
20 or more	2.5	0.1 to 22.1	

*Stratified on attained age and ocastration (radiotherapic or surgical), adjusted on the other variables.
†Test for trend.

castration, radiation dose to the breast (in Grays), and chemotherapy as yes versus no were taken into account, the risk for developing a BC was higher in any breast of patients previously treated for Hodgkin's disease (RR, 7.01; 95% CI, 1.4 to 30.9) or, nonsignificantly, for neuroblastoma (RR, 2.9; 95% CI, 0.6 to 11.6) than in those treated for any other FC combined (Table 5).

Of the 264 patients who underwent a surgical or radiologic splenectomy (> 20 Gy to the spleen), three developed a BC. No evidence for a spontaneous higher risk of BC (RR, 1.8; 95% CI, 0.6 to 5.5) was found. Similarly, a modification of the risk of BC was not evidenced among the 242 patients (of whom three had a secondary BC) who had received a mean dose to active bone marrow exceeding 10 Gy (RR, 1.4; 95% CI, 0.3 to 5.9). Age at FC does not affect the risk of BC, whereas risk of BC increased with increasing doses to the breasts up to 20 Gy (P = .06; Table 5).

DISCUSSION

On the basis of the analysis of a cohort of 1,814 3-year survivors of a childhood cancer, the risk for developing a BC was found to be nonsignificantly linearly linked to the total radiation dose received by the breasts, was possibly increased by chemotherapy, and was higher for children treated for Hodgkin's disease or possibly for neuroblastoma. For the same total dose delivered to the breast, the risk seemed to be higher for children treated with a lower number of fractions.

The women lost to follow-up (n = 210) were not different from the others in terms of the date of the diagnosis (1974 on average). They did, however, receive fewer moles of drugs per square meter (13 v 30 moles/m²; P = .04), but the average radiation dose to the breasts was

the same (3.4 v 3.4 Gy). Given that the cumulative dose of chemotherapy can be linked to relapses, the difference in the amount of chemotherapy administered appears to indicate that we were more likely to lose to follow-up patients who did not experience relapse (ie, patients with less aggressive therapy), and this could lead to an overestimation of the long-term incidence of BC. However, the likelihood of overestimation is probably limited given the low rate of patients lost to follow-up in our cohort (12%).

The first limitation is the relatively small size of our cohort, which included 1,814 patients and only 16 BCs. This allows us to satisfactorily only risk factors associated with substantially increased risks. A possible bias was the heightened medical surveillance of women who survived a childhood cancer, leading to a greater likelihood of detecting other diseases, including second malignancies. Because there is no French national cancer registry, the follow-up of cohorts such as ours must be active, which means that this bias could never be eliminated. Furthermore, screening for BC is likely to increase the observed incidence of breast tumors.[31] In our opinion, this potential bias is low because no routine BC screening program existed during our study follow-up period, and the size and extent of the 16 BCs diagnosed in our cohort were more aggressive (Scarff, Bloom, and Richardson scale grade II or III) than those usually found during screening for prevention.

In our cohort, the cumulative incidence of BC at 40 years of age was 5.1% (95% CI, 2.1 to 8.2) corresponding to 16.9-fold the rate expected (95% CI, 9.9 to 26.6) in the general population. Although no patients with leukemia are included in our cohort, this global SIR is within the range observed for BC in hospital-based studies,[4,10,32] but higher than that observed in registry-based cohorts.[6,8] However, an overall comparison between BC SIR observed in cohorts is very difficult to interpret because it is highly dependent on the duration of follow-up, the average attained age, and the expected BC incidence, which is unstable before 45 years of age because it is based on small numbers, and because of differences in the FC types between cohorts.

For the SIR with attained age, we observed a decrease from 185 (95% CI, 31 to 573) in the 10- to 19-year age group to 23.2 (95% CI, 12 to 41) in the 30- to 39-year age group. One BC (0.35 expected) was observed in our cohort after 40 years of age, but only 60 women had reached this age during the follow-up period. Variation in BC SIR with attained age or time since FC was examined in detail in only one study, which obtained similar results.[8] Because of the strong increase in expected BC incidence with attained age, this reduction in SIR nevertheless corresponds to a substantial increase in excess incidence with attained age, at least during the first four decades.[8]

We confirm previously reported[8,11-13,16,17] higher BC incidence after Hodgkin's disease (RR, 7.01 compared with BC risk after other FC) and demonstrate, for the first

time, that this excess is not due to higher radiation doses and/or chemotherapy.

In addition, we found that survivors of childhood neuroblastoma could be at a greater risk (RR, 2.9) of developing a BC. To date, this result has not been reported in any other study. Although Wilms' tumor was the most frequent FC in our cohort (n = 373), it was not associated with an increased BC risk.[10,33] However, one BC was observed among Hodgkin's disease and neuroblastoma patients who had no radiotherapy or a low dose to breasts (Web Table 3). Thus, the observed increased risks of BC after such FC suggest either a specific susceptibility for developing a BC or a particular susceptibility to radiation and/or chemotherapy, or both.

Although the number of patients treated by radiotherapy in our study is relatively limited (n = 1,258), the range of the doses available for the investigation of a dose-response relationship was wide (from 0.0015 to 88.0 Gy received by the breast): 514 breasts received less than 0.2 Gy and 197 received more than 20 Gy. Radiotherapy was not found to be a risk factor for BC occurrence when considered as a dichotomous variable. Nevertheless, this risk was found to be nonsignificantly linearly linked to the radiation dose received by any breast with an ERR/Gy of 0.13 (95% CI, < 0.0 to 0.75). This result confirms established effects of radiation exposure[1,34] and has been described in many studies. To our knowledge, no other study using individual radiation dose estimation to breasts has provided an estimate of a coefficient for BC occurrence after radiotherapy treatment for a malignancy. Our result is consistent with that observed after radiotherapy for benign diseases in childhood: hemangioma,[35-37] tinea capitis,[38] and multiple diagnosis x-rays.[39,40] On the contrary, it is lower than that described for the Hiroshima-Nagasaki survivors.[41,42]

The higher risk observed for the same total dose to a breast delivered in less than 20 fractions (ERR/Gy = 0.12) compared with delivery in more fractions (ERR/Gy = −0.02) appears to be in contradiction with the linear dose-response we estimated with a negative exponential term. Nevertheless, it is noteworthy that model 1 (total dose) is not adequate for fractionated irradiation.[43] Women subjected to repeated fluoroscopy examinations during the follow-up of tuberculosis had a BC risk that was similar to that of female atomic bomb survivors who had received a similar total dose.[40,44]

We were unable to identify any substantial decrease in the doses delivered to the breasts after changes of treatment instruments and energy (low-energy x-rays, high-energy x-rays, electrons, cobalt). Seven BCs occurred after low-energy x-ray therapy. A follow-up of these patients (mean, 26 years; range, 3 to 46 years) longer than that attained in patients treated by the other instruments (mean, 14 years; range, 3 to 36 years) can explain this high number.

In this cohort, after stratification on castration and attained age and adjustment on radiation dose and FC type, the RR associated with chemotherapy was weak (RR, 2.7; 95% CI, 0.9 to 7.6) and chemotherapeutic drug classes were not found to increase the risk of BC except for the NSI class (only methotrexate), which seemed more likely to be associated with an increased risk of BC. However, only two BCs occurred after the administration of this cytotoxic agent. This increased risk due to chemotherapy is in agreement with one study[45] in which alkylating agents and vinca alkaloids, but not NSI, were associated with a more frequent occurrence of BC, but not with another study,[10] which failed to determine such an association. In these two studies, adjustment for radiotherapy was only addressed as yes or no.

The distribution of laterality of the 16 BCs observed in this cohort is different from that observed in the French breast cancer registries. Thus, 11 of the 14 BCs (approximately 80%) for which information was available were located in the left breast (the percentage is usually approximately 50%).[26] Regarding the histologic type, three among the 14 BCs with this information are infrequent malignant phyllodes tumors; the percentage in the French BC registries is 0.18%.[26]

We also investigated the potential effect of radiation doses to organs influencing the immunologic status (spleen or active bone marrow) on the occurrence of BC. We did not find any role like that found by others after splenectomy, following a childhood cancer[9,10] as after trauma.[46,47]

In conclusion, our study confirms that the previously reported excess BC observed after Hodgkin's disease in childhood is due not only to chemotherapy and higher radiation dose to the breast, but also to a susceptibility that appears to be specific. Children treated for a neuroblastoma could also be at higher risk of developing BC. These results have to be confirmed by studies including more occurrences of BC.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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