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Surveillance for Breast Cancer in Women Treated with Chest Radiation for a Childhood, Adolescent or Young Adult Cancer: A Report from the Children's Oncology Group

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Abstract

Background—Women treated with therapeutic chest radiation may develop breast cancer.

Purpose—Summarize breast cancer risk and breast cancer surveillance in women following chest radiation for a pediatric or young adult cancer.

Data Sources—Studies from MEDLINE, EMBASE, Cochrane Library, and CINAHL (1966 through December 2008).

Study Selection—Articles selected to answer any of 3 questions: 1) What is the incidence and excess risk of breast cancer in women following chest radiation for a pediatric or young adult cancer? 2) For these women, are the clinical characteristics of the breast cancer and the outcomes following therapy different than for women with sporadic breast cancer in the general population? 3) What are the potential benefits and harms associated with breast cancer surveillance among women exposed to chest radiation?

Data Extraction—Three investigators independently extracted data and assessed study quality.

Data Synthesis—Standardized incidence ratios ranged from 13.3 to 55.5; cumulative incidence of breast cancer by 40–45 years of age ranged from 13–20%. Risk of breast cancer increased linearly with chest radiation dose. Available limited evidence suggests that the characteristics of the breast cancers in these women and the outcomes following diagnosis are similar to those in the general population; these breast cancers can be detected by mammography, though sensitivity is limited.

Limitations—Limitations include study heterogeneity, design and small sample size.

Conclusions—Women treated with chest radiation have a substantially elevated risk of breast cancer at a young age, which does not appear to plateau. Among this high risk population, there appears to be a benefit associated with early detection. Further research is required to better define the harms and benefits of lifelong surveillance.

BACKGROUND

An estimated 50,000 – 55,000 women in the United States have been treated with moderate to high-dose chest radiation (≥20 Gy) for a pediatric or young adult cancer (2–5), and these women are at significantly increased risk of breast cancer and breast cancer mortality following cure of their primary malignancy (1). Breast cancer risk is greatest among women treated for Hodgkin's lymphoma with high-dose mantle radiation, but it is also elevated among women who received moderate-dose chest radiation (e.g., mediastinal, lung) for other pediatric and young adult cancers, such as non-Hodgkin’s lymphoma, Wilms tumor, leukemia, bone cancer, neuroblastoma and soft tissue sarcoma.

Recognizing the high incidence of second cancers and other health problems affecting survivors of pediatric and young adult cancer, the Institute of Medicine in January 2002 charged the Children’s Oncology Group (COG) with the development of comprehensive clinical practice guidelines for the long-term follow-up care of childhood cancer survivors. In September 2003, the COG released the *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (6). The following is a report of our background systematic review of the literature that was conducted to inform and update the COG breast cancer surveillance recommendations.

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METHODS

Study Population

We focused the review on studies of girls and women with a pediatric or young adult cancer (diagnosis ≤30 years of age) who were exposed to moderate to high doses of therapeutic radiation targeted to mantle and modified mantle fields, mediastinum, lung, and chest (thorax). Hereafter, the term ‘chest radiation’ refers to any of these exposures. Women treated for Hodgkin’s lymphoma with mantle or modified mantle radiation represent about two-thirds of this population.

Key Questions

We structured the review around three key questions:

Key question 1: What is the incidence and excess risk of breast cancer in women following chest radiation for a pediatric or young adult cancer?

Key question 2: For these women, are the clinical characteristics of the breast cancer and the outcomes following therapy different than for women with sporadic breast cancer in the general population?

Key question 3: What are the potential benefits and harms associated with breast cancer surveillance among women exposed to chest radiation?

Data Sources

We searched MEDLINE, EMBASE, the Cochrane Library, and CINAHL between1966 - December 2008 using the search strategy detailed in Appendix A. Literature searches were supplemented by examining bibliographies of included studies and selected literature reviews.

Study Selection and Quality Assessment

Inclusion and exclusion criteria were developed for each question (Table 1). Three investigators (TOH, AA, KCO) reviewed the full text of papers that appeared to meet eligibility criteria based on Abstract review. Discrepancies regarding which studies to include were resolved by consensus. Appendix B summarizes the literature search and review process. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting criteria (7,8) for all studies included in the review is provided in Appendix C.

Data Extraction

For question 1, we extracted measures of breast cancer risk [standardized incidence ratio (SIR), odds ratio (OR), absolute excess risk (AER), cumulative incidence]. For question 2, we extracted information about affected women’s clinical characteristics: median interval from primary cancer to breast cancer, stage and location at breast cancer diagnosis, pathological features, and percent with bilateral breast cancer (metachronous and synchronous cancers). For question 3, we extracted data on the number of breast cancer cases detected by surveillance per person-year of follow-up.

Role of the Funding Sources

This systematic review was not funded through an independent agency but was conducted through the COG.

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RESULTS

Question 1: Incidence and Excess Risk

Eleven retrospective cohort (9–19) and three case-control (20–24) studies met eligibility criteria and assessed the risk of breast cancer in women following chest radiation for a pediatric or young adult cancer.

The cohort studies included over 14,000 women, most of whom were treated for a pediatric or young adult cancer over a four decade period (1960–2000). Among these, about 7000 women were treated with chest radiation and 422 women subsequently developed breast cancer. Study objectives and designs varied. Most focused on the risks of Hodgkin's lymphoma survivors; only four estimated risk among women treated with chest radiation for other cancer types (11,13,20,22). The precision or generalizability of risk estimates of some of the cohort studies were limited by a lack of information regarding chest radiation (11,14), relatively small sample sizes or number of breast cancer cases (9,15–18), or single institution cohorts (9,12,17). Most assessed risk of different types of second malignancies (10,11,14,15,17,18,20), so detail regarding breast cancer risk was often limited. Six were well-designed with representative samples, adequate length of follow-up, and risk estimates based upon detailed treatment exposures (10,13,15,16,18,19).

Heterogeneity notwithstanding, each of the studies reported a significantly increased incidence and/or absolute excess risk of breast cancer associated with chest radiation (Table 2). Among the higher quality cohort studies, the SIR ranged from 13.3 to 55.5 and the absolute excess risk ranged from 18.6 to 79.0 per 10,000 person-years (10,13,15,16,18,19). Risk of breast cancer was found to increase as early as 8 years following chest radiation and did not plateau with increasing length of follow-up (9,10,13,14,16). The cumulative incidence of breast cancer by 40–45 years of age ranged from 13–20% and by 25–30 years of follow-up ranged from 12–26% (10,13,16,19). This incidence is similar to that in women with a *BRCA* gene mutation, where by age 40 the cumulative incidence ranges from 10–19% (25–29) and is substantially higher than in young women in the general population in whom the cumulative incidence of invasive breast cancer by age 45 is only 1% (30–32).

Two of the three case-control studies focused on breast cancer, included diverse and large populations of cases and appropriately matched controls within a cohort, and had detailed treatment information including radiation dosimetry estimates (21–24).

In the first, a well-designed case-control study (21–23), Travis et al estimated that among women diagnosed with Hodgkin's at age 15 years and counseled for screening at the age of 25, 9.2% of those treated with 20–39 Gy and 11.1% of those treated with ≥ 40 Gy would develop breast cancer by age 45 (22).

In the other well-designed case-control study, Inskip and colleagues reported that the odds of being diagnosed with breast cancer increased linearly with chest radiation dose, reaching 10.8 (95% CI, 3.8–31) for 40 Gy relative to no radiation (24). Their data suggested that women exposed to 20–30 Gy have odds ratios of breast cancer between about 6.0 and 9.0.

Yet another study suggests that risk may be associated with radiation field volume, given increased risk (odds ratio 2.7 (95% CI, 1.1–6.9)) in women treated with mantle field irradiation compared to women with similarly dosed mediastinal irradiation (omitting the axillary nodes) (19).

Certain factors appear to modify the risk of breast cancer associated with chest radiation. A history of breast cancer in a close relative modestly increases risk in women treated with chest

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radiation (13,23). Inskip et al reported that risk was sharply reduced among women with ovarian radiation strongly associated with acute ovarian failure (OR per Gy 0.06 for women who received ovarian doses > 5 Gy compared with OR per Gy 0.36 for those who received doses less than 5 Gy) (24), a finding confirmed in other studies (13,19,21). High dose alkylating agent chemotherapy, which can lead to premature menopause, may also lower the risk of breast cancer (13,19,21,22). Notably, risk in women treated in prepubertal years is not lower than those treated during adolescence, as suggested by some early studies (33) which did not account for the natural age-associated increase of risk (34). Updated studies with extended years of follow-up that have accounted for attained ages at follow-up have not found a difference in breast cancer risk among women treated with chest radiation in their prepubertal years compared with those treated in their adolescent years (10,13,24).

Question 2: Clinical Characteristics and Outcomes

Only 3 studies reported on the clinical characteristics of breast cancer among women treated for a pediatric or young adult cancer with chest radiation (12,13,16), so we included five studies (35–39) of women with breast cancer following Hodgkin’s lymphoma diagnosed at any age. These eight studies reported on a total of 400 women with 451 cases of breast cancer with median ages of diagnosis of their primary cancers between 13 and 27 years.

The cohorts were predominantly from single institutions (12,35–39). The amount of detail regarding the characteristics of the breast cancer cases varied substantially across studies, including the location of the cancer and the stage at diagnosis. Recognizing these limitations, available retrospective evidence of fair quality suggests that once the breast cancer is diagnosed, women (and their cancers) in our target population are similar to women in the general population (12,13,16,35–39).

Table 3 summarizes the breast cancer characteristics of the cases reported in the eight cohort studies and general population estimates from Surveillance, Epidemiology and End Results (SEER) (3). The median age of breast cancer in women treated with chest radiation prior to age 20 was 35 years (13,16). For women whose Hodgkin’s was diagnosed at any age, the median age at breast cancer diagnosis was 40–45 years (12,35–39). In contrast, the median age of diagnosis for breast cancer in the general population is 61 years of age, with 1.9% of cases occurring between ages 20–34 and 10.6% between ages 35–44 (3).

The majority (77–85%) of breast cancer pathology in pediatric and young adult cancer survivors is invasive ductal carcinoma (12,13,35,37–39). This is similar to the 70–80% invasive ductal carcinomas among cases in the general population (40). In a small but well-designed case-control study of 26 women with breast cancer following Hodgkin’s lymphoma and 26 women with sporadic breast cancer who were matched for age and stage of breast cancer, there were no statistically significant differences between groups in nodal status, histology, estrogen receptor status, or lymphatic vessel invasion (41).

Survival rates in women previously exposed to radiation appear to be strongly associated with stage of disease at diagnosis (35,38,39), similar to the general population (3). Importantly for women with node-positive breast cancer, therapy for the initial cancer may limit options for adjuvant therapy for secondary breast cancer, which in turn may be associated with poorer outcomes. For example, in a small retrospective study of 53 women with breast cancer following a lymphoma (66% Hodgkin’s, 34% Non-Hodgkin's lymphoma) and 103 controls matched for age, stage and year of breast cancer diagnosis, and estrogen and progesterone status, Sanna et al reported a statistically significantly lower 5-year overall survival among the lymphoma cases compared to the controls (86.6% vs 98.6%, P=0.03) (42). This difference was attributed to less aggressive adjuvant therapy used for node-positive lymphoma survivors; because of their previous lymphoma therapy, only 36% of the lymphoma survivors were treated

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with doxorubicin, a standard adjuvant option for patients with nodal involvement, in comparison to 69% of breast cancer patients in the control group (*P*=0.03).

Bilateral breast cancer incidence appears increased in women treated with chest radiation for a pediatric or young adult cancer. From the large Childhood Cancer Survivor Study cohort, Kenney et al reported bilateral disease in 17% of breast cancer cases: 5% synchronous, 12% metachronous (13). In the three Hodgkin's lymphoma studies, information regarding bilateral cancer was provided (35,38,39). Of 219 women with breast cancer, 12.8% had bilateral disease; 5.5% synchronous, 7.3% metachronous. In contrast, in three population-based studies of the general population, 3.3–5.3% of the women had bilateral disease; 1.5–3.1% synchronous, 1.2–3.8% metachronous (43–45). However, the population at risk for breast cancer following chest radiation is still relatively young, so the percent of cases with metachronous disease will likely increase over time.

Question 3: Benefits and Harms Associated with Breast Cancer Surveillance

Two retrospective and three prospective surveillance studies provide information about the benefits and harms of breast cancer surveillance.

The two retrospective studies report the method of breast cancer detection for 92 women from two institutions at a time when breast magnetic resonance imaging (MRI) was not available (all breast cancers diagnosed before 1997) (38,46). Dershaw et al reported in a retrospective review that mammography demonstrated 90% of the cancers in 27 women (55% under the age of 45 years), with 38% being detected only by mammography (46). Wolden et al retrospectively examined 71 cases of breast cancer in 65 women and noted 27% of breast cancers were initially detected by screening mammograms (38).Notably, 75% of the women at time of breast cancer diagnosis were premenopausal (median age, 43 years). They reported that following a 1990 institutional recommendation for mammographic screening in women with a history of mantle radiation, 27 of 37 cases (73%) were stage 0 or 1 at diagnosis compared to 13 of 28 women (46%) with stage 0 or 1 cases prior to 1990 (*P*=0.05) (38). Interpretation of these findings is limited by the retrospective nature of the studies and the very small sample sizes. Nevertheless, these two studies suggest that mammography can detect breast cancers in this population of women, including those who are premenopausal.

Three prospective surveillance studies assessed surveillance in 320 women, ages 24–55 years (47–49) (Table 4). Kwong et al (48) reported only data from the baseline mammogram of participants, while Diller et al report data from continued breast cancer surveillance for a median of 3.1 years and Lee et al report data for a median follow-up of 5 years (47,49). Almost all of these women were screened with mammography alone; fewer than 5% were screened with MRI or ultrasound. None of the studies evaluated the cost of surveillance. Strengths of these studies included the prospective design, details regarding breast density, reporting of prevalent and incident (47,49) cases of breast cancer, and recall/false positive rates (47,48). The women in these studies were from three different regions of North America and had socioeconomic indicators similar to that of women in the Childhood Cancer Survivor Study, thus suggesting that the studies, while small, appear representative of the target population.

Of the 239 baseline mammograms reviewed for breast density, 60.6% were described as moderately to very/extremely dense (47–49). Following the baseline mammogram, 27 (15.2%) of 178 women were recalled for further testing (47,48). Fifteen women had unremarkable magnification views and/or ultrasounds and did not require additional testing. The remaining 12 women underwent biopsy with the following results: invasive breast cancer (N=2), ductal carcinoma-in-situ (N=1), lobular carcinoma-in-situ (N=1), follicular small-cleaved cell lymphoma (N=1), benign conditions including atypical hyperplasia (N=7).

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Among 205 women followed prospectively, 20 developed 22 incident cases of breast cancer (7 ductal carcinoma-in-situ, 15 invasive breast cancer) over 1074.8 person-years of follow-up (47,49), for about 2.05 cases per 100 person-years of follow-up. In the United States during this time period, for women younger than 50, the incidence of breast cancer (ductal carcinoma-in-situ and invasive) was 0.05 cases per 100 person-years of follow-up (3). Including incident and prevalent cases, 58% of the breast cancers were detected initially by mammography while 42% were detected by palpation. Of the invasive breast cancers detected initially by mammography, all were T1 (size < 2 cm). At the time of last contact, only one woman from these two studies died secondary to her breast cancer (T size 5 cm; detected initially on physical examination) (47,49).

Among the 178 women in the Diller and Kwong studies, 12.3% had a false-positive mammogram: 8.4% who were recalled and needed only additional imaging studies and 3.9% who required a biopsy (47,48). While Lee et al (49) did not provide data regarding false-positive mammograms, they reported that the false-negative rate of annual mammography was 5%. Lastly, among the women in the Kwong study, a telephone-based counseling intervention aimed at increasing screening rates was tested. Notably, breast cancer worries and depressive symptoms did not increase from pre-intervention to post-intervention among women who were informed about their risk (50).

DISCUSSION

In summary, there is consistent observational evidence showing that women treated for a pediatric or young adult cancer with moderate- to high-dose therapeutic chest radiation (≥20 Gy) have a substantially elevated risk of breast cancer at a young age and that this excess risk does not appear to plateau with aging. Available limited evidence suggests that the characteristics of the breast cancers in these women and the outcomes following diagnosis are similar to those in the general population; and that there appears to be a benefit associated with early detection given that women diagnosed with early stage breast cancer following chest radiation have a high likelihood for a favorable outcome. However, many of these women may have fewer treatment options for their breast cancer (eg, additional radiation, doxorubicin chemotherapy) because of treatment exposures used to cure their first cancer (35,36,38,39, 42,51,52).

Mammography appears to detect the majority of cancers in these women. However, more than half of mammograms in women who had previous chest radiation have moderate to very dense breast tissue, thus limiting the sensitivity of mammography in detecting early cancers in this population. A systematic review of 11 prospective studies reported that screening with both MRI and mammography among women with a hereditary risk of breast cancer appears to rule out cancerous lesions better than mammography alone (53). While all 11 studies reported a higher sensitivity for MRI than mammography for invasive cancer, mammography was more sensitive than MRI for ductal carcinoma-in-situ. It is not known whether combining mammography with MRI is superior to either test alone for detecting early cancers among women who have been treated with chest radiation. However, given the similar incidence rates among young women between these two high risk populations, the increased likelihood of dense breast tissue, and the similar response to curative therapy for early diagnosed breast cancer, it is seems reasonable to speculate that the data from the hereditary risk-focused studies apply to women treated with chest radiation. Given the relatively limited size of both populations, an adequately powered randomized clinical trial to determine if surveillance with mammography and/or MRI (versus no surveillance) is associated with a reduction in mortality is unlikely to be feasible or ethical (53–56). However, ongoing prospective and high quality retrospective studies that further assess the screening metrics of different imaging approaches for women who have been treated with chest radiation might still provide useful information.

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It should be recognized that while women in this risk group may benefit from breast cancer surveillance at a younger age, there is still too little understood regarding the potential harms. For example, women initiating surveillance at 25 years of age would have at least 15 additional mammograms (prior to initiating screening at the usual age of 40) and thus an increased likelihood of experiencing false positive tests with the associated economic and emotional costs of additional testing and/or biopsies. Adding an MRI may further add to the false positive rate among these women and would substantially increase the economic cost of surveillance. Of note, the combination of mammography and MRI appears to be more cost-effective in screening young women with a hereditable risk of breast cancer than mammography alone (57–60).

Another potential harm with mammography is the additional radiation exposure and the potential for radiation-induced breast cancer. Among women in the general population (61–67) and those with a hereditary risk of breast cancer (68–70), much effort has been devoted to estimating the number of breast cancers induced by mammography. Because there are no studies that directly measure risk of breast cancer caused by radiation exposure with mammography, estimates have been based upon low-dose radiation exposure from other sources, such as atomic bomb radiation, chest fluoroscopy, and thymic irradiation (71). Combining this information with the number of breast cancers detected provides an indicator of the benefit/risk balance (63,64). The estimated mean breast dose with a contemporary standard 2-view screening mammogram is about 3.85 – 4.5 mGy (68,72,73). Thus, in a woman treated with 20 Gy chest radiation, fifteen additional surveillance mammograms from age 25 to 39 would increase the total radiation exposure to 20.05775 Gy or by about 0.3%. Faulkner and Law estimate that among women in the general population between the ages of 30–34, radiation exposure from a 2-view mammogram induces about 82 cancers per million women screened and detects about 630 cancers, giving a detected/induced ratio of almost 8 (74). For women ages 35–39, the detected/induced ratio is about 19. Based upon the lifetime risks of women treated with moderate to high-dose chest radiation at a young age, they estimate that detection/induction ratios will be at least 3–4 times higher than the general population (74). In addition, they emphasize that the induction rates from mammography used in the general population are likely not applicable to this population of women treated with high doses of therapeutic radiation (74).

In addition to better understanding the potential harms and benefits of specialized surveillance in this population, we need to better understand the multiple factors that may modify breast cancer risk of women who have received low or moderate dose chest radiation, especially given recent modifications in therapy including reduction in the radiation dose and reduction in the volume of developing breast tissue exposed (75). While it is anticipated that the incidence of breast cancer may decrease in women treated with contemporary therapy, it is not known what the long-term effect of these lower radiation doses will be on overall risk. Potentially, lower exposure may still be highly carcinogenic but associated with a longer latency period to induction of breast cancer.

Many women treated with chest radiation are unaware of their risks, are not followed at a cancer center, and are seen by clinicians who may be unfamiliar with their long-term health risks. In a recent survey of women in North America treated for a pediatric cancer with chest radiation, only 49% were aware that chest radiation increased the risk of breast cancer. Among women ages 25–39, nearly half had never had a mammogram (or other imaging study) and less than 20% were in a regular pattern of BC surveillance (76). While most women in this high risk group who were 40–50 years of age reported some level of breast cancer surveillance, only 53% had at least two mammograms in the previous four years. Thus, interventions aimed at informing women and their clinicians regarding these risks and options for breast cancer surveillance are needed.

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Finally, a continuing theme of research that aims to reduce the very serious long-term morbidity and premature mortality faced by pediatric and young adult cancer survivors (1,77–79) is that there is consistent evidence linking the exposure to the late effect (i.e., chest radiation and breast cancer), but limited evidence that specialized surveillance will benefit this high risk population. In balancing the potential life-saving benefits of a young and productive population of women with the potential harms of specialized breast cancer surveillance, various national and international groups, based upon consensus, recommend initiating surveillance at a young age (55,80–82) (Table 5). Current recommendations are based upon rather arbitrary radiation levels to the chest, which will need to be continually re-evaluated as research provides better estimates of dose-specific risks (24). Presently, for women treated for a pediatric or young adult cancer with chest radiation ≥20 Gy, the COG recommends annual surveillance mammography and MRI, starting at age 25 or eight years after completion of radiation therapy, whichever occurs last. These recommendations can be viewed in the *Long-Term Follow-Up Guidelines* document (pages 128–129) posted at www.survivorshipguidelines.org.

In summary, we identified consistent evidence that women treated for a pediatric or young adult cancer with moderate- to high-dose therapeutic chest radiation (≥20 Gy) have a substantially elevated risk of breast cancer at a young age and that this excess risk does not appear to plateau with aging. Available limited evidence suggests that the characteristics of the breast cancers in these women and the outcomes following diagnosis are similar to those in the general population; and that there appears to be a benefit associated with early detection given that women diagnosed with early stage breast cancer following chest radiation have a high likelihood for a favorable outcome. Further research is required to better define the harms and benefits of lifelong surveillance, and how estimates of risk and outcome might change given lower radiation doses use in contemporary treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Inclusion and exclusion criteria for the three key questions*

	Question 1	Question 2	Question 3
Inclusion Criteria			
Population			
Women diagnosed with breast cancer following chest radiation			
For a pediatric or young adult cancer (diagnosed ≤ 30 years)	X	X	X
For a Hodgkin's lymphoma at any age		X	X
Study Design			
Retrospective cohort	X	X	X
Retrospective case-control	X	X	
Prospective cohort or clinical trial			X
Outcomes			
Risk estimates of breast cancer: standardized incidence ratio, relative risk, absolute excess risk, or cumulative incidence Overall and treatment-based (radiation) risk estimates	X		
Clinical characteristics of breast cancer Breast cancer stage, location, pathological features, interval since primary cancer, bilateral breast cancer		X	
Breast cancer surveillance Harms and benefits			X
Exclusion Criteria			
Non-human study	X	X	X
Non-English language	X	X	X
Case report, review, editorial, letter	X	X	X
< 5 breast cancer cases in the study cohort	X	X	
Study population has been included in its entirety in a subsequent publication by the investigators	X		

*Key question 1: What is the incidence and excess risk of breast cancer in women following chest radiation for a pediatric or young adult cancer?

Key question 2: For these women, are the clinical characteristics of the breast cancer and the outcomes following therapy different than for women with sporadic breast cancer in the general population?

Key question 3: What are the potential benefits and harms associated with breast cancer surveillance among women exposed to chest radiation?

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Table 2

Breast cancer in women treated with chest radiation for a pediatric or young adult cancer*

Question 1. What is the incidence/excess risk of breast cancer in women following chest radiation for a pediatric or young adult cancer?

Study, Year (Reference) Population	STROBE Criteria§	Era	N	% Chest RT^	# BC¶	Yrs FU	SIR by Age of Primary Cancer			SIR by Years of Follow-Up			AER by Age of Primary	
							Age+	SIR	95% CI	Yrs FU€	SIR	95% CI	Age+	AER
Single Institution														
Hancock et al., 1993 (12) United States: Stanford	24/31	1961–1989	585	95%	22	10.0	0–14	136.0	34.0 to 371.0	< 15	26.0	4.3 to 85.3	0–14	38.4
							15–19	19.0	4.7 to 51.0	≥ 15	38.0	12.0 to 92.3	15–19	16.7
							20–24	19.0	9.3 to 35.0				20–24	47.2
							25–29	7.3	3.2 to 14.0				25–29	32.6
Wolden et al., 1998 (17) United States: Stanford	24/32	1960–1995	307	97%	16	12.3	0–20	26.2	15.0 to 42.6	5–10	24.0	NR	0–20	41.1
										11–15	35.2	NR		
										16–20	32.1	NR		
										21–32	19.0	NR		
Alm El-Din et al., 2008 (9) United States: Mass General	19/32	1964–2001	161	100%	25	15.2	0–14	279.2	56.1 to 652.1	NR			NR	
							15–19	74.5	37.2 to 178.2					
							20–24	16.4	7.0 to 35.8					
							25–29	4.5	0.9 to 9.4					
Multiple Institutions														
Ng et al., 2002 (15) Four institutions United States	26/32	1969–1997	397	97%	32	12.0	0–14	111.8	36.2 to 261.0	5–10	6.8	0.8 to 24.7	0–14	82.1
							15–19	32.0	14.6 to 60.7	10–15	4.1	0.5 to 14.9	15–19	58.2
							20–25	16.6	8.0 to 30.6	15–20	25.8	14.1 to 43.3	20–25	52.8
							26–29	8.4	3.6 to 16.5	≥ 20	24.5	13.4 to 41.1	26–29	57.2
Bhatia et al., 2003 (10) Fifteen institutions United States & Europe	26/33	1955–1986	480	NR	39	17.0	0–16	55.5	39.5 to 75.9	5–9	0.0	0.0 to 222.1	0–16	53.0
										10–14	71.3	22.9 to 166.4		
										15–19	90.8	49.6 to 152.3		
Kenney et al., 2004 (13) Twenty-six institutions United States & Canada	26/32	1970–1986	6068	21%†	95	19.0	0–20	24.7	19.3 to 31.0	10–14	26.0	14.0 to 48.2	NR	
										15–19	22.8	13.2 to 39.3		
										≥ 20	13.9	8.1 to 24.0		

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Study, Year (Reference) Population	STROBE Criteria§	Era	N	% Chest RT^	# BC¶	Yrs FU	SIR by Age of Primary Cancer			SIR by Years of Follow-Up			AER by Age of Primary	
							Age+	SIR	95% CI	Yrs FU€	SIR	95% CI	Age+	AER
Guibout et al., 2005 (11) Eight institutions France & Great Britain	28/32	1946–1986	1814	NR	16	16.0	0–16	16.9	11.6 to 40.6	10–19	185.0	30.8 to 572.6	NR	
										20–29	18.8	4.7 to 48.9		
										30–39	23.2	11.6 to 40.6		
Constine et al., 2008 (18) Five institutions United States	23/32	1960–1990	398	84%	29	16.8	0–19	37.3	25.0 to 53.6	NR			0–19	18.6
Population-based														
Metayer et al., 2000 (14) United States & Europe	22/32	1935–1994	2737	NR	52	11.0	10–16	22.9	14.0 to 35.4	10–14	34.1	NR	10–16	20.0
							17–20	11.6	8.0 to 16.4	15–19	19.7	NR	17–20	19.0
										≥ 20	11.7	NR		
Taylor et al., 2007 (16) Great Britain	26/32	1940–1991	383	68%	16	20.3	0–14	13.3	7.6 to 21.5	5–9	60.7	12.5 to 177.1	0–14	33.9
										10–19	21.4	8.6 to 44.1		
										≥ 20	12.6	4.6 to 27.4		
De Bruin et al., 2009 (19) Europe	23/32	1965–1995	737	86%	80	17.8	0–20	17.9	12.6 to 24.5	5–14	20.0	7.3 to 43.4	0–20	79.0
							21–30	7.0	5.1 to 9.5	15–24	20.8	12.6 to 32.6	21–30	62.0
										≥ 25	14.2	7.6 to 24.3		

* All studies except Kenney (13) and Guibout (11) include only women who had Hodgkin's lymphoma as the primary cancer; the Kenney and Guibout studies include women treated with chest radiation (RT) for childhood cancer

§ STROBE = Strengthening the Reporting of Observational Studies in Epidemiology (criteria to be included in cohort and case-control studies (7,8)). Provides the number of STROBE criteria satisfied by each study out of the number of applicable items.

^ % Chest RT = percent of entire cohort treated with chest RT (supradiaphragmatic, mantle, mediastinal, axial); in the Wolden (17), Alm El-Din (9), Bhatia (10), Taylor (16), and De Bruin (19) studies, all breast cancers were in women treated with chest RT; in the Guibout (11) study, 13/16 breast cancers were in women treated with chest RT and 3/16 not treated with chest RT; in the Kenney (13) study, 73/95 breast cancers were in women treated with chest RT, 20/95 not treated with chest RT, and 2/95 with RT status unknown; in the Constine (18), Ng (15), Metayer (14), and Hancock (12) studies, the percent treated with chest RT was not reported separately for women who developed breast cancer.

¶ #BC = number of women with breast cancer; five studies limit BC to invasive only (Hancock (12), Bhatia (10), Guibout (11), Taylor (16), De Bruin (19)); two studies include carcinoma in situ (Kenney (13), Constine (18)); four studies do not specify (Wolden (17), Alm El-Din (9), Ng (15), Metayer (14))

€ All studies except Ng (15) report SIR estimates by years of follow-up for women diagnosed prior to 21 years of age; the estimates in the Ng study are for women diagnosed ≤ 30 years

+ Age = age range, in years, at time of diagnosis of primary cancer

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† Breast cancer risk estimates are only based upon women treated with chest RT for Hodgkin's lymphoma

Era, year of diagnosis of primary cancer; N, number of women diagnosed with a pediatric or young adult cancer at <30 years of age; FU is mean or median for entire cohort of the study (may include males or survivors who were older than 30 years of age at time of primary cancer); SIR, standardized incidence ratio; 95% CI, 95% confidence interval; AER, absolute excess risk, excess cases per 10,000 person-years; NR, not reported

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Table 3

Breast cancer characteristics in women treated with chest radiation
Question 2: For these women, are the clinical characteristics of the breast cancer following therapy different than for women with sporadic breast cancer in the general population?

	Comparison	Pediatric cancer		Hodgkin's lymphoma, any age¶					
Study	**General Population****	**Kenney**	**Taylor**	**Yahalom**	**Hancock**	**Gervais-Fagnou**	**Wolden**	**Wahner-Roedler**	**Cutuli**
Year of publication	2000–2003	2004	2007	1992	1993	1999	2000	2003	2001
Reference	(3)	(13)	(16)	(39)	(12)	(36)	(38)	(37)	(35)
STROBE criteria	NA	26/32	26/32	25/32	24/31	21/30	21/31	26/33	22/31
Study design	NA	MCC	Pop-based	SINC	SINC	SINC	SINC	SINC	MCC
Median age at first cancer, y Range		16 5–20	13 12–14	27 11–60	25 14–71	25 19–30	25 13–72	23 13–52	24 7–67
Number of women with BC (# cases)	NA	95 (111)	16 (18)	37 (45)	25	15 (17)	65 (71)	30 (34)	117 (132)
% of women with chest RT		77	100	100	96	100	98	100	100
Median age at breast cancer (BC)*, y	61	35	35.4	43	40	41	42.6	44.4	42
Median interval from first cancer to BC, y	NA	19	21.6	15	15	17	17.4	19.9	16
Stage of breast cancer, %									
DCIS	--	24	NR	NR	4	NR	14	23	T0 11.3
I	61	34			38		48	37	T1 33.1
II		31			50		28	30	T2 27.1
III	31	5			8		7	10	T3 6.7
IV	6	6			--		3	--	T4 11.3
									Tx 10.5
Location of breast cancer^, %									
Upper outer quadrant	60	NR	NR	48	54	33	51	65	NR
Lower outer quadrant	12			9	--	--	8	16	
Upper inner quadrant	13			24	12	20	13	7	
Lower inner quadrant	8			15	--	13	7	--	
Central	8			4	--	--	4	--	

	Comparison	Pediatric cancer		Hodgkin's lymphoma, any age[¶]					
Study	**General Population**[**]	**Kenney**	**Taylor**	**Yahalom**	**Hancock**	**Gervais-Fagnou**	**Wolden**	**Wahner-Roedler**	**Cutuli**
Diffuse	--			--	--	--	4	--	
Unknown	0			0	6	33	13	--	
Bilateral breast cancer, %									
Total	NR	17	13	22	NR	13	10	13	12
Metachronous	NR	12	NR	11	NR	13	5	NR	8
Synchronous	NR	5	NR	11	NR	NR	5	NR	4

Abbreviations: MCC, multi-center cohort study; Pop-based, population-based cohort study; SINC, single institution cohort study; NA, not applicable; NR, not reported; DCIS, ductal carcinoma-in-situ

[*] Mean reported in the Taylor and Hancock studies

[^] Percent of all cases; the location of all cases may not have been reported and thus, may not add to 100%

[**] Not age specific

[¶] For question 2, there were few studies reporting on the clinical characteristics of breast cancer among women treated for a pediatric or young adult cancer with chest radiation and so we also included five studies (35–39) of women with breast cancer following Hodgkin's lymphoma diagnosed at any age.

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Table 4

Results of breast cancer early detection tests in women treated with chest radiation for a Hodgkin's lymphoma (HL)

Question 3: What are the potential benefits and harms associated with breast cancer surveillance among women exposed to chest radiation?

Study	Diller	Kwong	Lee
Year of publication	2002	2008	2008
Reference	(47)	(48)	(49)
STROBE criteria	26/32	20/27	25/32
Institution, country	Dana-Farber Cancer Institute United States	Stanford United States	Princess Margaret Hospital Canada
Years of study	1995–1999	2002	1997–2006
Number in cohort	90	115	115
Median age at HL, y Range	20 13–30	24 13–34	22 9–31
Median chest radiation dose, Gy Range	37.5 30.0–41.5	NR	35.0 15.0–60.0
Median age at study, y Range	38 24–51	41 25–55	35 24–55
Baseline mammogram			
Breast density, number evaluable	*N=43*	*N=99*	*N=97*
Moderately to extremely dense, N (%)	34 (79%)	60 (60%)	51 (52%)
Mildly dense or scattered, N (%)	0 (0%)	29 (29%)	39 (40%)
Mildly fatty or fatty, N (%)	9 (21%)	10 (10%)	7 (7%)
Recalls, number evaluable	*N=79*	*N=99*	NR
Biopsy	5 (6%)	7 (7%)	
Further imaging	5 (6%)	10 (10%)	
Prevalent and incident breast cancer			
Total number evaluable	*N=90*	*N=115*	*N=115*
DCIS, N (%)	2 (2%)	2 (1.7%)	5 (4%)
Invasive, N (%)	10 (11%)	2 (1.7%)	7 (6%)
Person-years of follow-up	219.8	NA	855
BC screening test, N (%)[†]			
Mammogram alone	84 (100%)	115 (100%)	82 (84%)
Mammogram + MRI			12 (12%)
Mammogram + ultrasound			3 (3%)
MRI alone			1 (1%)

Abbreviations: DCIS, ductal carcinoma-in-situ; NR, not reported; NA, not applicable

[†]Among women who were screened during the study (Diller, N excludes 6 who refused mammography; Lee, N excludes 7 who deferred radiographic imaging due to pregnancy or lactation and 10 who did not have annual screening for other reasons)

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Table 5

Summary of consensus-based recommendations for breast imaging surveillance from different national and international organizations.

Organization	Breast Imaging Surveillance Recommendation	Source / Public Link
Children's Oncology Group	For women treated with ≥20 Gy radiation to the chest for a childhood, adolescent, or young adult cancer, initiate annual screening mammography with adjunct breast MRI at 25 years of age or 8 years after completion of radiation therapy, whichever occurs last.	Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (Version 3) www.survivorshipguidelines.org
American Cancer Society (55)	For women treated with radiation to the chest between the ages of 10 and 30 years, recommend annual screening mammography with adjunct breast MRI, beginning at 30 years of age or as determined by the patient and her physician based upon her personal circumstances and preferences.	Can Breast Cancer Be Found Early? (guide for patients) http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_Can_breast_cancer_be_found_early_5.asp
United Kingdom Department of Health: United Kingdom Children's Cancer Study Group (80,81)	For women treated with mediastinal radiation prior to age 17, recommend annual breast MRI from 25–29 years of age, followed by a baseline 2-view mammogram at 30 years of age Thereafter, annual 2-view mammography is recommended from 30–50 years of age. For women with dense breast tissue at the baseline mammogram, an annual breast MRI is combined with mammography. If the breast tissue becomes predominantly fatty prior to age 50, surveillance continues with annual mammography alone. Over the age of 50 years, recommendations do not differ from the	Therapy Based Long Term Follow Up: Practice Statement (2nd Edition) http://ukccsg.org/public/followup/PracticeStatement/16.pdf

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Organization	Breast Imaging Surveillance Recommendation	Source / Public Link
	standard NHS Breast Cancer Screening Programme.	
The Netherlands Cancer Institute (82)	Screening based upon the dose and type of radiation. For women treated with chest RT ≥20 Gy or with total body irradiation of any dose, an annual breast MRI is recommended, starting at age 25. Then, starting at age 30, a mammogram is recommended with the MRI. For women treated with 7–19 Gy chest RT, an annual mammogram without an MRI is recommended, starting at age 30.	Website not currently available.