

1. What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with 1-19 Gy chest radiation?

Guibout et al. Malignant breast tumors after radiotherapy for a first cancer during childhood. J Clin Oncol 2005;23:197–204

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-centre cohort study 1946-1986 Follow-up: Mean 16 (range 3-46) yr Person-years of follow-up: 20,323	1,814 female 3-yr childhood cancer survivors aged <17 yr at diagnosis Breast cancer: 16/1814 (0.9%)	Chest radiation: 13/16 (81.3%) survivors with breast cancer 1245/1798 (69.2%) survivors without breast cancer Absorbed radiation dose: Mean 5.06 (range 0-78.6) Gy	<i>Relative risk (95% CI)</i> <i>Breast dose</i> >0-<1 Gy vs. 0 Gy: 1.3 (0.3-6.3) 1-<10 Gy vs. 0 Gy: 1.5 (0.3-8.1) 10-<20 Gy vs. 0 Gy: 3.7 (0.6-24.2) ≥20 Gy vs. 0 Gy: 2.5 (0.1-22.1) <i>P</i> for trend = 0.06 <i>Excess relative risk per Gy to the breasts (95% CI)</i> 0.13 (<0.0-0.75)	Analyses were adjusted for age at childhood cancer, attained age, castration, chemotherapy, and childhood cancer diagnosis. There is a significant methodological issue with this paper. The authors estimated the dose to the nipple and called it the dose to the breast throughout the paper. The nipple in a mantle field is generally near the edge or possibly under the blocking, therefore the dose to the nipple is not a mean dose to all of the breast. The unblocked portion of the breast receives the highest dose. Hodgkin lymphoma represented 5 of 13 breast cancer cases with radiation in their analysis and so this issue affects the interpretation of the findings. This methodological limitation may have resulted in an underestimation of the risk.

1. What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with 1-19 Gy chest radiation?

Inskip et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol 2009;27:3901-7

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-centre case-control study 1970-1986 Follow-up: Median 19·4 (range 6·7-29·6) yr	6,647 5-yr childhood cancer survivors aged ≤21 yr at diagnosis 120 childhood cancer survivors with breast cancer matched to 464 childhood cancer survivors without breast cancer	Chest radiation: 107/120 (89%) cases 328/464 (71%) controls Absorbed radiation dose: Mean 13·4 Gy controls Dose cases not reported (range >0·0-13 Gy to 30·0-60·0 Gy)	<i>Odds ratio (95% CI)</i> <i>Breast dose</i> >0·0-13 Gy vs. 0 Gy: 1·4 (0·5-4·4) 0·14-1·29 Gy vs. 0 Gy: 1·9 (0·7-5·4) 1·30-11·39 Gy vs. 0 Gy: 1·9 (0·7-5·0) 11·40-29·99 Gy vs. 0 Gy: 7·1 (2·9-17·0) 30·0-60·0 Gy vs. 0 Gy: 10·8 (3·8-31·0) <i>P for trend <0·001</i> <i>Excess odds ratio per Gy to the breasts (95% CI)</i> 0·27 (0·10-0·67) <i>Recalculated odds ratio (95% CI)</i> <i>Breast dose</i> 1·3-9·9 Gy vs. 0 Gy: 1·9 (0·7-5·4) 10·0-19·9 Gy vs. 0 Gy: 6·5 (2·3-18·5)	Analyses were adjusted for type of childhood cancer diagnosis.

* Personal communication from Peter Inskip, PhD, May 18, 2012.

1. What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with 1-19 Gy chest radiation?

Taylor et al. Second primary neoplasms in survivors of Wilms' tumour – a population-based cohort study from the British Childhood Cancer Survivor Study. *Int J Cancer* 2008;122:2085–93

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Population-based cohort study 1940-1991 Follow-up: Mean 19.3 yr; Person-years of follow-up since 5-yr survival: 27,841	1,441 5-yr Wilms tumour survivors aged <15 yr at diagnosis	Radiotherapy: 1269/1441 (88.1%) Radiation dose not reported	<i>Breast cancer</i> 9/1441 (0.6%); 8 females, 1 male <i>Standardized incidence ratio (95% CI)</i> 5.8 (2.6-11.0)	For the females, 1 had 3000 cGy to the right and left lower lobes of the lung in addition to 3000 cGy to the right and left abdomen; 4 women had 1200-1500 cGy whole lung radiation in addition to their abdominal radiation and 1 woman had unknown radiation. In summary, of the 7 women with known radiation fields, 5 had chest radiation in addition to abdominal radiation. Thus, we do not know whether the breast cancer was secondary to the low dose chest radiation (12-15 Gy), the high abdominal fields, or a combination.

1. What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with 1-19 Gy chest radiation?

Travis et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465–75

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Population-based nested case-control study 1965-1994 Follow-up: Median 18 (range 7-30) yr	3,817 female 1-yr Hodgkin lymphoma survivors aged ≤30 yr at diagnosis (20% <18) 105 survivors with breast cancer matched to 266 survivors without breast cancer	Chest radiation: 104/105 (99%) cases 256/266 (96%) controls Absorbed radiation dose: Mean 37.7 ± 4.7 Gy cases Mean 37.3 ± 4.1 Gy controls	<i>Relative risk (95% CI)</i> <i>Breast dose median (range)</i> 4.6 (4.0-6.9) Gy vs. 3.2 (0.3-9) Gy: 1.8 (0.7-4.5) 21.0 (7.0-23.1) Gy vs. 3.2 (0.3-9) Gy: 4.1 (1.4-12.3) 24.5 (23.2-27.9) Gy vs. 3.2 (0.3-9) Gy: 2.0 (0.7-5.9) 35.2 (28.0-37.1) Gy vs. 3.2 (0.3-9) Gy: 6.8 (2.3-22.3) 39.8 (37.2-40.4) Gy vs. 3.2 (0.3-9) Gy: 4.0 (1.3-13.4) 41.7 (40.5-61.3) Gy vs. 3.2 (0.3-9) Gy: 8.0 (2.6-26.4) <i>Excess relative risk per Gy to the breasts (95% CI)</i> 0.15 (95% CI: 0.04-0.73) <i>Detailed estimation relative risk (95% CI)*</i> <i>Breast dose</i> 1 Gy: 1.15 (1.04-1.73) 5 Gy: 1.75 (1.20-4.65) 6 Gy: 1.90 (1.24-5.38) 7 Gy: 2.05 (1.28-6.11) 13 Gy: 2.95 (1.52-10.49) 14 Gy: 3.10 (1.56-11.22) 19 Gy: 3.85 (1.76-14.87) 20 Gy: 4.00 (1.80-15.60) 30 Gy: 5.50 (2.20-22.90) 40 Gy: 7.00 (2.60-30.20)	Analyses were adjusted for number of cycles of alkylating agents and radiation dose delivered to the ovaries.

* Post hoc analysis performed by Cecile Ronckers, PhD, 2010.

1. What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with 1-19 Gy chest radiation?

van Leeuwen et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003;95:971–80

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Population-based nested case- control study 1965-1988 Follow-up: Median 18·7 yr	650 female 5-yr Hodgkin lymphoma survivors aged ≤40 yr at diagnosis (30% <20 yr) 48 survivors with breast cancer matched to 175 survivors without breast cancer	Chest radiation: 48/48 (100%) cases 172/175 (98%) controls Absorbed radiation dose: Mean 38·5 Gy cases Mean 37·6 Gy controls	<i>Relative risk (95% CI)</i> <i>Breast dose median (range)</i> 15·5 (4·23·2) Gy vs. 3·6 (0·26·3·9) Gy: 1·11 (0·32-3·58) 30·2 (24·38·2) Gy vs. 3·6 (0·26·3·9) Gy: 4·20 (0·99-17·8) 40·7 (38·5-56) Gy vs. 3·6 (0·26·3·9) Gy: 5·16 (1·27-21·0) <i>Excess relative risk per Gy (95% CI)</i> 0·06 (0·01-0·13)	Analyses were adjusted for ovary radiation dose and chemotherapy.

This cohort was also included in the cohort of Travis 2003.

2. What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with TBI?

Friedman et al. Increased risk of breast cancer among survivors of allogeneic hematopoietic cell transplantation: a report from the FHCRC and the EBMT-Late Effect Working Party. *Blood* 2008;111:939–44

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-centre cohort study 1969-2000 Follow-up: Median 9.9 (range 7.0-32.2) yr	3,337 female 5-yr HCT survivors aged 28.1 (0.2-70.3) yr at treatment (14% <18 yr) Breast cancer: 52/3337 (1.6%)	TBI: 47/52 (90.4%) survivors with breast cancer 2115/3285 (64.4%) survivors without breast cancer TBI dose: 8-15.75 Gy fractionated 9.2-10 Gy single fraction Absorbed radiation dose: Mean 5.06 Gy (range 0-78.6)	<i>10 yr cumulative incidence (95% CI)</i> No TBI: 0.1 (0.02-0.8) TBI: 1.1 (0.6-1.7) <i>20 yr cumulative incidence (95% CI)</i> No TBI: 1.3 (0.4-3.3) TBI: 6.1 (3.9-8.9) <i>25 yr cumulative incidence (95% CI)</i> No TBI: 2.8 (0.7-7.4) TBI: 16.9 (9.4-26.2) <i>Hazard ratio (95% CI)</i> TBI vs. no TBI: 4.0 (1.6-10.3) HCT <18 yr vs. HCT >40 yr: 9.5 (1.8-51.0)	No TBI group may not be an appropriate reference category, since patients in no TBI group are more likely to have ovarian failure due to high-dose alkylating agent preconditioning therapy (article did not provide information about therapy administered to non-TBI group or their menopausal status). This may have resulted in an overestimation of the risk. 25-yr cumulative breast cancer incidence was 6.5% (95%CI 2.3-13.8) among women <18 yr at HCT. Although, unclear how many were treated with TBI. Analyses were adjusted for follow-up time, age at transplantation and HCT location.

HCT = haematopoietic cell transplantation, TBI = total body irradiation.

3. What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with high abdominal field radiation (with or without chest radiation)?

Taylor et al. Second primary neoplasms in survivors of Wilms' tumour – a population-based cohort study from the British Childhood Cancer Survivor Study. *Int J Cancer* 2008;122:2085–93

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Population-based cohort study 1940-1991 Follow-up: Mean 19.3 yr; Person-years of follow-up since 5-yr survival: 27,841	1,441 5-yr Wilms tumour survivors aged <15 yr at diagnosis	Radiotherapy: 1269/1441 (88.1%) Radiation dose not reported	<i>Breast cancer</i> 9/1441 (0.6%); 8 females, 1 male All treated with abdominal field radiation (20-35 Gy) <i>Standardized incidence ratio (95% CI)</i> 5.8 (2.6-11.0)	For the females, 1 had 3000 cGy to the right and left lower lobes of the lung in addition to 3000 cGy to the right and left abdomen; 4 women had 1200-1500 cGy whole lung radiation in addition to their abdominal radiation and 1 woman had unknown radiation. In summary, of the 7 women with known radiation fields, 5 had chest radiation in addition to abdominal radiation. Thus, we do not know whether the breast cancer was secondary to the low dose chest radiation (12-15 Gy), the high abdominal fields, or a combination.

4. Does alkylating agent chemotherapy lower the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with chest radiation?

Bhatia et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol* 2003;21:386-94

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-centre cohort study 1955-1986 Follow-up: Median 18·1 (range 4·3-28·2) yr; Person-years of follow-up: 20,340	1,380 5-yr childhood Hodgkin lymphoma survivors aged ≤16 yr at diagnosis Breast cancer: 30/1380 (2·2%); 42 breast cancers in 30 patients (29 females, 1 male)	Chest radiation: 30/30 (100%) survivors with breast cancer Prescribed radiation dose: Median 35 (range 26-46) Gy in survivors with breast cancer Number of patients treated with alkylating agents not reported	<i>Relative risk (95% CI)</i> Alkylating agent score 3-9 vs. <3: 0·62 (0·09-2·48)	Analyses were adjusted for age at diagnosis, clinical stage, treatment groups (radiotherapy, chemotherapy, both) and recurrence of Hodgkin lymphoma. Alkylating agent score is an approximate measure of the total amount alkylating agents received.

4. Does alkylating agent chemotherapy lower the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with chest radiation?

Kenney et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med* 2004;141:590–7

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-centre cohort study 1970-1986 Follow-up: Median 19 (range 6-29) yr	6,068 5-yr childhood cancer survivors aged ≤21 yr at diagnosis Breast cancer: 95/6068 (1.6%)	Chest radiation: 73/95 (77%) survivors with breast cancer 1185/5973 (20%) survivors without breast cancer Radiation dose not reported Alkylating agents: 47/95 (50%) survivors with breast cancer 2939/5973 (49%) survivors without breast cancer	<i>Relative rate (95% CI)</i> Alkylating agent score 1-2 vs. 0: 0·8 (0·4-1·6) Alkylating agent score 3-4 vs. 0: 0·8 (0·4-1·4) Alkylating agent score ≥5 vs. 0: 1·11 (0·6-2·0) <i>P</i> for trend > 0·2	Analyses were adjusted for chest radiation. Alkylating agent score accounts for exposure to various alkylating agents and range of doses.

4. Does alkylating agent chemotherapy lower the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with chest radiation?

Inskip et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol 2009;27:3901–7

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-centre case-control study 1970-1986 Follow-up: Median 19·4 (range 6·7-29·6) yr	6,647 5-yr childhood cancer survivors aged ≤21 yr at diagnosis 120 childhood cancer survivors with breast cancer matched to 464 childhood cancer survivors without breast cancer	Chest radiation: 107/120 (89%) cases 328/464 (71%) controls Absorbed radiation dose: Mean 13·4 Gy controls Dose cases not reported Alkylating agents: 53/120 (44%) cases 200/464 (43%) controls	<i>Odds ratio (95% CI)</i> Chest radiation vs. no chest radiation: 2·7 (1·4-5·4) Alkylating agents vs. no alkylating agents: 0·93 (0·56-1·55) Alkylating agent score 1 vs. 0: 0·67 (0·30-1·51) Alkylating agent score 2 vs. 0: 1·40 (0·58-3·39) Alkylating agent score 3 vs. 0: 1·15 (0·55-2·41)	Analyses on alkylating agents were adjusted for radiation dose delivered to the breasts and ovaries, and for type of childhood cancer diagnosis. Alkylating agent dose scores were assigned to individual alkylating agents on the basis of the distributions of doses to each agent, and these scores were summed across agents.

4. Does alkylating agent chemotherapy lower the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with chest radiation?

Travis et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003; 290: 465–75

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Population-based nested case-control study 1965-1994 Follow-up: Median 18 (range 7-30) yr	3,817 female 1-yr Hodgkin lymphoma survivors aged ≤30 yr at diagnosis (20% <18) 105 survivors with breast cancer matched to 266 survivors without breast cancer	Chest radiation: 104/105 (99%) cases; 256/266 (96%) controls Absorbed radiation dose: Mean 37.7 ± 4.7 Gy cases Mean 37.3 ± 4.1 Gy controls Alkylating agents: 31/105 (30%) cases 104/266 (39%) controls	<i>Relative risk (95% CI)</i> Chest radiation only vs. none: 3.2 (1.4-8.2) Alkylating agents only vs. none: 0.6 (0.2-2.0) Alkylating agents and chest radiation vs. none: 1.4 (0.6-3.4) 1-4 cycles alkylating agents vs. 0 cycles: 0.7 (0.3-1.7) 5-8 cycles alkylating agents vs. 0 cycles: 0.6 (0.3-1.1) ≥9 cycles alkylating agents vs. 0 cycles: 0.2 (0.1-0.7) <i>P</i> for trend = 0.003	Analyses on alkylating agents were adjusted for radiation dose delivered to the breasts and ovaries.

Same cohort as Travis 2005.

4. Does alkylating agent chemotherapy lower the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with chest radiation?

Travis et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst 2005;97:1428–37

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Population-based cohort study 1965-1994 Follow-up: Median 18 (range 7-30) yr	3,817 female 1-yr Hodgkin lymphoma survivors aged ≤30 yr at diagnosis (20% <18 yrs) Breast cancer: 105/3817 (2.8%)	Chest radiation: 104/105 (99%) survivors with breast cancer 256/266 (96%) survivors without breast cancer Absorbed radiation dose: Mean 38.9 Gy cases Mean 38.6 Gy controls Alkylating agents: 31/105 (30%) survivors with breast cancer 104/266 (39%) survivors without breast cancer	<i>Relative risk (95% CI)</i> <i>Reference ≥40 Gy mediastinal radiation without alkylating agents</i> Alkylating agents without mediastinal radiation: 0.07 (0.02-0.36) No alkylating agents, no mediastinal radiation: 0.16 (0.47-0.72) Alkylating agents with 20-<40 Gy mediastinal radiation: 0.38 (0.19-0.77) Alkylating agents with ≥40 Gy mediastinal radiation: 0.47 (0.27-0.79) No alkylating agents with 20-<40 Gy mediastinal radiation: 0.82 (0.47-1.43)	<i>Relative risk (95% CI)</i> <i>Reference general population</i> Alkylating agents without mediastinal radiation: 0.8 (0.3-2.6) No alkylating agents, no mediastinal radiation: 1.7 (0.6-5.2) Alkylating agents with 20-<40 Gy mediastinal radiation: 4.0 (2.5-5.9) Alkylating agents with ≥40 Gy mediastinal radiation: 4.9 (2.9-7.5) No alkylating agents with 20-<40 Gy mediastinal radiation: 8.5 (5.4-13.2) No alkylating agents with ≥40 Gy mediastinal radiation: 10.5 (6.8-16.0)

Same cohort as Travis 2003.

4. Does alkylating agent chemotherapy lower the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with chest radiation?

van Leeuwen et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003;95:971–80

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Population-based nested case-control study 1965-1988 Follow-up: Median 18.7 yr	650 female 5-yr Hodgkin lymphoma survivors aged ≤40 yr at diagnosis (30% <20 yr) 48 survivors with breast cancer matched to 175 survivors without breast cancer	Chest radiation: 48/48 (100%) cases 172/175 (98%) controls Absorbed radiation dose: Mean 38.5 Gy cases Mean 37.6 Gy controls Alkylating agents: 12/48 (25%) cases 92/175 (53%) control	<i>Relative risk (95% CI)</i> <6 cycles alkylating agents vs chest radiation only: 0.31 (0.09-1.05) ≥6 cycles alkylating agents vs chest radiation only: 0.33 (0.13-0.86)	Analyses were adjusted for radiation dose delivered to the breasts and ovaries.

This cohort was also included in the cohort of Travis 2003 and Travis 2005.

4. Does alkylating agent chemotherapy lower the risk of breast cancer in childhood, adolescent and young adult cancer survivors treated with chest radiation?

de Bruin et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol 2009;27:4239–46

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Population-based cohort study 1965-1995 Follow-up: Median 17·8 (range 5-40) yr	1,122 female 5-yr Hodgkin lymphoma survivors aged <51 yr at diagnosis (30% ≤20 yr) Breast cancer: 120/1222 (9·8%)	Chest radiation: 119/120 (99·2%) survivors with breast cancer 813/1002 (81·1%) survivors without breast cancer Prescribed radiation dose not reported (patients usually received 40 Gy (36-44 Gy)) Alkylating agents: 33/120 (27·5%) survivors with breast cancer 448/1002 (44·7%) survivors without breast cancer	<i>Hazard ratio (95% CI)</i> Mantle radiation vs. mediastinal radiation: 2·7 (1·1-6·9) ≤8·4 g/m² procarbazine vs. no alkylating agents: 0·6 (0·3-0·9) >8·4 g/m² procarbazine vs. no alkylating agents: 0·4 (0·1-1·3) Chest radiation and MOPP vs. chest radiation only: 0·5 (0·3-0·9) Chest radiation and MOPP/ABV vs. chest radiation only: 0·5 (0·2-1·1) Chest radiation, MOPP and other alkylating agent vs. chest radiation only: 0·5 (0·2-1·2) Chest radiation and other alkylating agent vs. chest radiation only: 0·2 (0·1-0·6)	Analyses were based on 782 women treated with mantle field, axillary, or mediastinal radiation before age 41. Analyses on alkylating agents were adjusted for chest radiation, age at first radiation to the breast, time since first radiation to the breast, and pelvic radiation.

5. What is the diagnostic value of surveillance with a mammography in childhood, adolescent and young adult cancer survivors?

Dershaw et al. Breast carcinoma in women previously treated for Hodgkin disease: mammographic evaluation. *Radiology* 1992;184:421–3

Study design Study years Years of follow-up	Participants Age at study	Diagnostic test	Main outcomes	Additional remarks
<p>Single-centre retrospective cohort study</p> <p>Study years not reported</p> <p>Follow-up: Mean 18 (range 8-34) yr after diagnosis</p>	<p>27 female Hodgkin lymphoma survivors treated with chest radiation with 29 secondary breast cancers</p> <p>Prescribed radiation dose: 20-50 Gy</p> <p>Age at study: Mean 48 (range 33-75) yr at breast cancer diagnosis; 9/29 (31.0%) aged 33-39 yr</p>	<p>Mammography, physical findings</p>	<p>26/29 (89.7%) breast cancers detectable by mammography</p> <p>11/29 (37.9%) breast cancers only detected by mammography</p> <p>18/29 (62.1%) breast cancers detected by physical findings</p>	<p>Interpretation of the results is limited by the retrospective study design and small number of cases.</p>

5. What is the diagnostic value of surveillance with a mammography in childhood, adolescent and young adult cancer survivors?

Wolden et al. Management of breast cancer after Hodgkin's disease. J Clin Oncol 2000;18:765–72

Study design Study years Years of follow-up	Participants Age at study	Diagnostic test	Main outcomes	Additional remarks
<p>Single-centre retrospective cohort study</p> <p>Until 1997</p> <p>Follow-up: Median 17·4 (range 1·5-32·7) yr after diagnosis</p>	<p>65 female Hodgkin lymphoma survivors treated with chest radiation aged 13·3-71·8 (median 24·6) yr at diagnosis with 71 secondary breast cancers</p> <p>Prescribed radiation dose: mean 43·3 (range 24·0-51·0) Gy</p> <p>Age at study: Median 42·6 (range 23·0-79·1) yr at breast cancer diagnosis</p>	<p>Self-examination, clinical breast exam, mammography</p>	<p>19/71 (26·8%) breast cancers detected by mammography; of which 4 detected in women aged 33-38 yr</p> <p>7/71 (9·9%) breast cancer detected by clinical breast exam</p> <p>45/71 (63·3%) breast cancers detected by self-examination</p>	<p>Interpretation of the results is limited by the retrospective study design.</p>

5. What is the diagnostic value of surveillance with a mammography in childhood, adolescent and young adult cancer survivors?

Diller et al. Breast cancer screening in women previously treated for Hodgkin's disease: a prospective cohort study. *J Clin Oncol* 2002;20:2085–91

Study design Study years Years of follow-up	Participants Age at study	Diagnostic test	Main outcomes	Additional remarks
<p>Single-centre prospective cohort study</p> <p>1995-1999</p> <p>Follow-up: Median 16 (range 8-30) yr after diagnosis Median 3.1 (range 0-4.2) yr during study; Person-years of follow-up: 219.8</p>	<p>90 female 8-yr Hodgkin lymphoma survivors treated with mantle radiation; Age at diagnosis: Median 20 (range 13-30) yr</p> <p>Prescribed radiation dose: median 37.5 (range 30.0-41.5) Gy</p> <p>Age at study: Median 38 (range 24-51) yr; 40% <35 yr</p>	<p>Mammography: 79/90 (87.8%) at baseline; 84/90 (93.3%) during study</p>	<p><i>Baseline mammography</i> 10/79 (12.7%) abnormal mammography</p> <p><i>Recalls</i> 5/79 (6.3%) further imaging 5/79 (6.3%) biopsy 2/10 (20.0%) breast cancer</p> <p><i>Prevalent and incident breast cancers</i> 12/90 (13.3%) breast cancers detected in 10 patients; 10 invasive, 2 DCIS</p> <p>7/12 (58.3%) breast cancers initially detected by mammography; 12/12 (100%) detectable by mammography</p>	<p>1/12 (8.3%) breast cancers in women aged 25-29 yr; 2/12 (16.7%) breast cancers in women aged 30-34 yr; 0/12 (0%) breast cancers in women aged 35-39 yr.</p>

DCIS = ductal carcinoma-in-situ.

5. What is the diagnostic value of surveillance with a mammography in childhood, adolescent and young adult cancer survivors?

Kwong et al. Mammographic screening in women at increased risk of breast cancer after treatment of Hodgkin's disease. *Breast J* 2008;14:39–48

Study design Study years Years of follow-up	Participants Age at study	Diagnostic test	Main outcomes	Additional remarks
<p>Single-centre prospective cohort study</p> <p>2002</p> <p>Follow-up: Median 16.9 (range 4.5-32.5) yr after radiation</p> <p>No follow-up years during study, only baseline examinations</p>	<p>115 female Hodgkin lymphoma survivors treated with chest radiation; Age at diagnosis: Median 24 (range 13-24) yr</p> <p>Prescribed radiation dose: 15-≥44 Gy</p> <p>Age at study: Mean 40.4 (range 26-55) yr</p>	<p>Mammography: 99/115 (86.1%)</p>	<p><i>Baseline mammography</i> 17/99 (17.2%) abnormal mammography</p> <p><i>Recalls</i> 10/99 (10.1%) further imaging 7/99 (7.1%) biopsy 1/17 (5.9%) breast cancer</p> <p><i>Prevalent and incident breast cancers</i> 4/115 (3.5%) breast cancers detected in 4 patients; 2 invasive, 2 DCIS</p> <p>3/4 (75.0%) breast cancers initially detected by mammography; 4/4 (100%) detectable by mammography</p>	<p>1/4 (25.0%) breast cancers in women aged 25-29 yr; 0/4 (0%) breast cancers in women aged 30-34 yr; 2/4 (50.0%) breast cancers in women aged 35-39 yr.</p>

5. What is the diagnostic value of surveillance with a mammography in childhood, adolescent and young adult cancer survivors?

Lee et al. Screening mammography for young women treated with supradiaphragmatic radiation for Hodgkin's lymphoma. *Ann Oncol* 2008;19:62–7

Study design Study years Years of follow-up	Participants Age at study	Diagnostic test	Main outcomes	Additional remarks
Single-centre prospective cohort study 1997-2006 Follow-up: Median 13 (range 6-29) yr after diagnosis Median 5 (range 1-9) yr during study; Person-years of follow-up 855	115 female 8-yr Hodgkin lymphoma survivors treated with chest radiation; Age at diagnosis: Median 22 (9-31) yr Prescribed radiation dose: Median 35 (range 15-60) Gy Age at study: Median 35 (range 24-55) yr	Mammography only: 82/115 (71.3%) Mammography + MRI: 12/115 (10.4%) Mammography + ultrasound: 3/115 (2.6%) MRI only: 1/115 (0.7%)	Recalls not reported <i>Prevalent and incident breast cancers</i> 12/115 (10.4%) breast cancers detected in 12 patients; 7 invasive, 5 DCIS 5/12 (41.7%) breast cancers initially detected by mammography; 11/12 (91.7%) detectable by mammography	0/12 (0%) breast cancers in women aged 25-29 yr; 2/12 (16.7%) breast cancers in women aged 30-34 yr; 3/12 (25.0%) breast cancers in women aged 35-39 yr. 6 of 7 breast cancer cases presented with palpable masses were large, invasive ductal carcinomas with nodal involvement.

DCIS = ductal carcinoma-in-situ.

5. What is the diagnostic value of surveillance with a mammography in childhood, adolescent and young adult cancer survivors?

Howell et al. The UK national breast cancer screening programme for survivors of Hodgkin lymphoma detects breast cancer at an early stage. Br J Cancer 2009;101:582–8

Study design Study years Years of follow-up	Participants Age at study	Diagnostic test	Main outcomes	Additional remarks
Population-based retrospective cohort study 2003-2007 Follow-up: Mean 14.6 ± 9.1 yr after diagnosis Follow-up during study not reported	243 female 8-yr Hodgkin lymphoma survivors treated with chest radiation; Age at diagnosis: Mean 25.5 ± 5.3 yr Prescribed radiation dose: 35.2 ± 4.6 Gy for breast cancer cases; 33.92 ± 4.8 Gy for controls Age at study: Mean 40.3 ± 9.09 yr (none aged <30 yr)	Mammography's in the national notification risk assessment and screening program: 171/243 (70.4%); 370 in 171 patients	<i>Mammography within screening program</i> 39/370 (10.5%) abnormal mammography <i>Recalls</i> 31/370 (8.4%) further imaging 8/370 (2.2%) biopsy 5/39 (12.8%) breast cancer <i>Prevalent and incident breast cancers</i> 28/243 (11.5%) breast cancers detected in 23 patients; 25 invasive, 3 DCIS 10/28 (35.7%) breast cancers initially detected by mammography	-

DCIS = ductal carcinoma-in-situ.

6. What is the diagnostic value of a mammography, compared to a breast MRI, to detect breast cancer in an early stage in women in a young age group compared to another age group?

Kriege et al. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer. *Breast Cancer Res Treat* 2006;100:109–19

Study design Study years Years of follow-up	Participants Age at study	Diagnostic test Breast cancer	Main outcomes	Additional remarks
Multi-centre prospective cohort study 1999-2003 Follow-up: Median 2.9 (range 0.1-3.9) yr; 5,249 person-years at risk	1,779 women with a high familial risk of breast cancer (≥15% lifetime) without prior history of breast cancer Age at study: Mean 40 (range 19-72) yr	Mammography, MRI Screening examinations: 4134 Breast cancer: 45/1779 (2.5%); 39 invasive, 6 DCIS Cases of interval cancer: 4/45 (8.9%)	<i>Sensitivity mammography; odds ratio (95% CI)</i> ≥50 yr: 55.6%; ref 40-49 yr: 38.9%; 0.58 (0.11-3.0) <40 yr: 33.3%; 0.53 (0.09-3.04) P = 0.75 <i>Sensitivity MRI; odds ratio (95% CI)</i> ≥50 yr: 66.7%; ref 40-49 yr: 83.3%; 2.77 (0.34-22.25) <40 yr: 61.1%; 0.74 (0.09-5.94) P = 0.36 <i>Positive predictive value mammography</i> ≥50 yr: 7.8% 40-49 yr: 7.4% <40 yr: 9.6% P = 0.89 <i>Positive predictive value MRI</i> ≥50 yr: 5.7% 40-49 yr: 8.2% <40 yr: 8.2% P = 0.60 <i>False positive rate mammography; odds ratio (95% CI)</i> ≥50 yr: 5.4%; ref 40-49 yr: 6.3%; 1.10 (0.76-1.60) <40 yr: 3.9%; 0.64 (0.43-0.59) P = 0.004 <i>False positive rate MRI; odds ratio (95% CI)</i> ≥50 yr: 7.6%; ref 40-49 yr: 12.1%; 1.58 (1.17-2.13) <40 yr: 9.9%; 1.28 (0.95-1.73) P = 0.009 <i>Discriminating capacity MRI vs. mammography; AUC difference</i> ≥50 yr: 0.114 (P = 0.53) 40-49 yr: 0.227 (P = 0.02) <40 yr: 0.068 (P = 0.47)	Screening exam was defined positive if BI-RADS score was 0, 3, 4 or 5. Results were blinded so that the two examinations were not linked. Analyses were adjusted for hereditary risk and breast density. The precision of sensitivity estimates was affected by the small number of detected breast cancers resulting in wide confidence intervals. BI-RADS = Breast Imaging-Reporting and Data System.

6. What is the diagnostic value of a mammography, compared to a breast MRI, to detect breast cancer in an early stage in women in a young age group compared to another age group?

Sardanelli et al. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results. Invest Radiol 2011;46:94–105

Study design Study years Years of follow-up	Participants Age at study	Diagnostic test Breast cancer	Main outcomes	Additional remarks
<p>Multi-centre prospective cohort study</p> <p>2000-2007</p> <p>Follow-up not reported</p>	<p>501 women with a high familial risk of breast cancer; 44% prior history of breast and/or ovarian cancer</p> <p>Age at study: Median 45.0 (range 22-79) yr</p>	<p>Mammography, MRI , ultrasound, clinical breast exam</p> <p>Screening examinations: 1592; mean 3.2 per patient</p> <p>Breast cancer: 52/501 (10.4%); 44 invasive, 8 DCIS</p> <p>Cases of interval cancer: 3/52 (5.8%)</p> <p>2/52 (3.8%) breast cancers in women aged 20-29 yr 9/52 (17.3%) breast cancers in women aged 30-39 yr</p>	<p>Cancer detection rate per woman-year (95% CI): 3.1 (2.3-4.0)</p> <p><i>Mammography women <50 yr</i> Sensitivity: 45.5% (24.5-67.8) Specificity: 98.7% (97.5-99.5) Positive predictive value: 55.6% (30.8-78.5) Negative predictive value: 98.1% (96.7-99.0)</p> <p><i>Mammography women ≥50 yr</i> Sensitivity: 53.6% (33.9-72.5) Specificity: 99.5% (98.2-99.9) Positive predictive value: 88.2% (63.6-98.5) Negative predictive value: 96.9% (94.8-98.3)</p> <p><i>MRI women <50 yr</i> Sensitivity: 88.9% (65.3-98.6) Specificity: 96.6% (94.8-97.9) Positive predictive value: 43.2% (27.1-60.5) Negative predictive value: 99.7% (98.8-100)</p> <p><i>MRI women ≥50 yr</i> Sensitivity: 92.9% (76.5-99.1) Specificity: 96.9% (94.6-98.4) Positive predictive value: 68.4% (51.3-82.5) Negative predictive value: 99.5% (98.1-99.9)</p>	<p>Screening exam was defined positive if BI-RADS score was 4 or 5.</p> <p>Results were blinded so that the two examinations were not linked.</p> <p>BI-RADS = Breast Imaging-Reporting and Data System.</p>

7. What is the risk of breast cancer in childhood, adolescent and young adult cancer survivors aged >50 years treated with chest radiation?

No studies identified in childhood, adolescent and young adult cancer survivors or in other populations.

8. What is the diagnostic value of a clinical breast exam to detect breast cancer in an early stage in women aged <25 years?

No studies identified in childhood, adolescent and young adult cancer survivors or in other populations.

9. What is the diagnostic value of a breast MRI and a mammogram compared to a breast MRI to detect breast cancer in an early stage in women aged 25-35 years?

No studies identified in childhood, adolescent and young adult cancer survivors or in other populations.