Evidence tables breast cancer surveillance

From update

Who needs breast cancer surveillance?				
Veiga et al. Association of breast cancer risk after childhood cancer with radiation dose to the breast and anthracycline use: A report from the Childhood Cancer Survivors Study. JAMA Pediatr 2019; epub ahead of print				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center hospital-based nested case-control study 1970-1986 <u>Follow-up:</u> Range 5-40 yr since primary cancer diagnosis	10,440 5-yr female childhood cancer survivors aged <21 yr at diagnosis 271 childhood cancer survivors with breast cancer matched to 1,044 childhood cancer survivors without breast cancer <u>Age at diagnosis:</u> Cases: Median 15 (range 3-20) yr <u>Age at follow-up:</u> Range <30-58 yr <u>Age at breast cancer diagnosis:</u> Median 39 (range 20-57) yr <u>Pathogenic/likely pathogenic breast cancer gene mutation:</u> Not reported;	<u>Radiotherapy:</u> - Cases: 242 (89.3%) - Controls: 753 (72.1%) <u>Prescribed chest radiation dose:</u> Not reported <u>Alkylating agents:</u> - Cases: 154 (56.8%) - Controls: 520 (49.8%) <u>Anthracyclines:</u> - Cases: 94 (34.7%) - Controls: 317 (30.4%)	<u>Standardized incidence ratio (95% CI):</u> - Total group 4.6 (3.5-6.0) - Sarcoma survivors treated with chemotherapy only: 5.3 (3.5-7.8) - Leukemia and lymphoma survivors: 4.6 (2.7-7.3) - Neuroblastoma survivors: 4.1 (0.1-23.0) - Wilms tumor survivors: 2.1 (0.0-11.7) <u>Odds ratios (95% CI) in multivariable regression analysis:</u> - Chest radiation per 10 Gy: 3.9 (2.5-6.5) - Chest radiation <5 Gy vs. none: 1.7 (1.0-3.0) - Ovarian radiation any dose per 10 Gy chest radiation: 3.9 (2.5-6.9) - Ovarian radiation <1 Gy per 10 Gy chest radiation: 6.3 (3.6-12.0) - Ovarian radiation ≥1 Gy per 10 Gy chest radiation: 2.8 (1.8-5.2) *P = 0.01* - Anthracyclines per 100 mg/m^2: 1.23 (1.09-1.39) - Anthracyclines per 100 mg/m^2 in survivors with Li-Fraumeni syndrome associated cancers: 1.31 (1.1-1.5)	Controls were matched 4:1 to cases by age at primary cancer diagnosis and duration of follow-up (±2 yr). Li-Fraumeni syndrome associated cancers: leukemia, central nervous system tumors and non-Ewing sarcoma. Analyses were adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer, and chemotherapy. There was no evidence that type of first cancer, age at radiation exposure, age at menarche, or menopausal status modified the radiation dose-response relationship for breast cancer overall. The exception was radiotherapy after menarche, which was associated with a significantly lower dose response (*P* = 0.01). This difference was

	Family history of breast or ovarian cancer: - Cases: 21 (7.7%) - Controls: 45 (4.3%)		- Anthracyclines per 100 mg/m^2 in survivors with non Li-Fraumeni syndrome associated cancers: 1.16 (1.0-1.4) - Anthracyclines 1-223 mg/m^2 vs. none: 2.3 (1.3-4.2) - Anthracyclines 224-343 mg/m^2 vs. none: 2.4 (1.3-4.6) - Anthracyclines 344-455 mg/m^2 vs. none: 1.5 (0.7-3.2) - Anthracyclines >455 mg/m^2 vs. none: 3.8 (1.8-8.2) *Additive interaction between radiotherapy and anthracyclines (P = 0.04):* - No anthracyclines and 1-<10 Gy chest radiation vs. 0-<1 Gy chest radiation: 2.1 (0.9-4.8) - No anthracyclines and ≥10 Gy chest radiation vs. 0-<1 Gy chest radiation: 9.6 (4.4-20.7) - Anthracyclines and 1-<10 Gy chest radiation vs. 0-<1 Gy chest radiation: 3.7 (1.4-10.3) - Anthracyclines and ≥10 Gy chest radiation vs. 0-<1 Gy chest radiation: 19.1 (7.6-48.0) - Doxorubicin yes vs. no: 2.1 (1.3-3.3) - Doxorubicin >0-279 mg/m^2 vs. none: 2.0 (1.1-3.5) - Doxorubicin 279-<424 mg/m^2 vs. none: 1.8 (0.9-3.6) - Doxorubicin ≥424 mg/m^2 vs. none: 2.7 (1.3-5.8) - Daunorubicin yes vs. no: 1.1 (0.5-2.6) - Alkylating agents yes vs. no: 1.1 (0.8-1.5) - Cyclophosphamide equivalent dose >0-<5,201 mg/m^2 vs. none: 0.8 (0.4-1.4) - Cyclophosphamide equivalent dose	reduced and nonsignificant, however, when analysis were restricted to patients receiving ovarian doses <1 Gy (*P* = 0.53). **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, for all participants the follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer, and chemotherapy.

			5,201-<9,435 mg/m^2 vs. none: 1.4 (0.8-2.3) - Cyclophosphamide equivalent dose 9,435-<13,955 mg/m^2 vs. none: 1.1 (0.7-1.9) - Cyclophosphamide equivalent dose ≥13,955 mg/m^2 vs. none: 0.9 (0.5-1.5)	

Who needs breast cancer surveillance?				
Turcotte et al. Chemotherapy and risk of subsequent malignant neoplasms in the Childhood Cancer Survivor Study Cohort. J Clin Oncol 2019;37:3310-3319.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study 1970-1999 Follow-up: Range 5-46.7 yr since primary cancer diagnosis	10,440 5-yr female childhood cancer survivors aged <21 yr at diagnosis *Data of total cohort including men* Age at diagnosis: Median 7.0 (range 0-20.9) yr Age at follow-up: Median 31.9 (range 5.6-65.9) yr Age at breast cancer diagnosis: Not reported Pathogenic/likely pathogenic breast cancer gene mutation:	*Treatment data of total cohort including men* Chest radiation: Not reported Any radiotherapy: 11,791 (53.2%) Cyclophosphamide equivalent dose: - 1-3,999 mg/m^2: 2,585 (11.7%) - 4,000-7,999 mg/m^2: 2,670 (12.1%) - ≥8,000 mg/m^2: 5,190 (23.4%) Anthracyclines: - 0-100 mg/m^2: 1,404 (6.3%) - 101-300 mg/m^2: 5,040 (22.7%) - >300 mg/m^2: 3,363 (15.2%)	Breast cancer: 51/10,440 (0.5%) Standardized incidence ratio (95% CI): - Total group 4.6 (3.5-6.0) - Sarcoma survivors treated with chemotherapy only: 5.3 (3.5-7.8) - Leukemia and lymphoma survivors: 4.6 (2.7-7.3) - Neuroblastoma survivors: 4.1 (0.1-23.0) - Wilms tumor survivors: 2.1 (0.0-11.7) Relative risks (95% CI) in multivariable regression analysis in survivors treated with chemotherapy only: - Anthracyclines per 100 mg/m^2: 1.3 (1.2-1.6) (linear dose-response) - Anthracyclines 0-100 mg/m^2 vs. none: 0.9 (0.1-9.1) - Anthracyclines 101-300 mg/m^2 vs. none: 1.8 (0.6-6.0) - Anthracyclines 301-600 mg/m^2 vs. none: 3.7 (1.3-10.8)	There were no separate analyses performed for survivors with and without pathogenic/likely pathogenic mutations that predispose to breast cancer. Analyses were adjusted for age at primary cancer diagnosis, treatment era, history of splenectomy, cyclophosphamide equivalent dose, anthracyclines, epipodophyllotoxins and platinum agents. **Risk of bias:** - Selection bias: 24,355 out of 35,918 (67.8%) eligible survivors were included in the study - Attrition bias: low risk, for all participants the follow-up was complete. - Detection bias: unclear if the

	Not reported		- Anthracyclines >600 mg/m^2 vs. none: 8.1 (1.2-56.0) - Cyclophosphamide equivalent dose 1-2,000 mg/m^2 vs. none: 0.8 (0.1-6.9) - Cyclophosphamide equivalent dose 2,001-4,000 mg/m^2 vs. none: 0.5 (0.1-3.8) - Cyclophosphamide equivalent dose 4,001-7,000 mg/m^2 vs. none: 2.6 (0.9-7.4) - Cyclophosphamide equivalent dose 7,001-10,000 mg/m^2 vs. none: 1.5 (0.5-5.3) - Cyclophosphamide equivalent dose >10,000 mg/m^2 vs. none: 1.4 (0.5-4.3)	outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for age at primary cancer diagnosis, treatment era, history of splenectomy, cyclophosphamide equivalent dose, anthracyclines, epipodophyllotoxins and platinum agents.

Who needs breast cancer surveillance? At what age should breast cancer surveillance be stopped?				
Ehrhardt et al. Subsequent breast cancer in female childhood cancer survivors in the St Jude Lifetime Cohort Study (SJLIFE). J Clin Oncol 2019;37:1647-1656.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single center cohort study Treatment era not reported Follow-up: Median 22.7 (range 10.5-48.2) yr since primary cancer diagnosis	1,467 female 10-yr childhood cancer survivors with an attained age of at least 18 yr Age at diagnosis: Median 6.9 (range 0-22.7) yr Age at follow-up: Median 30.5 (range 18.5-64.6) yr Age at breast cancer diagnosis:	Chest radiation: 436 (29.7%) Chest radiation field: - TBI: 66 (6.0%) - Whole lung: 112 (10.1%) - Mantle: 594 (53.6%) - Mediastinal: 217 (19.6%) - Other chest fields: 119 (10.7%) Chest radiation dose: - >0-9 Gy: 103 (7.0%) - 10-19 Gy: 84 (5.7%) - 20-29 Gy: 150 (10.2%) - ≥30 Gy: 99 (6.8%)	Breast cancer: 56/1,467 (17.5%) developed 68 breast cancers Cumulative incidence: - By age 35 yr unexposed to chest radiation: 1% - By age 50 yr unexposed to chest radiation: 15% - By age 35 yr ≥10 Gy chest radiation: 8% - By age 50 yr ≥10 Gy chest radiation: 41% - By age 35 yr unexposed to anthracyclines: 2% - By age 50 yr unexposed to anthracyclines: 15% - By age 35 yr ≥250 mg/m^2 anthracyclines:	976 (66.5%) total and 37 (66.1%) with breast cancer were also participants in the Childhood Cancer Survivor Study. 17 breast cancers were diagnosed by physical findings, 33 by imaging, 7 by prophylactic mastectomy, 11 unknown. **Risk of bias:** - Selection bias: high risk, 1,467/2,246 (65.3%) were included in the study group. - Attrition bias: low risk, for all participants the follow-up was

	Median 38.6 (range 24.5-53.0) yr <u>Pathogenic/likely pathogenic breast cancer gene mutation:</u> - None: 1,317 (89.8%) - BRCA1: 7 (0.5%) - BRCA2: 5 (0.2%) - ATM: 1 (0.1%) - CDH1: 0 (0.0%) - CHEK 2: 1 (0.1%) - PALB2: 3 (0.2%) - PTEN: 1 (0.1%) - STK11: 0 (0.0%) - TP53: 8 (0.5%) - Unknown/not tested: 124 (8.5%)	<u>Pelvic radiation:</u> - 0 Gy: 1,121 (76.4%) - >0-9 Gy: 73 (5.0%) - 10-19 Gy: 98 (6.7%) - 20-29 Gy: 84 (5.7%) - ≥30 Gy: 91 (6.2%) <u>Alkylating agents:</u> 839 (57.2%) <u>Anthracyclines:</u> 849 (57.98%)	7% - By age 50 yr ≥250 mg/m^2 anthracyclines: 46% <u>Hazard ratios (95% CI) in multivariable Cox regression analysis:</u> *Total study group* - Chest radiation >0 - <10 Gy vs. none: 0.7 (0.2-2.8) - Chest radiation 10 - <20 Gy vs. none: 2.4 (0.4-15.0) - Chest radiation ≥20 Gy vs. none: 7.6 (2.9-20.4) - Pelvic radiation yes vs. no: 1.8 (0.9-3.9) - Alkylating agents <0 - 5,999 mg/m^2 vs. none: 1.0 (0.4-2.6) - Alkylating agents ≥6,000 mg/m^2 vs. none: 0.4 (0.2-0.9) - Anthracyclines 1-249 mg/m^2 vs. none: 2.6 (1.1-6.2) - Anthracyclines ≥250 mg/m^2 vs. none: 13.4 (5.5-13.4) - Pathogenic/likely pathogenic mutation ≥1 vs. none: 23.0 (7.3-72.2) - Age at childhood cancer diagnosis per yr: 1.0 (1.0-1.1) *Excluding survivors with pathogenic/likely pathogenic mutations* - Chest radiation >0 - <10 Gy vs. none: 1.2 (0.3-5.0) - Chest radiation 10 - <20 Gy vs. none: 8.0 (1.1-56.3) - Chest radiation ≥20 Gy vs. none: 10.0 (3.3-30.5) - Pelvic radiation yes vs. no: 1.8 (0.8-4.0) - Alkylating agents <0 - 5,999 mg/m^2 vs. none: 1.5 (0.6-4.1) - Alkylating agents ≥6,000 mg/m^2 vs. none:	complete. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, analyses were adjusted for chest radiation, age at primary childhood cancer diagnosis, alkylating agents, pelvic radiation and anthracyclines.

			0.4 (0.2-1.1) - Anthracyclines 1-249 mg/m^2 vs. none: 2.5 (1.0-6.1) - Anthracyclines ≥250 mg/m^2 vs. none: 15.1 (6.1-37.6) - Age at childhood cancer diagnosis per yr: 1.0 (1.0-1.1) *Excluding survivors with ≥10 Gy chest radiation and pathogenic/likely pathogenic mutations* - Alkylating agents <0 - 5,999 mg/m^2 vs. none: 0.8 (0.1-7.0) - Alkylating agents ≥6,000 mg/m^2 vs. none: 0.6 (0.1-3.9) - Anthracyclines 1-249 mg/m^2 vs. none: 2.1 (0.2-27.0) - Anthracyclines ≥250 mg/m^2 vs. none: 16.9 (2.2-126.6) - Age at childhood cancer diagnosis per yr: 1.0 (0.9-1.2)	

What surveillance modality should be used?				
Ehrhardt et al. Subsequent breast cancer in female childhood cancer survivors in the St Jude Lifetime Cohort Study (SJLIFE). J Clin Oncol 2019;37:1647-1656.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Single center cohort study Treatment era not reported <u>Follow-up:</u> Median 22.7 (range 10.5-48.2) yr since primary cancer diagnosis	1,467 female 10-yr childhood cancer survivors with an attained age of at least 18 yr, of whom 263 were eligible for breast cancer screening <u>Age at diagnosis:</u> Median 6.9 (range 0-22.7) yr <u>Age at follow-up:</u> Median 30.5 (range 18.5-64.6) yr <u>Age at breast cancer diagnosis:</u> Median 38.6 (range 24.5-53.0) yr <u>Chest radiation:</u> 436 (29.7%)	<u>Mammogram:</u> - Total group: 206/263 (78.3%) - ≥20 Gy chest radiation: 167/192 (87.0%) <u>MRI:</u> - Total group: 180/263 (68.14%) - ≥20 Gy chest radiation: 147/192 (76.5%) <u>Both mammogram and MRI:</u> - Total group: 179 (68.1%) - ≥20 Gy chest radiation: 147/192 (76.5%) <u>Breast cancer:</u> 56/1,467 (17.5%) developed 68 breast cancers; 33 detected by imaging (17 invasive ductal carcinoma, 16 DCIS) <u>Mean age at screening:</u> 36.9 ± 7.8 yr	<u>Sensitivity (95% CI):</u> - Mammogram: 53.8% (26.8% -80.9%) - MRI: 69.2% (44.1%-94.3%) - Mammogram and MRI: 85.8% (72.4%-99.2%; either image positive) <u>Specificity:</u> - Mammogram: 96.3% (94.1%-98.4%) - MRI: 91.4% (88.1%-94.6%) - Mammogram and MRI: 99.7% (99.3%-100.0%; both images negative)	Screening exam was defined positive if BI-RADS score was 4 or 5. **Risk of bias:** - <u>Selection bias:</u> high risk, 1,467/2,246 (65.3%) were included in the study group. - <u>Index test bias:</u> low risk, radiologists blinded to clinical outcomes retrospectively reviewed images (n = 156) for a subset of individuals (n = 139) for whom both mammography and MRI were performed in parallel. - <u>Verification bias:</u> low risk, biopsies were performed when imaging detected a mass. Interval between mammogram and MRI was less than 4 months. - <u>Attrition bias:</u> low risk, 206/263 (78.3%) women underwent breast cancer screening.

DCIS = ductal carcinoma-in-situ.

Who needs breast cancer surveillance? At what age should breast cancer surveillance be stopped?				
Holmqvist et al. Risk of solid subsequent malignant neoplasms after childhood Hodgkin lymphoma – Identification of high-risk populations to guide surveillance: A report from the Late Effects Study Group. Cancer 2019;125:1373-1383.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter cohort study 1955-1986 Follow-up: 23,212 person-years from time of Hodgkin lymphoma diagnosis (data from total study group including males) Time between Hodgkin lymphoma and of breast cancer: Median 25 (range 10-40) yr	1,136 childhood Hodgkin lymphoma survivors aged <16 yr at diagnosis of whom 389 females Age at diagnosis: Median 11 (range 0-16) yr Age at follow-up: Not reported Age at breast cancer diagnosis: Median 37 (range 24-49) yr	*Whole cohort including males and females* Radiotherapy only: 253 (22%) Chemotherapy only: 111 (10%) Radiotherapy and chemotherapy: 162 (67%) Chest radiation field and dose: Not reported Alkylating agent score: - 0: 309 (28%) - 1: 216 (19%) - 2: 401 (36%) - 3+: 185 (17%)	Breast cancer: 42/389 (10.8%) 40-yr cumulative incidence (95% CI): 20.1% (14.5-26.3) Cumulative incidence by age 50 yr (95% CI): 23.5% (16.9-30.7) Standardized incidence ratio (95% CI) - Overall: 25.8 (19.3-33.5) - Aged 0-9 yr at Hodgkin lymphoma diagnosis: 5.9 (1.5-15.3) - Aged 10-16 yr at Hodgkin lymphoma diagnosis: 32.7 (24.3-42.8) Absolute excess risk per 1,000 person-years: - Overall: 6.4 - Attained age ≤29 yr: 2.4 - Attained age 30-39 yr: 12.0 - Attained age ≥40 yr: 23.3 Hazard ratios (95% CI) in multivariable Cox regression analysis: - Chest radiation yes vs. no: 5.0 (1.5-30.7) - Alkylating agent score ≥2 vs. 0 or 1: 0.5 (0.3-0.9) - Anthracyclines yes vs. no: 0.83 (0.3-1.9) - Age at Hodgkin lymphoma diagnosis 10-16 vs. 0-9 yr: 9.01 (2.8-55.4)	Of the 42 women with breast cancer, 9 developed contralateral breast cancer after a median of 5.9 (range 1.6-10.5) years. The incidence of a contralateral breast cancer was 26.6% at 10 years from diagnosis of the first breast cancer. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many survivors follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for chest radiation, age at primary childhood cancer diagnosis, alkylating agents and anthracyclines.

Who needs breast cancer surveillance? At what age should breast cancer surveillance be stopped?				
Demoor-Goldschmidt et al. Clinical and histological features of second breast cancers following radiotherapy for childhood and young adult malignancy. British Journal of Radiology 2018;91:20170824				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter retrospective cohort study 1950-2000 Follow-up: Time between primary cancer and breast cancer: Median 21.0 (range 3.0-48.0) yr	121 childhood cancer survivors aged <31 yr at diagnosis with secondary breast cancer aged <51 yr Age at diagnosis: Mean 15.3 (range 0.5-30.6) yr Age at breast cancer diagnosis: Median 38 (range 25.0-50.5) yr	Mean prescribed radiation dose: 37 (range 10-45) Gy Chemotherapy type: Not reported	Breast cancer: 121 women developed 141 breast cancers Breast cancer by treatment exposure: - Supradiaphragmatic radiation: 99 (81.8%) - TBI: 5 (4.1%) - Abdominal radiation: 16 (13.2%) - Craniospinal: 1 (0.8%) - Max estimated breast dose <10 Gy: 17 (14.0%) - Max estimated breast dose 10-20 Gy: 19 (15.7%) - Max estimated breast dose ≥20 Gy: 85 (70.2%) - Chemotherapy: 96 (79.3%); 52% with anthracyclines Breast cancer by pubertal stage at radiotherapy: - Pre-puberty: 26 (21.5%) - Puberty: 20 (16.5%) - Post-puberty: 75 (62.0%)	**Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, follow-up was complete for all survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: not applicable, only descriptive data reported.

Who needs breast cancer surveillance?				
Moskowitz et al. Radiation-associated breast cancer and gonadal hormone exposure: a report from the Childhood Cancer Survivor Study. British Journal of Cancer 2017;117:290-299.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter cohort study 1970-1986 <u>Follow-up:</u> Median 26 (range 5-38) yr	1,108 female 5-yr childhood cancer survivors aged <21 yr at diagnosis treated with chest radiation within 5 years of childhood cancer diagnosis and survived until at least 20 years of age <u>Age at diagnosis:</u> Range 0-20 yr <u>Age at follow-up:</u> Range 20-59 yr <u>Age at breast cancer diagnosis:</u> Median 38 (range 23-58) yr <u>Age at menarche:</u> Breast cancer cases: median 13 (range 9-20) yr; Whole cohort: never (5.8%), 9-10 yr (4.2%), 11-12 yr (35.4%), 13-14 yr (35.6%), 15-16 yr (10.7%), ≥17 yr (2.4%)	<u>Chest radiation:</u> 1,108 (100%) <u>Chest radiation field:</u> - TBI: 66 (6.0%) - Whole lung: 112 (10.1%) - Mantle: 594 (53.6%) - Mediastinal: 217 (19.6%) - Other chest fields: 119 (10.7%) <u>Delivered chest radiation dose:</u> - 1-19 Gy: 212 (19.1%) - 20-29 Gy: 190 (17.2%) - 30-39 Gy: 284 (25.6%) - ≥40 Gy: 418 (37.7%) <u>Cyclophosphamide equivalence dose (CED):</u> - 544 (49.1%) - 1-8,499 mg/m^2: 208 (18.8%) - 8,500-13,999 mg/m^2: 196 (17.7%) - ≥14,000 mg/m^2: 140 (12.6%) <u>Ovaries in concurrent radiation field:</u> 120 (10.8%) <u>Anthracyclines:</u> 385 (34.8%)	<u>Breast cancer:</u> 195/1,108 (17.6%) <u>Hazard ratios (95% CI) in multivariable Cox regression analysis:</u> - CED >0<14,000 mg/m2 vs. none: 0.86 (0.61-1.20) - CED ≥14,000 mg/m2 vs. none: 0.41 (0.21-0.79), *P trend* = 0.025 - CED >0<14,000 mg/m2 vs. none in survivors with breast cancer diagnosis <40 yrs of age: 0.89 (0.57-1.39) - CED ≥14,000 mg/m2 vs. none in survivors with breast cancer diagnosis <40 yrs of age: 0.50 (0.23-1.08) - CED >0<14,000 mg/m2 vs. none in survivors with breast cancer diagnosis ≥40 yr of age: 0.80 (0.47-1.36) - CED ≥14,000 mg/m2 vs. none in survivors with breast cancer diagnosis ≥40 yr of age: 0.26 (0.08-0.87) - Procarbazine 1-4,200 mg/m^2 vs. none: 0.97 (0.61-1.54) - Procarbazine 4,201-7,036 mg/m^2 vs. none: 1.03 (0.66-1.62) - Procarbazine ≥7,037 mg/m^2 vs. none: : 0.58 (0.31-1.11) *P trend* = 0.415 - Ovarian radiation yes vs. no: 0.35 (0.18-	Analyses of each potential risk factor were adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines. Analysis on estrogen and progestin were also adjusted for age at menopause. Years of gonadal hormone exposure was calculated as years of ovarian function (endogenous hormone exposure) plus years of subsequent exogenous hormone exposure. **Risk of bias:** - <u>Selection bias:</u> unclear how many patients were included in the original cohort of survivors. - <u>Attrition bias:</u> high risk, 694/1108 (63%) returned the third follow-up questionnaire. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, analyses were adjusted for chest radiation field and dose, age at primary childhood cancer

	<u>Age at menopause:</u> Breast cancer cases: median 33 (range 11-54) yr; Whole cohort: still menstruating at last contact (47.5%), <20 yr (4.7%), 20-29 yr (3.6%), 30-39 yr (7.1%), ≥40 yr (7.5%), no menarche (5.8%), unknown due to hysterectomy (4.1%)	<u>Exogenous hormone exposure:</u> - None reported (23.1%) - Estrogen only (3.3%) - Progestin only (3.5%) - Combination (50.1%)	0.69) - Years of ovarian function after chest radiation ≥10 yr vs. <10 yr: 2.89 (1.56-5.35) - Years of ovarian function after chest radiation ≥10 yr vs. <10 yr in survivors with breast cancer diagnosis <40 yr of age: 3.30 (1.50-7.25) - Years of ovarian function after chest radiation ≥10 yr vs. <10 yr in survivors with breast cancer diagnosis ≥40 yr of age: 2.57 (0.91-7.23) - No menarche vs. still menstruating: 0.12 (0.02-0.89) - Age at menopause <20 yr vs. still menstruating: 0.60 (0.32-1.13) - Age at menopause 20-39 yr vs. still menstruating: 0.82 (0.49-1.36) - Age at menopause ≥40 yr vs. still menstruating: 0.87 (0.43-1.80) *P trend* = 0.014 - No menarche vs. chest radiation >3 yr after menarche: 0.16 (0.02-1.18) - Chest radiation >3 yr before menarche vs. >3 yr after menarche: 1.31 (0.53-3.29) - Chest radiation 1-3 yr before menarche vs. >3 yr after menarche: 1.08 (0.45-2.56) - Chest radiation ± 1 yr of menarche vs. >3 yr after menarche: 2.04 (1.18-3.53) - Chest radiation 1-2 yr after menarche vs. >3 yr after menarche: 1.42 (0.78-2.57) - Chest radiation 2-3 yr after menarche vs. >3 yr after menarche: 1.49 (0.89-2.47) - Chest radiation <1 yr of menarche vs. ≥1 yr from menarche: 1.80 (1.19-2.72) - Years of gonadal hormone exposure ≥10	diagnosis and anthracyclines.

			yr vs. <10 yr: 1.59 (0.88-2.90) - Years of gonadal hormone exposure ≥10 yr vs. <10 yr in survivors with breast cancer diagnosis <40 yr of age: 2.00 (0.92-4.36) - Years of gonadal hormone exposure ≥10 yr vs. <10 yr in survivors with breast cancer diagnosis ≥40 yr of age: 1.08 (0.43-2.72) - Combined estrogen and progestin use yes vs. no: 1.54 (0.70-3.40)	

Who needs breast cancer surveillance?				
Teepen et al. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: Role of chemotherapy. J Clin Oncol 2017;35:2288-2298.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter nationwide retrospective cohort study 1963-2001 Follow-up: Median 20.7 (range 5.0-49.8) yr since primary cancer diagnosis	6,165 5-yr childhood cancer survivors aged <18 yr at diagnosis of whom 2,731 females Age at diagnosis: Range 0-18 yr Age at follow-up: Median 28.1 (range 5.3-65.1) yr	*Whole cohort including males and females* Chest radiation: 395/6165 (6.4%) Chest radiation dose: Not reported TBI: 221/6165 (3.6%) TBI dose females: 7.5 (range 1.6-12) Gy Spinal radiation: 443/6165 (7.2%) Abdominal/pelvic radiation: 467/6165 (7.6%) Alkylating agents: 3136/6165 (50.9%) Anthracyclines: 2788/6165 (45.2%)	Standardized incidence ratio female breast cancer: 5.1 (3.8-6.9); n=45 Hazard ratio (95% CI) in multiple Cox regression analysis: *All childhood cancer survivors* Model 1 - Chest radiation yes vs. no: 2.5 (1.3-4.9) - TBI yes vs. no: 10.6 (3.7-30.2) - Doxorubicin ≤270 mg/m^2 vs. none: 1.1 (0.4-2.9) - Doxorubicin 271-443 mg/m^2 vs. none: 2.6 (1.1-6.5) - Doxorubicin >443 mg/m^2 vs. none: 5.8 (2.7-12.5) *P trend* < 0.001 - Ifosfamide yes vs. no: 3.4 (1.3-8.8) Model 2 - Anthracyclines 1-249 mg/m^2 vs. none: 1.3 (0.5-3.2) - Anthracyclines ≥250 mg/m^2 vs. none: 3.1 (1.4-6.5) *P trend* = 0.004 - Cyclophosphamide equivalence dose <6,000 mg/m^2 vs. none: 2.0 (0.9-4.8) - Cyclophosphamide equivalence dose 6,000-17,999 mg/m^2 vs. none: 1.7 (0.7-3.9) - Cyclophosphamide equivalence dose ≥18,000 mg/m^2 vs. none: 1.0 (0.2-4.5) *P trend* = 0.99	Analyses on radiation were adjusted for alkylating agents, anthracyclines and type of radiation (as shown in the results). Analyses on chemotherapy were adjusted for chest radiation, TBI and chemotherapy groups (as shown in the results). Out of 77 patients treated with TBI, 5 developed breast cancer. TBI dose breast cancer cases: median 12 (range 7.5-12) Gy, 7.5, 8, 12, 12, and 12 Gy respectively; TBI dose non-breast cancer cases: median 7.5 (range 1.2-12) Gy. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, for 6026 /6165 (98%) survivors follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for chest

			Childhood leukemia, CNS tumor and sarcoma (except Ewing) survivors (potentially Li-Fraumeni syndrome associated) - Doxorubicin ≤270 mg/m^2 vs. none: 0.6 (0.1-3.2) - Doxorubicin 271-443 mg/m^2 vs. none: 9.1 (2.5-32.8) - Doxorubicin >443 mg/m^2 vs. none: 14.8 (5.1-43.2) *P trend* <0.001 - Ifosfamide yes vs. no: 2.8 (0.9-8.8) *Non-LFS childhood cancer survivors* - Doxorubicin ≤270 mg/m^2 vs. none: 1.9 (0.6-6.2) - Doxorubicin 271-443 mg/m^2 vs. none: 1.1 (0.2-4.9) - Doxorubicin >443 mg/m^2 vs. none: 2.4 (0.7-8.4) *P trend* = 0.94 - Ifosfamide yes vs. no: 5.1 (1.1-24.3) *Childhood cancer survivors treated without chest radiation* - Ifosfamide yes vs. no: 2.3 (0.6-0.8) - Doxorubicin ≤270 mg/m^2 vs. none: 1.3 (0.3-6.1) - Doxorubicin 271-443 mg/m^2 vs. none: 5.6 (1.9-16.2) - Doxorubicin >443 mg/m^2 vs. none: 9.9 (4.2-23.8) *P trend* = 0.002	radiation, alkylating agents, anthracyclines and type of radiation.

Who needs breast cancer surveillance?				
Krul et al. Breast cancer risk after radiation therapy for Hodgkin lymphoma: influence of gonadal hormone exposure. International Journal of Radiation Oncology Biology and Physics 2017;99:843-853.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter nested case-control study 1965-2000 <u>Follow-up:</u> Not reported (Time to breast cancer diagnosis median 21.9 (interquartile range 16.9-26.8) yr	3,905 female 5-yr Hodgkin lymphoma survivors treated before age 41 yr 174 Hodgkin lymphoma survivors with breast cancer matched to 466 Hodgkin lymphoma survivors without breast cancer <u>Age at diagnosis:</u> Median 23.5 (interquartile range 19.6-28.8) yr <u>Age at follow-up:</u> Not reported (age at breast cancer diagnosis median 46.1 (interquartile range 16.9-26.8) yr	<u>Chest radiation:</u> - Cases: 172 (98.9%) - Controls: 419 (89.9%) <u>Chest radiation dose to breast tumor location:</u> Cases: - 0.0-2.9 (median 1.2) Gy: 18 (10.3%) - 3.0-7.9 (median 4.9) Gy: 25 (14.4%) - 8.0-27.9 (median 17.5) Gy: 36 (20.7%) - 28.0-35.9 (median 33.9) Gy: 33 (19.0%) - 36.0-61.2 (median 39.4) Gy: 62 (35.6%) Controls: - 0.0-2.9 (median 1.2) Gy: 112 (24.0%) - 3.0-7.9 (median 4.9) Gy: 86 (18.5%) - 8.0-27.9 (median 17.5) Gy: 87 (18.7%) - 28.0-35.9 (median 33.9) Gy: 85 (18.2%) - 36.0-61.2 (median 39.4) Gy: 96 (20.6%) <u>Pelvic radiation:</u> - Cases: 6 (3.5%) - Controls: 45 (9.7%)	<u>Odds ratio (95% CI) for breast cancer in multiple regression analysis:</u> - Chest radiation 3.0-7.9 Gy (median 4.9 Gy) vs. 0-2.9 Gy (median 1.2 Gy): 1.33 (0.64-2.77) - Chest radiation 8.0-27.9 Gy (median 17.5 Gy) chest radiation vs. 0-2.9 Gy (median 1.2 Gy): 2.21 (1.09-4.46) - Procarbazine ≤4.2 g/m^2 vs. chest radiation only: 0.95 (0.53-1.70) - Procarbazine >4.2 g/m^2 vs. chest radiation only: 0.62 (0.38-1.00) - Chemotherapy without procarbazine: 0.99 (0.56-1.76) - Procarbazine ≤4.2 g/m^2 without pelvic radiation vs. chest radiation only: 1.09 (0.68-1.75) - Procarbazine >4.2 g/m^2 or pelvic radiation vs. chest radiation only: 0.54 (0.34-0.86) - Pelvic radiation yes vs. no: 0.33 (0.13-0.84) - Mediastinal radiation prescribed dose ≤35 Gy vs. no chest radiation: 5.52 (0.91-33.6) - Mediastinal radiation prescribed dose >35 Gy vs. no chest radiation: 6.77 (1.2-35.7) - (In)complete mantle field radiation prescribed dose ≤35 Gy vs. no chest radiation <10 yr ovarian function: 3.04 (0.46-20.2) 10-19 yr ovarian function: 4.81 (0.85-27.2) ≥20 yr ovarian function: 11.3 (2.08-61.6) - (In)complete mantle field radiation	Analyses on radiation dose to breast tumor location were adjusted for duration of post-radiation intact ovarian function. Analyses on alkylating agents were adjusted for radiation dose to breast tumor location. Pelvic radiation was additionally adjusted for alkylating agents. Analyses on menopause were adjusted for radiation dose to breast tumor location. Analyses on time between menarche and HL treatment were adjusted for radiation dose to breast tumor location, intact ovarian function, and age at menarche. Analyses on hormone replacement therapy were also adjusted for duration of post-radiation intact ovarian function. **Risk of bias:** - <u>Selection bias:</u> low risk,

		Procarbazine: Cases: - ≤4.2 g/m^2: 23 (13.2%) - >4.2 g/m^2: 37 (21.3%) Controls: - ≤4.2 g/m^2: 68 (14.6%) - >4.2 g/m^2: 156 (33.5%)	prescribed dose ≤35 Gy vs. no chest radiation <10 yr ovarian function: 6.80 (1.48-31.3) 10-19 yr ovarian function: 9.87 (2.22-43.9) ≥20 yr ovarian function: 14.1 (3.17-62.5) - Menopause <40 yr vs. menopause ≥40 yr/premenopausal ≥40 yr: 0.43 (0.25-0.75) - Pre/perimenopausal <40 yr vs. menopause ≥40 yr/premenopausal ≥40 yr: 1.03 (0.40-2.64) - Age at menopause 18-29 yr vs. ≥50 yr: 0.13 (0.03-0.51) - Age at menopause 30-39 yr vs. ≥50 yr: 0.48 (0.20-1.15) - Age at menopause 40-49 yr vs. ≥50 yr: 0.61 (0.27-1.36) - Duration of post-radiation intact ovarian function 5-9 yr vs. <5 yr: 1.53 (0.63-3.72) - Duration of post-radiation intact ovarian function 10-14 yr vs. <5 yr: 1.45 (0.62-3.37) - Duration of post-radiation intact ovarian function 15-19 yr vs. <5 yr: 2.69 (1.20-6.05) - Duration of post-radiation intact ovarian function 20-24 yr vs. <5 yr: 4.42 (1.80-10.9) - Duration of post-radiation intact ovarian function ≥25 yr vs. <5 yr: 3.82 (1.27-11.5) - Hormone replacement therapy yes vs. no: 0.82 (0.48-1.39) - <5 yr hormone replacement therapy vs. none: 0.93 (0.49-1.77) - 5-9 yr hormone replacement therapy vs. none: 0.91 (0.34-2.46) - ≥10 yr hormone replacement therapy vs. none: 0.84 (0.30-2.32) - Time between menarche and HL treatment 10-14 yr vs. ≥15 yr: 1.16 (0.48-2.85)	174/193 (98%) cases could be matched to controls. - Attrition bias: low risk, follow-up data was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for chest radiation and alkylating agents.

			- Time between menarche and HL treatment 5-9 yr vs. ≥15 yr: 1.13 (0.43-3.01) - Time between menarche and HL treatment 2-4 yr vs. ≥15 yr: 1.25 (0.38-4.15) - Time between menarche and HL treatment <2 yr before or <2 yr after HL treatment vs. ≥15 yr: 0.94 (0.16-5.71) <u>Linear radiation dose-response curve</u> with an adjusted excess odds ratio of 6.1%/Gy (95% CI: 2.1-15.4). <u>Prediction of cumulative incidence 35 yr since start HL treatment:</u> - (In)complete mantle field radiation >35 Gy, ≥20 yr ovarian function: 27.6% - (In)complete mantle field radiation ≤35 Gy, ≥20 yr ovarian function: 22.4%), - (In)complete mantle field radiation >35 Gy, 10-19 yr ovarian function: 19.6% - (In)complete mantle field radiation >35 Gy, <10 yr ovarian function: 13.8%, - Mediastinal radiation >35 Gy: 13.5% - Mediastinal radiation ≤35 Gy: 11.2% - (In)complete mantle field radiation ≤35 Gy, 10-19 yr ovarian function: Not reported (only plotted in figure) - (In)complete mantle field radiation ≤35 Gy, <10 yr ovarian function: Not reported (only plotted in figure) - No chest radiation: 2.1%	

Who needs breast cancer surveillance?				
Henderson et al. Breast cancer risk in childhood cancer survivors without a history of chest radiotherapy: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2016;34:910-919.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Population-based cohort study 1970-1986 Follow-up: Median 25.5 (range 8.3-38.9) yr; 27,493 person-years at risk	3,768 5-yr female childhood cancer survivors aged <21 yr at diagnosis treated without chest radiation within 5 yr of their childhood cancer diagnosis Age at diagnosis: Median 5.0 (range 0-120) yr Age at follow-up: Median 31 (range 8-58) yr	Chest radiation: 0 (0%) Pelvic radiation: 1,892 (50.2%) Any other radiation: 1,892 (50.2%) Alkylating agents: 1,649 (43.8%) Cyclophosphamide: 1,567 (41.6%) Cyclophosphamide equivalent dose, mg/m^2: - 0: 2,116 (59.0%) - 1-5,999: 624 (17.4%) - 6,000-17,999: 675 (18.8%) - ≥18,000: 169 (4.7%) Anthracycline cumulative dose, mg/m^2: - 0: 2,321 (63.4%) - 1-249: 541 (14.8%) - ≥250: 799 (21.8%) Platinum chemotherapy: 181 (14.8%) Antimetabolites: 1,962 (52.1%) Plant alkaloids: 2,774 (73.6%)	Breast cancer: 47/3,768 (1.2%) 45-yr cumulative incidence (95% CI): 4.5% (3.2-6.2) Standardized incidence ratio (95% CI): - All survivors: 4.0 (3.0-5.3) - Leukemia: 4.1 (2.4-6.9) - Sarcoma: 5.3 (3.6-7.8) - CNS tumor: 1.4 (0.4-5.6) - Lymphoma: 1.6 (0.4-6.3) - Embryonal tumors: 3.6 (1.2-11.3) - Cyclophosphamide equivalent dose 0 mg/m^2: 2.6 (1.6-4.2) - Cyclophosphamide equivalent dose 1-5,999 mg/m^2: 2.8 (1.1-7.5) - Cyclophosphamide equivalent dose 6,000-17,999 mg/m^2: 7.9 (4.8-12.9) - Cyclophosphamide equivalent dose ≥18,000 mg/m^2: 9.4 (4.5-19.7) - Anthracycline dose 0 mg/m^2: 2.0 (1.2-3.3) - Anthracycline dose 1-249 mg/m^2: 4.0 (1.5-10.7) - Anthracycline dose ≥250 mg/m^2: 8.3 (5.7-12.2) - Attained age 20-39 yr: 3.5 (2.0-6.2) - Attained age 40-49 yr: 4.7 (3.3-6.6) - Attained age 50-59 yr: 1.9 (0.6-6.0) Absolute excess risk per 10,000 person-years (95% CI):	To exclude the effect of scatter radiation (radiation from fields other than chest) on breast cancer risk, the risk from exposure to any radiation was examined. No association was found in univariate analysis. Pelvic radiation was not associated with a reduced breast cancer risk in univariate analysis. Other variables included in the risk factor analysis were age at primary cancer diagnosis, ethnicity and current age. When the risk factor analysis was restricted to only sarcoma and leukemia survivors, alkylating agents and anthracyclines were also associated with breast cancer development in a dose-dependent fashion (*P for trend* <0.01). They were limited in the ability to assess the association between chemotherapy exposures and breast cancer risk in the primary cancer diagnoses other than leukemia and sarcoma,

		Epipodophyllotoxins: 260 (6.9%)	- All survivors: 4.9 (3.0-6.7) Relative standardized incidence ratio (95% CI) in multivariable analysis: *Childhood cancer survivors* - Cyclophosphamide equivalent dose 1-5,999 vs. 0 mg/m^2: 0.6 (0.2-2.0) - Cyclophosphamide equivalent dose 6,000-17,999 vs. 0 mg/m^2: 1.6 (0.7-3.5) - Cyclophosphamide equivalent dose ≥18,000 vs. 0 mg/m^2: 3.0 (1.2-7.7) *P for trend* = 0.044 - Anthracycline dose 1-249 vs. 0 mg/m^2: 2.6 (0.8-8.7) - Anthracycline dose ≥250 vs. 0 mg/m^2: 3.8 (1.7-8.3) *P for trend* = 0.004 *Childhood leukemia and sarcoma survivors* - Cyclophosphamide equivalent dose 1-5,999 vs. 0 mg/m^2: 0.7 (0.2-2.3) - Cyclophosphamide equivalent dose 6,000-17,999 vs. 0 mg/m^2: 1.9 (0.8-4.5) - Cyclophosphamide equivalent dose ≥18,000 vs. 0 mg/m^2: 3.4 (1.2-9.7) *P for trend* = 0.045 - Anthracycline dose 1-249 vs. 0 mg/m^2: 4.3 (1.1-16.6) - Anthracycline dose ≥250 vs. 0 mg/m^2: 5.1 (1.9-13.7) *P for trend* = 0.005	given the small number of cases of breast cancer among them (n=7). **Risk of bias:** - Selection bias: high risk, 14,358/20,690 (69%) were included in the study group. - Attrition bias: low risk, for 12596 /14358 (88%) survivors follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for anthracycline dose, cyclophosphamide, equivalent dose, age at primary cancer diagnosis, race/ethnicity (white, non-Hispanic, and other) and attained age.

What breast cancer surveillance modality should be used?				
Horst et al. Breast imaging in women previously irradiated for Hodgkin lymphoma. Am J Clin Oncol 2016;39:114-119.				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Single-center retrospective cohort study <1995->2007 Follow-up: 21 (range 6-36) yr from Hodgkin lymphoma treatment to breast cancer diagnosis	118 female Hodgkin lymphoma survivors treated with chest radiation Age at diagnosis: Median 28 (range 10-69) yr Prescribed radiation dose: Median 36 (range 20-45) Gy Age at study: Not reported	Mammogram: 117/118 (99.2%) MRI: 39/118 (33.1%) Screening rounds: Not reported Screening examinations: Not reported Breast cancer: 35/118 (29.7%) in 33 women; 24 invasive, 11 DCIS Cases of interval cancer: 7/118 (5.9%) Age at breast cancer diagnosis: Median 44 (range 34-79) yr	True-positives (n): - Mammogram: 34 in 32 patients - MRI: 0 False-positives (n): - Mammogram: 23 - MRI: 2 False-negatives (n): - Mammogram: 1 - MRI: 1 Recalls: - Mammogram: 24/118 (20.3%) women biopsy for malignant lesions 23/118 (17.7%) women biopsy for benign lesions - MRI: 0/118 (0%) women biopsy for malignant lesions 2/118 (1.7%) women biopsy for benign lesions	Screening exam was defined positive if BI-RADS score was 4 or 5. 79 (67%) underwent mammogram screening only; 1 (1%) underwent MRI screening only; 38 (32%) received both mammogram and MRI screening. Of the 38 patients that underwent both mammogram and MRI 19 patients underwent 54 breast MRI studies, 13 underwent a preoperative breast MRI and 6 initiated MRI of the contralateral breast after breast cancer diagnosis. All diagnostic MRI studies identified the index lesion. **Risk of bias:** Selection bias: unclear how many survivors were included in the original cohort of survivors. - Index test bias: unclear if radiologists who retrospectively reviewed images were blinded to clinical outcomes. - Verification bias: low risk,

				biopsies were performed when imaging detected a mass. Interval between mammogram and MRI was more than 4 months (mammogram and MRI alternating every 6 months). - Attrition bias: low risk, 118/118 (100%) women underwent breast cancer screening.

Who needs breast cancer surveillance? At what age should breast cancer surveillance be stopped?				
Schaapveld et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. New Eng J Med 2015;373:2499-2511.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter cohort study 1965-2000 Follow-up: Median 19.1 (range 5.0-47.2) yr (data of total cohort including men)	1,698 female 5-yr Hodgkin lymphoma survivors aged <50 yr at diagnosis Age at diagnosis: Median 28.6 (range 15-50) yr (data of total cohort including men) Age at follow-up: Median 50.4 yr (data of total cohort including men)	*Treatment data of total cohort including men* Full mantle field only: 815 (20.9%) Full mantle field + infradiaphragmatic radiation: 1,176 (30.1%) Other supradiaphragmatic field only: 824 (21.1%) Other supradiaphragmatic field + infradiaphragmatic radiation: 219 (5.6%) Infradiaphragmatic radiation only: 202 (5.2%) Radiotherapy, field unknown: 196 (5.0%) Prescribed radiation dose: Patients usually received 40 Gy (range 36 to 44 Gy) No radiation: 473 (12.1%)	Breast cancer: 183/1,698 (10.8%) Standardized incidence ratio (95% CI): 4.7 (4.0-5.4) Absolute excess risk per 10,000 person-years (95% CI): 54.3 (44.7-65.0) Hazard ratios (95% CI) in multivariable Cox analysis: - Other supradiaphragmatic field with axilla vs. full mantle field: 0.41 (0.17-1.01) - Other supradiaphragmatic field vs. full mantle field: 0.37 (0.19-0.72) - Other radiotherapy and field unknown vs. full mantle field: 0.35 (0.14-0.85) - No radiotherapy vs. full mantle field: 0.24 (0.09-0.67) - No procarbazine vs. no chemotherapy: 0.75 (0.47-1.20) - ≤4.2 g/m^2 procarbazine vs. no chemotherapy: 0.84 (0.52-1.36) - 4.3-8.4 g/m^2 procarbazine vs. no chemotherapy: 0.71 (0.47-1.07) - >8.4 g/m^2 procarbazine vs. no chemotherapy: 0.33 (0.16-0.68) - Chemotherapy but unknown whether procarbazine vs. no chemotherapy: 0.42 (0.13-1.34)	Overlap with analysis by Krul et al. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: low risk, information on second cancers and vital status was complete up to at least January 1, 2010. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for age, chest radiation field and dose and procarbazine.

		No chemotherapy: 1,068 (27.4%) Chemotherapy, non-alkylating: 243 (6.2%) <4 cycles alkylating agents: 887 (22.7%) 4-6 cycles alkylating agents: 852 (21.8%) 7-9 cycles alkylating agents: 290 (7.4%) >10 cycles alkylating agents: 319 (8.2%) Alkylating agents, cycles unknown: 16 (0.4%) Chemotherapy, unknown if alkylating agents: 230 (5.9%)	Standardized incidence ratio (95% CI) by attained age: - 50-59 years, 15-24 years at HL: 8.6 (5.1-13.4) - ≥60 years, 15-24 years at HL: 7.4 (1.5-21.7) - 50-59 years, 25-34 years at HL: 4.0 (2.4-6.3) - ≥60 years, 25-34 years at HL: 2.7 (0.7-6.9)	

Who needs breast cancer surveillance? At what age should breast cancer surveillance be stopped?				
Moskowitz et al. Breast cancer after chest radiation therapy for childhood cancer. J Clin Oncol 2014;32:2217-2223.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter cohort study 1970-1986 <u>Follow-up:</u> Median 25.9 (range 8.4-40.6) yr	1,230 female 5-yr childhood cancer survivors aged <21 yr at diagnosis treated with chest radiation <u>Age at diagnosis:</u> Median 13.0 (range 0-20) yr <u>Age at follow-up:</u> Median 37.3 (range 6.0-58.8) yr	<u>Chest radiation:</u> 1,230 (100%) <u>Delivered radiation dose:</u> - Mantle: median 40 (range 5-54) Gy - Mediastinal: median 30 (range 3-54) Gy - Whole lung: median 14 (range 2-20) Gy - Total body: median 12 (range 4-16) Gy - High abdominal: median 20 (range 4-40) Gy - Posterior chest: median 31 (range 6-54) Gy - Other one-sided anterior: median 41 (range 10-61) <u>Alkylating agents:</u> - 608 (49.4%) - 81/203 (39.9%) survivors with breast cancer - 527/1,027 (51.3%) survivors without breast cancer <u>Pelvic radiation:</u> - 128 (10.4%) - 10/203 (4.9%) survivors with breast cancer - 118/1,027 (11.5%) survivors without breast cancer	<u>Breast cancer:</u> 203/1230 (16.5%) <u>Standardized incidence ratio (95% CI):</u> - Total group: 21.9 (19.1-25.2) - Mantle (median 40 (range 5-54) Gy): 24.2 (20.7-28.3) - Mediastinal (median 30 (range 3-54) Gy): 13.0 (8.4-20.2) - Whole lung (median 14 (range 2-20) Gy): 43.6 (27.1-70.1) - Total body (median 12 (range 4-16) Gy): 19.3 (7.3-51.5) - High abdominal (median 20 (range 4-40) Gy): 10.8 (2.7-43.2) - Posterior chest (median 31 (range 6-54) Gy): 0.0 - Other one-sided anterior (median 41 (range 10-61)): 9.9 (3.2-30.6) - 10-19 Gy: 30.6 (18.4-50.7) - ≥20 Gy: 21.2 (18.3-24.5) - No alkylating agents: 22.7 (18.4-28.0) - Alkylating agents: 21.4 (17.8-25.8) - Ovaries not irradiated: 23.7 (20.6-27.3) - Ovaries irradiated: 8.8 (4.7-16.4) <u>Incidence rate ratio (95% CI) adjusted for chest radiation dose:</u> - Whole lung vs. mantle radiation: 1.8 (0.9-3.7) - Whole lung vs. mediastinal radiation: 3.4 (1.6-7.2)	Elevated risk in patients treated with TBI and abdominal field radiation should be interpreted with caution because of small numbers. When analyses were repeated censoring patients who had a relapse of their pediatric cancer, there were no substantive differences. Out of 69 patients treated with TBI, 4 developed breast cancer. **Risk of bias:** - <u>Selection bias:</u> unclear how many patients were included in the original cohort of survivors. - <u>Attrition bias:</u> unclear for how many survivors follow-up was complete. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, the ratios of the observed number of CCSS participants with breast cancer to the expected number of women with breast cancer in the general US population using age- and calendar year–

			- Mediastinal vs. mantle radiation: 0.5 (0.3-0.9) - Radiation to fields exposing ovaries yes vs. no: 0.3 (0.2-0.7) - Alkylating agents yes vs. no: 1.1 (0.8-1.4) <u>Cumulative incidence by age 50 yr (95% CI):</u> - All childhood cancer survivors: 30% (25-34) - Hodgkin lymphoma survivors: 35% (29-40) - BRCA1 mutation carriers: 31% (15-48) - BRCA2 mutation carriers: 10% (1-23) - Cumulative incidence continues to increase by age 55 years (no effect measures reported)	specific rates from the SEER program.

Who needs breast cancer surveillance?				
Lange et al. Breast cancer in female survivors of Wilms tumor: A report from the National Wilms Tumor Late Effects Study. Cancer 2014;120:3722-3730.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter cohort study 1969-1995 <u>Follow-up:</u> not mentioned (at least 5 years from primary cancer diagnosis)	2,492 female 5-yr Wilms tumor survivors aged <19 yr at diagnosis <u>Age at diagnosis:</u> Range 0-19 yr <u>Age at follow-up:</u> Median 27.3 yr (IQ range: 21.5-33.2 yr, maximum: 55.2 yr)	<u>Chest radiation:</u> - 369 (14.8%) - 16/28 (57.1%) survivors with breast cancer - 353/2464 (14.3%) survivors without breast cancer <u>Average chest radiation dose:</u> - 12-14 Gy - 1-12 Gy: 4% - 12 Gy: 64% - 13-15 Gy: 19% - >15 Gy: 13% <u>Abdominal radiation only:</u> 849 (34.1%) <u>Alkylating agents:</u> Not reported	<u>Breast cancer:</u> - 29 breast cancers in 28/2,492 (1.1%) patients - 16/369 (4.3%) treated with chest radiation - 10/894 (1.1%) treated with abdominal radiation only <u>Cumulative incidence (95% CI) at age 40 yr:</u> - No radiation: 0.3% (0.0-2.3) - Any chest radiation: 14.8% (8.7-24.5) - No chest radiation: 2.3% (1.0-5.1) - 1-12 Gy chest radiation: 14.4% (7.6-30.1) - >12 Gy chest radiation: 14.2% (7.1-29.3) - Abdominal radiation only: 3.1% (1.3-7.1) <u>Standardized incidence ratio (95% CI):</u> - No radiation: 2.2 - Any chest radiation: 27.6 (16.1-44.2) - No chest radiation: 4.6 - 1-12 Gy chest radiation: 46.8 - >12 Gy chest radiation: 18.9 - Abdominal radiation only: 6.0 (2.9-11.0) - Whole abdominal radiation: 7.2 - Flank radiation: 5.8 <u>Hazard ratios (95% CI) from Cox multiple regression analysis:</u> - Log (1+chest dose)-ipsilateral: 1.96 (1.45-2.69) - Log (1+flank dose)-ipsilateral: 1.09 (0.88-1.35)	The SIR of 6.0 for patients treated with abdominal radiation only compared with the SIR of 2.2 for patients treated without radiation was not statistically significant (P = 0.23), nor was the SIR of 7.2 for patients treated with whole-abdominal radiation compared with the SIR of 5.8 for patients treated with radiation to the flank or other portions of the abdomen (P = 0.68). **Risk of bias:** - <u>Selection bias:</u> unclear how many patients were included in the original cohort of survivors. - <u>Attrition bias:</u> unclear for hoe many patients follow-up was complete.. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, analyses were adjusted for chest and flank radiation dose, age at Wilms tumor diagnosis and doxorubicin.

			- Doxorubicin: 2.24 (0.80-6.22) - Age ≥10 yr at Wilms tumor diagnosis: 4.59 (1.88-11.2) <u>Hazard ratios (95% CI) from Cox multiple regression analysis in patients who not received chest radiation:</u> - Log (1+flank dose)-ipsilateral: 1.51 (1.13-2.03) - Doxorubicin: 1.49 (0.36-6.19) - Age ≥10 yr at Wilms tumor diagnosis: 14.61 (4.20-50.1)	

Who needs breast cancer surveillance? **Breast cancer risk after <1 Gy chest radiation and alkylating agents**				
Little et al. Breast cancer risk after radiotherapy for heritable and non-heritable retinoblastoma: a US-UK study. Br J Cancer 2014;110:2623-2632.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter nested case-control study US: 1914-1984 UK: 1940-1991 <u>Follow-up:</u> US: Mean 26.9 yr; 45,590 person-years UK: Mean 27.3 yr; 15,838 person-years	US: 1,584 female 1-yr retinoblastoma survivors UK: 581 female 5-yr retinoblastoma survivors aged <15 yr at diagnosis US: 20 female and 1 male survivors with breast cancer matched to 56 survivors without breast cancer UK: 10 female survivors with breast cancer matched to 21 survivors without breast cancer <u>Age at diagnosis:</u> US: Mean 1.3 yr UK: Mean 1.8 yr <u>Age at follow-up:</u> Not reported (age at breast cancer diagnosis mean 43.6 (range 25-61.9) yr	<u>Chest radiation:</u> - Cases: 16 (51.6%) - Controls: 32 (41.6%) <u>Absorbed radiation dose by retrospective dose reconstruction:</u> Cases: - Mean 0.33 Gy - 0.01-<0.25 Gy: 6 (19.4%) - 0.25-0.49 Gy: 6 (19.4%) - ≥0.50 Gy: 4 (12.9%) Controls: - Mean 0.22 Gy - 0.01-<0.25 Gy: 10 (13.0%) - 0.25-0.49 Gy: 9 (11.7%) - ≥0.50 Gy: 13 (16.9%) <u>Cyclophosphamide:</u> - Cases: 2 (6.5%) - Controls: 3 (3.9%)	<u>Breast cancer:</u> 36 breast cancers in 31/2165 (1.4%) patients <u>Standardized incidence ratio (95% CI):</u> - Chest radiation: 3.89 (2.34-6.07) - No radiation: 3.04 (1.77-4.87) <u>Odds ratio (95% CI):</u> - 0.01-0.24 Gy vs. 0 Gy: 1.79 (0.55-∞) - 0.25-0.49 Gy vs. 0 Gy: 1.98 (0.61-∞) - ≥0.50 Gy vs. 0 Gy: 0.92 (0.24-∞) - ≥0.01 Gy vs. 0 Gy: 1.49 (0.68-∞) - Cyclophosphamide yes vs. no: 2.13 (0.15-65.89) <u>Excess odd ratio per Gy to the breasts (95% CI):</u> - All cases: -0.32 (-2.36-1.63) - Non-heritable retinoblastoma: 6.72 (0.57-∞) - Heritable retinoblastoma: -2.50 (-5.84-0.20)	A maximum of three controls were selected for each case matched on sex, retinoblastoma heritable status, and date of birth within 5 years. Analyses on radiation dose were not adjusted for alkylating agents. Analyses on alkylating agents were not adjusted for chest radiation. **Risk of bias:** - <u>Selection bias:</u> low risk, 99% of the original cohort was included in the study group. - <u>Attrition bias:</u> unclear for how many patients follow-up was complete. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> high risk, analyses were not adjusted for chest radiation and alkylating agents.

What breast cancer surveillance modality should be used?				
Tieu et al. Breast cancer detection among young survivors of pediatric Hodgkin lymphoma with screening magnetic resonance imaging. Cancer 2014;120:2507-2513.*				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Multi-center prospective cohort study 2005-2012 Follow-up: Median 16 (range 19-59) yr from Hodgkin lymphoma diagnosis	96 female Hodgkin lymphoma survivors treated with chest radiation and >8 yr after end of treatment Age at diagnosis: Median 15 (range 2-19) yr Prescribed radiation dose: Median 22.5 (range 14-45) Gy Age at study: Median 30 (range 19-59) yr at first screening round	Mammogram: 85/96 (88.5%) MRI: 96/96 (100%) Screening rounds: - MRI: Median 3 (range 1-7) per patient - Mammogram: Median 3 (range 0-5) per patient Screening examinations: - MRI: 274 - Mammogram: not reported Breast cancer: 10/96 (10.4%) in 9 women; 5 invasive, 5 DCIS Cases of interval cancer: Not reported Age at breast cancer diagnosis: Median 39 (range 24-43) yr	Sensitivity: - Mammogram: 70.0% - MRI: 80.0% - Mammogram and MRI: 100% Specificity (95% CI): - Mammogram: 95.0% - MRI: 93.5% - Mammogram and MRI: 88.6% Recalls: - 9/96 (9.4%) women biopsy for malignant lesions - 17/96 (17.7%) biopsy for benign lesions - Earlier additional testing: 30 MRIs, 26 mammograms, 65 ultrasounds	In total, 96 of 104 (92.3%) eligible patients were screened with MRI. Eight patients dropped out of the screening program with an overall compliance rate of 88 of 104 (84.6%). Eleven patients did not receive a mammogram (refusal n=10, breastfeeding n=1). Of the 10 detected breast cancers, 5 were detected by both mammogram and MRI, 3 by MRI only, and 2 by mammogram only. MRI detected all invasive breast cancers. **Risk of bias:** - Selection bias: low risk, 96/104 (92.3%) were included in the study group. - Index test bias: low risk, radiologists were blinded to clinical outcomes as this is a prospective study. - Verification bias: low risk, biopsies were performed when imaging detected a mass. Interval between mammogram and MRI was less than 4

				months. - Attrition bias: low risk, 88/104 (84.6%) women underwent breast cancer screening.

* Possible overlap in patients with Ng et al. and Freitas et al.

Who needs breast cancer surveillance?				
Cooke et al. Breast cancer risk following Hodgkin lymphoma radiotherapy in relation to menstrual and reproductive factors. British Journal of Cancer 2013;108:2399-2406.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter cohort study 1956-2003 <u>Follow-up:</u> 0-≥30 yr	2,497 female Hodgkin lymphoma survivors aged <36 yr at diagnosis treated with supradiaphragmatic radiation <u>Age at diagnosis:</u> Median 24.3 (range 0-35) yr <u>Age at follow-up:</u> Not reported	<u>Chest radiation only:</u> 801 (32.1%) <u>Radiation dose:</u> Not reported <u>Chest radiation and ≥5 Gy pelvic radiation:</u> 19 (0.8%) <u>Chest radiation and alkylating agents:</u> 1461 (58.5%) <u>Chest radiation, ≥5 Gy pelvic radiation and alkylating agents:</u> 49 (2.0%) <u>Chest radiation, unknown if pelvic radiation or alkylating agents:</u> 167 (6.7%)	<u>Breast cancer:</u> 260/2,497 (10.4%) <u>Odds ratio (95% CI):</u> - Menopause before age 40 yes vs. no: 0.65 (0.44-0.94) - Menopause within 5 yr of start of treatment yes vs. no: 0.55 (0.35-0.85) - Premenopausal yrs after start of treatment 1-4 vs. <1: 0.96 (0.34-2.69) - Premenopausal yrs after start of treatment 5-9 vs. <1: 1.02 (0.36-2.87) - Premenopausal yrs after start of treatment 10-14 vs. <1: 1.49 (0.63-3.55) - Premenopausal yrs after start of treatment 15-24 vs. <1: 1.62 (0.76-3.44) - Premenopausal yrs after start of treatment ≥25 vs. <1: 3.56 (1.50-8.45); *P trend* = 0.003 - Chest radiation ≥5 yr before menarche vs. chest radiation ≥10 yr after menarche: 0.94 (0.10-8.46) - Chest radiation 2-5 yr before menarche vs. chest radiation ≥10 yr after menarche: 4.08 (1.27-13.14) - Chest radiation 0.5-2 yr before menarche vs. chest radiation ≥10 yr after menarche: 4.90 (1.60-14.98) - Chest radiation within 0.5 yr of menarche vs. chest radiation ≥10 yr after menarche: 5.52 (1.97-5.46)	Questionnaires from 2508 women from the cohort of 5002. Of the remainder, 1105 had died, 999 were mailed but did not complete a questionnaire, 35 had emigrated, and 355 were not known to have died or emigrated but were not contacted for other reasons. Patients who were alive but did not complete a questionnaire did not differ significantly from those who did in terms of calendar year or age of treatment, or type of treatment received. Analyses were adjusted for age and year of treatment, duration between treatment and questionnaire completion, calendar year of birth, chest radiation field and ovarian-toxic treatment. **Risk of bias:** - <u>Selection bias:</u> high risk, 3507/5002 (70.1%) patients from the original cohort of survivors were included in the study group.

			- Chest radiation 0.5-2 yr after menarche vs. chest radiation ≥10 yr after menarche: 3.47 (1.40-8.58) - Chest radiation 2-5 yr after menarche vs. chest radiation ≥10 yr after menarche: 2.38 (1.43-3.97) - Chest radiation 5-10 yr after menarche vs. chest radiation ≥10 yr after menarche: 1.33 (0.89-1.98) - No menarche vs. chest radiation ≥10 yr after menarche: 2.14 (0.20-22.56) *P trend* <0.001	- Attrition bias: low risk, follow-up was complete for 97% of patients. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for age and year of treatment, duration between treatment and questionnaire completion, calendar year of birth, chest radiation field and ovarian-toxic treatment.

What breast cancer surveillance modality should be used?				
Ng et al. Prospective study of the efficacy of breast magnetic resonance imaging and mammographic screening in survivors of Hodgkin lymphoma. J Clin Oncol 2013;31:2282-2288.				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center prospective cohort study 2005-2010 Follow-up: Median 17.5 yr after Hodgkin lymphoma diagnosis	148 female Hodgkin lymphoma survivors treated with chest radiation and were >8 yr after end of treatment Age at diagnosis: Median 23 (range 12-35) yr Radiation dose to mediastinum: Median 39.5 (range 19.6-58) Gy Age at study: Median 43 (range 22-65) yr	Annual mammogram: 134/148 (90.5%) Annual MRI: 134/148 (90.5%) Screening rounds: - 1 screening set: 134 (90%) - 2 screening sets: 111 (75%) - 3 screening sets: 100 (68%) Screening examinations: 345 sets of annual screening Breast cancer: 18/148 (12.2%); 8 invasive, 9 DCIS, 1 phyllodes Cases of interval cancer: 0 (0.0%) Age at breast cancer diagnosis: Range 23-65 yr	Sensitivity: - Mammogram: 68% - MRI: 67% *P* = 1.0 - Mammogram and MRI: 94% Specificity: - Mammogram: 93% - MRI: 94% - Mammogram and MRI: 90% Breast cancer detection rates per screening round: - Year 1: 5% - Year 2: 6% - Year 3: 4% Percentage false-positive cases with MRI screening per screening round: - Year 1: 13.4% - Year 2: 9.0% - Year 3: 2% Specificity MRI per screening round: - Year 1: 86% - Year 2: 90% - Year 3: 98% Recalls: - Total: 63 biopsies in 45 women; 18 biopsies (29%) showed malignancy, of which 5 detected by MRI alone, 6 by	Screening exam was defined positive if BI-RADS score was 4 or 5. 134 (90%) underwent 1 screening set, 111 (75%) underwent 2 screening sets, 100 (68%) underwent 3 screening sets. For premenopausal women screening was performed in the second week of the menstrual cycle to reduce cycle-related breast changes. Of the 13 detected breast cancers, 7 were detected by both mammogram and MRI, 5 by MRI only, and 6 by mammogram only. MRI detected all but one invasive breast cancers. BI-RADS = Breast Imaging-Reporting and Data System. **Risk of bias:** - Selection bias: unclear how many patients from the original cohort were included in the study group. - Index test bias: low risk,

			mammogram only, and 7 by both modalities - Mammogram and/or MRI: 18/148 (12.2%) women biopsy for malignant lesions 45 biopsies for benign lesions in 29/148 (19.6%) women - Mammogram only: 6/148 (4.1%) women biopsy for malignant lesions 15 biopsies for benign lesions in 10/148 (6.8%) women - MRI only: 5/148 (3.4%) women biopsy for malignant lesions 20 biopsies for benign lesions in 17/148 (11.5%) women - Both MRI and mammogram: 7/148 (4.7%) women biopsy for malignant lesions 10 biopsies for benign lesions in 6/148 (4.1%) women	radiologists were blinded to clinical outcomes as this is a prospective study. - Verification bias: low risk, biopsies were performed when imaging detected a mass. Interval between mammogram and MRI was less than 4 months. - Attrition bias: low risk, 134/148 (90.5%) women underwent at least 1 breast cancer screening round.

* Possible overlap in patients with Tieu et al.

What breast cancer surveillance modality should be used?				
Freitas et al. Added cancer yield of breast magnetic resonance imaging screening in women with a prior history of chest radiation therapy. Cancer 2013;119:495-503.				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Multi-center retrospective cohort study 2004-2010 Follow-up: Median 13 (range 2-34) yr from end of radiation treatment	98 female childhood and young adult cancer survivors (majority Hodgkin lymphoma) treated with ≥15 Gy chest radiation Age at diagnosis: Not reported Prescribed radiation dose: 15-35 Gy Age at study: Mean 37 (range 19-65) yr	Mammogram: 98/98 (100%) MRI: 98/98 (100%) Screening rounds: - Total: 558 - Mammogram: 296; mean 3.02 (range 1-7) per patient - MRI: 262; mean 2.67 (range 1-8) per patient Screening examinations: - Mammogram: 310 - MRI: 303 Breast cancer: 13/98 (13.3%); 10 invasive, 3 DCIS Cases of interval cancer: 0 (0.0%) Age at breast cancer diagnosis: Range 29-65 yr	Sensitivity (95% CI): - Mammogram: 69% (60-78%) - MRI: 100% (93-100%) *P* = 0.375 Specificity (95% CI): - Mammogram: 98% (93-99%) - MRI: 94% (87-97%) *P* = 0.375 Positive predictive value (95% CI): - Mammogram: 82% (74-89%) - MRI: 71% (62-79%) *P* = 0.945 Negative predictive value (95% CI): - Mammogram: 95% (89-98%) - MRI: 99% (94-99%) *P* = 0.950 Added cancer yield per patient (95% CI): - Mammogram: 1 (0.2-5.6) - MRI: 4.1 (1.6-10) *P* = 0.175 Recalls: - Mammogram and/or MRI: 13/98 (13.3%) women biopsy for malignant lesions 6/98 (6.1%) women biopsy for benign lesions - Mammogram only:	In total, 120 patients were identified and referred for screening. Of those, 22 (18.3%) were excluded because the interval between mammogram and MRI was more than 4 months. Screening exam was defined positive if BI-RADS score was 4 or 5. Of the 13 detected breast cancers, 8 were detected by both mammogram and MRI, 4 by MRI only, and 1 by mammogram only. MRI detected all invasive breast cancers. BI-RADS = Breast Imaging-Reporting and Data System. **Risk of bias:** - Selection bias: low risk, 98/120 (81.7%) were included in the study group. - Index test bias: unclear if radiologists who assessed the imaging studies were blinded to clinical outcomes. - Verification bias: low risk,

			1/98 (1.0%) women biopsy for malignant lesions 1/98 (1.0%) women biopsy for benign lesions - MRI only: 4/98 (4.1%) women biopsy for malignant lesions 4/98 (4.1%) women biopsy for benign lesions - Both MRI and mammogram: 8/95 (8.4%) women biopsy for malignant lesions 1/98 (1.0%) women biopsy for benign lesions	biopsies were performed when imaging detected a mass. Interval between mammogram and MRI was less than 4 months. - Attrition bias: low risk, 206/263 (78.3%) women underwent breast cancer screening.

* Possible overlap in patients with Tieu et al.

What breast cancer surveillance modality should be used?				
Terenziani et al. Occurrence of breast cancer after chest wall irradiation for pediatric cancer, as detected by a multimodal screening program. Int J Rad Oncol Biol Phys 2013;85:35-39.				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Single-center prospective cohort study 2002-2010 Follow-up: >5 yr disease free	86 female childhood cancer survivors (majority Hodgkin lymphoma) treated with chest radiation Age at diagnosis: 0-18 yr Prescribed radiation dose: 2-54 Gy Age at study: Median 25 (range 14-45) yr at first screening round	Annual mammogram, MRI, ultrasound, clinical breast exam: 86/86 (100%) Screening rounds: Median 5 (range 2-8) per patient Screening examinations: 381 Breast cancer: 11/86 (12.8%); 9 invasive, 2 DCIS Cases of interval cancer: 1/86 (1.2%) Age at breast cancer diagnosis: Median 33 (range 26-49) yr	Sensitivity (95% CI): - Mammogram: 73% (39-94%) - MRI: 100% (93-100%) - Clinical breast exam: 36% (11-69%) - Ultrasound: 55% (23-83%) Specificity (95% CI): - Mammogram: 99% (98-100%) - MRI: 80% (68-88%) - Clinical breast exam: 91% (87-93%) - Ultrasound: 95% (92-97%) Recalls: - 11/86 (12.8%) women biopsy for malignant lesions - 4/86 (4.7%) women biopsy for benign lesions - 8/86 (9.3%) short-term stricter follow-up	Screening exam was defined positive if BI-RADS score was 4 or 5. From 2007 onwards MRI was added to the screening rounds. Three cancers were diagnosed after MRI had been added to the screening program. All three cancers were positive on MRI and two were detectable only by MRI. Three patients had micro calcifications detected only by mammogram. It was calculated that the overall cost of the screening process would be €5500 for each breast cancer detected. BI-RADS = Breast Imaging-Reporting and Data System. **Risk of bias:** - Selection bias: low risk, 86/106 (81.1%) eligible patients were included in the study. - Index test bias: low risk, radiologists were blinded to

				clinical outcomes as this is a prospective study. - Verification bias: low risk, biopsies were performed when imaging detected a mass. Interval between mammogram and MRI was less than 4 months. - Attrition bias: low risk, 86/86 (100%) women underwent breast cancer screening.

Who needs breast cancer surveillance? At what age should breast cancer surveillance be stopped?				
Swerdlow et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: A national cohort study. J Clin Oncol 2012;30:2745-2752.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter cohort study 1956-2003 Follow-up: 89,478 person-years	5,002 female Hodgkin lymphoma patients aged <36 yr at diagnosis treated with supradiaphragmatic radiation Age at diagnosis: <15-35 years Age at follow-up: Not reported	Chest radiation: 5,002 (100%) Radiation dose: On average, 36 Gy for mantle and 31 to 33 Gy for mediastinum, axilla, and neck/clavicle Alkylating agents: 2,968 (59.3%) Pelvic radiation: 350 (7.0%)	Breast cancer: 373/5,002 (7.5%) Standardized incidence ratio (95% CI): - All patients: 5.0 (4.5-5.5) - Supradiaphragmatic radiation: 6.0 (5.2-7.0) - Supradiaphragmatic radiation and alkylating agents: 4.8 (4.0-5.6) - Supradiaphragmatic radiation and ≥5 Gy pelvic radiation: 1.4 (0.5-4.4) - Supradiaphragmatic radiation and alkylating agents and ≥5 Gy pelvic radiation: 3.8 (2.4-6.1) - Supradiaphragmatic radiation and unknown if alkylating agents and/or pelvic radiation: 4.2 (3.1-5.5) *P* for heterogeneity 0.006 - 0 alkylating agent cycles: 5.6 (4.8-6.6) - 1-5 alkylating agent cycles: 4.9 (3.4-7.1) - 6 alkylating agent cycles: 4.7 (3.6-6.1) - 7-12 alkylating agent cycles: 4.1 (2.9-5.8) - ≥13 alkylating agent cycles: 1.4 (0.2-10.1) *P* for trend 0.027 - Attained age 50-59 yr: 3.8 (3.1-4.7) - Attained age ≥60 yr: 2.7 (1.7-4.3) Absolute excess risk per 10,000 person-years (95% CI): - All patients: 33.3 (29.2-37.7) - Supradiaphragmatic radiation: 42.9 (35.3-51.4)	3,410 Hodgkin lymphoma patients were alive and free of breast cancer at end of follow-up, 1,093 died, 9 had immigrated, 106 were lost to follow-up. For patients treated at age <20 years, risks were slightly greater in those who received additional alkylating agents or pelvic radiation than in those who received supradiaphragmatic radiation alone, whereas at older ages, risk was less raised after additional alkylating agents or pelvic radiation than after solely supradiaphragmatic radiation. Authors stated that multivariable analyses produced similar results as the reported univariate analyses. **Risk of bias:** - Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many patients follow-up was complete. - Detection bias: unclear if the outcome assessors were

			- Supradiaphragmatic radiation and alkylating agents: 28.0 (22.4-34.3) - Supradiaphragmatic radiation and ≥5 Gy pelvic radiation: 4.7 (-8.2-35.8) - Supradiaphragmatic radiation and alkylating agents and ≥5 Gy pelvic radiation: 32.2 (14.0-58.5) - Supradiaphragmatic radiation and unknown if alkylating agents and/or pelvic radiation: 30.6 (20.1-43.6) *P for heterogeneity* 0.002 - 0 alkylating agent cycles: 41.3 (34.0-49.5) - 1-5 alkylating agent cycles: 29.1 (17.0-45.0) - 6 alkylating agent cycles: 29.3 (20.2-40.4) - 7-12 alkylating agent cycles: 26.8 (15.8-41.1) - ≥13 alkylating agent cycles: 4.1 (-9.5-68.4) *P for trend* 0.027 - Attained age 50-59 yr: 87.9 (64.3-115.5) - Attained age ≥60 yr: 62.0 (21.9-19.0)	blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, standardized incidence ratios and absolute excess risks (AERs) were then calculated, comparing breast cancer incidence in the cohort with that based on general population rates, allowing for age and calendar year.

What breast cancer surveillance modality should be used? Diagnostic value mammogram and MRI in CAYA cancer survivors				
Sung et al. Screening breast MR Imaging in women with a history of chest irradiation. Radiology 2011;259:65-71.				
Study design Study years Years of follow-up	**Participants**	**Diagnostic test Breast cancer**	**Main outcomes**	**Additional remarks**
Single-center retrospective cohort study 1999-2008 Follow-up: Not reported	91 female cancer survivors (majority Hodgkin lymphoma) treated with chest radiation Age at diagnosis: Median 24 (range 5-54) yr Prescribed radiation dose: 10->30 Gy Age at study: Median 40 (range 18-62) yr at first MRI examination	Mammogram: 83/91 (91.2%) MRI: 91/91 (100%) Screening rounds: MRI: Median 2 (range 1-9) per patient Screening examinations: MRI: 247 Breast cancer: 10/91 (11.0%) in 9 women; 4 invasive, 6 DCIS Cases of interval cancer: Not reported Age at breast cancer diagnosis: Range 41-62 yr	Sensitivity (95% CI): - Mammogram: 66.7% (29.9-92.5%) - MRI: 66.7% (29.9-92.5%) Specificity (95% CI): - Mammogram: 93.2% (84.9-97.8%) - MRI: 81.7% (71.6-89.4%) Positive predictive value (95% CI): - Mammogram: 54.5% (23.4-83.3%) - MRI: 28.6% (11.3-52.1%) Negative predictive value (95% CI): - Mammogram: 95.8% (88.3-99.1%) - MRI: 95.7% (88.8-99.1%) Accuracy (95% CI): - Mammogram: 90.4% (81.9-95.8%) - MRI: 80.2% (70.6-87.8%) Recalls: - Mammogram: 6/83 (7.2%) women biopsy for malignant lesions 5/83 (6.0%) women biopsy for benign lesions - MRI: 7/91 (7.7%) women biopsy for malignant lesions 14/91 (15.4%) women biopsy for benign lesions	There was a substantial variation in the number of MRI examinations performed per patient and in the timing of the mammographic and MRI examinations relative to one another. Mammogram was performed within 1 month of MRI in 66 of the 247 MRI examinations, between 1 month and 6 months in 114 of the MRI examinations, and between 7 and 12 months in 39 of the MRI examinations. No recent mammogram was available for 28 MRI examinations. Screening exam was defined positive if BI-RADS score was 4 or 5. Of the 10 breast cancers detected, 4 (40%) were detected by MRI alone, 3 by both MRI and mammogram and 3 by mammogram alone. BI-RADS = Breast Imaging-Reporting and Data System.

				Risk of bias: - Selection bias: unclear how many patients were included from the original cohort of survivors. - Index test bias: unclear if radiologists who assessed the imaging studies were blinded to clinical outcomes. - Verification bias: low risk, biopsies were performed when imaging detected a mass. Interval between mammogram and MRI was more than 4 months in at least 39 of the MRI examinations. - Attrition bias: low risk, 91/91 (100%) women underwent breast cancer screening.

Who needs breast cancer surveillance?				
Reulen et al. Long-term population-based risks of breast cancer after childhood cancer. Int J Cancer 2008;123:2156-2163.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Population-based cohort study 1940-1991 Follow-up: 5-≥40 yr; Person-years of follow-up since 5-yr survival: 162,285	8,093 5-yr female childhood cancer survivors aged <15 yr at diagnosis Age at diagnosis: Range 0-14 yr Age at follow-up: >16 yr	Any radiotherapy: - 4,045 (50.0%) - 63/81 (77.8%) survivors with breast cancer - 3,982/8,012 (49.7%) survivors without breast cancer Chemotherapy: - 2,926 (36.2%) - 29/81 (35.8%) survivors with breast cancer - 2,897/8,012 (36.2%) survivors without breast cancer	Breast cancer: 81/8,093 (1.0%) Cumulative incidence at age 50 yr: 2.7% Standardized incidence ratio (95% CI): - All survivors: 2.2 (1.7-27) - Wilms tumor: 3.2 (1.6-6.3) - Leukemia: 1.7 (0.7-4.1) - Hodgkin lymphoma: 8.2 (5.2-13.1) - Non-Hodgkin lymphoma: 1.1 (0.3-4.5) - CNS tumor: 1.0 (0.5-1.7) - Neuroblastoma: 0.9 (0.1-6.4) - Non-heritable retinoblastoma: 1.9 (0.7-5.1) - Heritable retinoblastoma: 4.2 (2.0-8.9) - Bone sarcoma: 3.9 (2.0-7.5) - Soft-tissue sarcoma: 2.6 (1.3-5.2) - Any radiotherapy: 2.9 (2.2-3.7) - No radiotherapy: 1.4 (0.9-3.7) - Chemotherapy: 4.9 (3.4-7.0) - No chemotherapy: 1.9 (1.4-2.5) - Chemotherapy and radiotherapy: 5.9 (4.0-8.7) - No chemotherapy and radiotherapy: 2.3 (1.7-3.2) - Chemotherapy and no radiotherapy: 2.1 (0.7-6.6) - No chemotherapy and no radiotherapy: 1.4 (0.8-2.3) - Attained age 0-19 yr: 10.9 (1.5-77.7) - Attained age 20-29 yr: 5.7 (3.3-9.8)	Other variables included in the risk factor analysis were attained age, start of initial treatment decade and age at primary cancer diagnosis. **Risk of bias:** - Selection bias: low risk, 99.9% of the original cohort was included in the study group. - Attrition bias: high risk, of the 6,917 eligible female survivors (in terms of age and vital status), 5,133 (74%) returned a completed questionnaire. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for radiation, chemotherapy and attained age.

			- Attained age 30-39 yr: 3.1 (2.3-4.3) - Attained age 40-49 yr: 1.5 (1.0-2.3) - Attained age ≥50 yr: 0.9 (0.5-1.8) <u>Absolute excess risk per 10,000 person-years (95% CI):</u> - All survivors: 1.9 (1.1-3.3) <u>Relative standardized incidence ratio (95% CI) in multivariable analysis:</u> - Leukemia vs. Wilms tumor: 0.3 (0.1-1.0) - Hodgkin lymphoma vs. Wilms tumor: 2.7 (0.9-7.5) - Non-Hodgkin lymphoma vs. Wilms tumor: 0.5 (0.1-2.8) - CNS tumor vs. Wilms tumor: 0.5 (0.2-1.5) - Neuroblastoma vs. Wilms tumor: 0.3 (0.0-2.8) - Non-heritable retinoblastoma vs. Wilms tumor: 1.3 (0.3-4.8) - Heritable retinoblastoma vs. Wilms tumor: 1.7 (0.6-4.9) - Bone sarcoma vs. Wilms tumor: 1.4 (0.4-4.4) - Soft-tissue sarcoma vs. Wilms tumor: 1.3 (0.4-4.0) *P for heterogeneity* <0.001 - Any radiotherapy yes vs. no: 1.8 (1.0-3.3) - Chemotherapy yes vs. no: 1.5 (0.8-2.8)	

Who needs breast cancer surveillance?				
Constine et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. Int J Radiation Oncology Biol Phys 2008;72:24-33.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study 1960-1990 <u>Follow-up:</u> Mean 16.8 (range 0.01-39.4) yr	398 females with childhood Hodgkin's disease aged ≤18 yr at diagnosis <u>Age at diagnosis:</u> Mean 13.6 (range 0.3-18.9) yr <u>Age at follow-up:</u> Not reported	*Treatment data of total cohort including men (n=930)* <u>Radiotherapy alone:</u> - 401 (43.1%) - Mantle alone: 87 (9.4%) - Mantle and para-aortic: 234 (25.1%) - Total lymphoid: 50 (5.4%) - Para-aortic and pelvic: 14 (1.5%) - Other: 16 (1.7%) - Radiation dose: Mean 37.1 (range 6-49.8) Gy <u>Radiotherapy and chemotherapy:</u> - 447 (48.1%) - Mantle alone: 96 (10.3%) - Mantle and para-aortic: 175 (18.8%) - Total lymphoid: 135 (14.5%) - Para-aortic and pelvic: 7 (0.8%) - Other: 34 (3.7%) - Radiation dose: Mean 32.9 (range 2-50) Gy <u>Chemotherapy alone:</u> - 82 (8.8%) <u>Chemotherapy agents:</u>	<u>Breast cancer:</u> 29/398 (7.3%) <u>Breast cancer in females treated with vs. without pelvic radiation:</u> 1/98 (1.0%) vs. 28/272 (10.3%); p = 0.0032 Alkylating agent and anthracycline dose was not significantly different for patients who did vs. did not develop breast cancer	After primary therapy, 227 patients relapsed and 120 of this group died (67 of HD, 14 of SMN, 19 of other toxic events, 20 unknown). Of the 703 patients who did not relapse, 80 died (10 of HD, 23 of SMN, 39 of other events, 8 unknown). **Risk of bias:** - <u>Selection bias:</u> unclear how many female survivors of the original cohort were included in the study group. - <u>Attrition bias:</u> unclear for how many patients follow-up was complete. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, all patients included in the analysis were treated with chest radiation.

		- Alkylating agents: 59 (6.3%) - Anthracyclines: 269 (28.9%) - Both: 265 (28.5%)		

Who needs breast cancer surveillance?				
Taylor et al. Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: A population-based study. Int J Cancer 2007;120:384-391.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Population-based cohort study 1940-1991 Follow-up: Mean 20.3 yr; Person-years of follow-up since 5-yr survival: 5,878	383 female 5-yr Hodgkin lymphoma survivors aged <15 yr at diagnosis Age at diagnosis: Mean 13.8 (range 12.7-14.9) yr Age at follow-up: >16 yr	Chest radiation: - 259 (67.6%) - 16/16 (100%) survivors with breast cancer - 243/367 (66.2%) survivors without breast cancer Absorbed radiation dose: - Mean 33 (range 12.3-52) Gy (available for 148/383) Alkylating agents: - 201 (67.6%) - 6/16 (37.5%) survivors with breast cancer - 195/367 (53.1%) survivors without breast cancer	Breast cancer: 16/383 (4.2%) 30-yr cumulative incidence (95% CI): - All survivors: 9.9% (3.3-16.6) - Supradiaphragmatic radiation: 12.2% (4.3-20.0) Standardized incidence ratio (95% CI): - All survivors: 11.5 (6.6-18.6) - Supradiaphragmatic radiation: 13.3 (7.6-21.5) Absolute excess risk per 10,000 person-years: - All survivors: 24.9 - Supradiaphragmatic radiation: 33.9 Relative risk (95% CI) among survivors treated with supradiaphragmatic radiation: - Alkylating agents yes vs. no: 0.49 (0.18-1.33)	**Risk of bias:** - Selection bias: low risk, 383 (100%) of the original cohort of survivors were included in the study. - Attrition bias: low risk, 240/302 (79%) returned the questionnaire. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for chest radiation.

Who needs breast cancer surveillance?				
Hill et al. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. Blood 2005;106:3358-3364.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center case-control study <1970-1994 <u>Follow-up:</u> >1 yr	3,817 female 1-yr Hodgkin lymphoma survivors aged ≤30 yr at diagnosis 105 Hodgkin lymphoma survivors with breast cancer matched to 266 Hodgkin lymphoma survivors without breast cancer <u>Age at diagnosis:</u> Median 22 (range 13-30) yr <u>Age at follow-up:</u> Median 41 (range 27-57) yr at breast cancer diagnosis	<u>Chest radiation:</u> - 0-4.9 Gy: 23/105 (21.9%) cases; 95/266 (35.7%) controls - 5.0-23.0 Gy: 23/105 (21.9%) cases; 47/266 (17.7%) controls - 23.1-37.1 Gy: 29/105 (27.6%) cases; 63/266 (23.7%) controls - 37.2-61.3 Gy: 30/105 (28.6%) cases; 61/266 (22.9%) controls <u>Alkylating agents:</u> - 37/105 (35.2%) cases - 134/266 (50.4%) controls <u>Radiation to ovaries:</u> - <5 Gy: 98/105 (93.3%) cases; 226/266 (85.0%) controls - ≥5 Gy: 7/105 (6.7%) cases; 40/266 (15.0%) controls	<u>Odds ratio (95% CI) for breast cancer from adjusted regression analysis:</u> - Breast radiation dose 5.0-61.3 Gy vs. 0-4.9 Gy: 2.7 (1.4-5.2) - Premenopausal women treated with alkylating agents or radiation to the ovaries ≥5 Gy vs. no alkylating agents and radiation to the ovaries <5 Gy: 0.7 (0.3-1.5) - Postmenopausal women treated with alkylating agents or radiation to the ovaries ≥5 Gy vs. no alkylating agents and radiation to the ovaries <5 Gy: 0.2 (0.1-1.3) - Age at menarche ≤12 yr vs. >12 yr: 1.2 (0.7-2.3) - Oral contraceptive use ever vs. never: 1.0 (0.5-2.2) - Oral contraceptive use 1-6 yr vs. never: 0.9 (0.3-2.4) - Oral contraceptive use ≥7 yr vs. never: 1.9 (0.7-5.0) - Breast radiation dose ≥5 Gy and no family history vs. breast radiation dose <5 Gy and no family history: 5.8 (2.1-16.3) - Breast radiation dose <5 Gy and family history vs. breast radiation dose <5 Gy and no family history: 11.5 (2.5-52.6) - Breast radiation dose ≥5 Gy and family history vs. breast radiation dose <5 Gy and no family history: 9.5 (3.0-30.1) - Breast radiation dose ≥5 Gy and family	Two controls were selected for each case matched on registry, age at Hodgkin lymphoma diagnosis, calendar year of Hodgkin lymphoma diagnosis, and survival after Hodgkin lymphoma. Analyses were adjusted for breast radiation dose, number of alkylating agent cycles and radiation dose of ≥5 Gy to the ovaries. Analyses regarding or oral contraceptive use and number of live births were limited to women who did not receive HL treatment with alkylating agents and who received less than 5 Gy radiation dose to the ovaries, as those treatments can alter ovarian function, induce menopause, influence childbearing, and also reduce breast cancer risk (n=68 cases; n=125 controls). Family history: history of breast and/or ovarian cancer in a first or second degree relative. **Risk of bias:**

			history vs. breast radiation dose <5 Gy and family history: 0.8 (0.2-3.4) - Breast radiation dose ≥5 Gy and no live births vs. breast radiation dose <5 Gy and no live births: 1.1 (0.3-4.7) - Breast radiation dose <5 Gy and live births vs. breast radiation dose <5 Gy and no live births: 0.4 (0.1-1.6) - Breast radiation dose ≥5 Gy and live births vs. breast radiation dose <5 Gy and no live births: 1.4 (0.4-4.8) - Breast radiation dose ≥5 Gy and live births vs. breast radiation dose <5 Gy and live births: 3.5 (1.4-8.9) Adjusted odds ratio per Gy to the breasts (95% CI): 1.04 (1.0-1.07)	- Selection bias: unclear how many patients were included in the original cohort of survivors. - Attrition bias: unclear for how many patients follow-up was complete. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, analyses were adjusted for breast radiation dose, number of alkylating agent cycles and radiation dose of ≥5 Gy to the ovaries.

From original guideline 2013

Who needs breast cancer surveillance? **Breast cancer risk after 1-9 and 10-19 Gy chest radiation, alkylating agents, pelvic radiation**				
Inskip et al. Radiation dose and breast cancer risk in the Childhood Cancer Survivor Study. J Clin Oncol 2009;27:3901-3907. [27]				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center case-control study 1970-1986 <u>Follow-up:</u> Median 19.4 (range 6.7-29.6) yr	6,647 female 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 <u>Age at diagnosis:</u> Median 16.0 (range 5.0-32.0) yr <u>Age at follow-up:</u> Range 18.0-51.0 yr	<u>Chest radiation:</u> - 107/120 (89%) cases - 328/464 (71%) controls <u>Absorbed radiation dose:</u> - Dose cases not reported (range >0-0.13 Gy to 30.0-60.0 Gy) - Mean 13.4 Gy controls <u>Alkylating agents:</u> - 53/120 (44%) cases - 200/464 (43%) controls <u>Radiation to ovaries <5 Gy:</u> - 99/120 (82.5%) cases - 342/464 (73.7%) controls <u>Radiation to ovaries ≥5 Gy:</u> - 8/120 (6.7%) cases - 47/464 (10.1%) controls	<u>Odds ratio (95% CI) for breast cancer from multivariable regression analysis:</u> - Chest radiation yes vs. no: 2.7 (1.4-5.4) - >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) *P for trend* <0.001 - Alkylating agents yes vs. no: 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) - Dacarbazine yes vs. no: 3.49 (0.96-12.68) - Dactinomycin yes vs. no: 2.40 (0.96-5.96) - Anthracyclines yes vs. no: 1.86 (0.99-3.48) <u>Excess odds ratio per Gy to the breasts (95% CI):</u> - Overall: 0.27 (0.10-0.67) - <5 Gy radiation to ovaries: 0.36 (0.14-0.93) - ≥5 Gy radiation to ovaries: 0.06 (-0.06-0.27)	Analyses on chest radiation were adjusted for type of childhood cancer diagnosis. Analyses on chemotherapy 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. Four controls were selected for each case matched on primary cancer diagnosis and follow-up years.

			P = 0.002 <u>Recalculated odds ratio (95% CI):*</u> - 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)	

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

Who needs breast cancer surveillance? **Breast cancer risk after 1-19 Gy chest radiation and abdominal field 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;122:2085-2093.[28]				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Population-based cohort study 1940-1991 <u>Follow-up:</u> Mean 19.3 yr; Person-years of follow-up since 5-yr survival: 27,841	1,441 5-yr Wilms tumor survivors aged <15 yr at diagnosis <u>Age at diagnosis:</u> Mean 3.3 (range 0-14.9) yr <u>Age at follow-up:</u> >16 years	<u>Chest radiation:</u> Not reported <u>Radiotherapy:</u> 1,269 (88.1%) <u>Chemotherapy:</u> 1,211 (84.0%) <u>Alkylating agents:</u> Not reported	<u>Breast cancer:</u> - 9/1,441 (0.6%); 8 females, 1 male - All treated with abdominal field radiation (20-35 Gy) <u>Standardized incidence ratio (95% CI):</u> 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.

Who needs breast cancer surveillance? **Breast cancer risk after 1-9 and 10-19 Gy chest radiation**				
Guibout et al. Malignant breast tumors after radiotherapy for a first cancer during childhood. J Clin Oncol 2005;23:197-204. [26]				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study 1946-1986 <u>Follow-up:</u> Mean 16 (range 3-46) yr since primary cancer diagnosis; Person-years of follow-up: 20,323	1,814 female 3-yr childhood cancer survivors aged <17 yr at diagnosis <u>Age at diagnosis:</u> median 5, mean 6 (range 0-16) yr <u>Age at follow-up:</u> range ≥3 - ≥40 yr	<u>Chest radiation:</u> - 1,258 (69.3%) - 13/16 (81.3%) survivors with breast cancer - 1,245/1,798 (69.2%) survivors without breast cancer <u>Absorbed radiation dose by retrospective dose reconstruction:</u> Mean 5.06, median 0.96 (range 0-78.6) Gy <u>Surgical or radiological castration:</u> 222 (12.2%) <u>Alkylating agents:</u> Not reported	<u>Breast cancer:</u> 16/1,814 (0.9%) <u>30-yr cumulative incidence (95% CI):</u> 2.8% (1.0-4.5) <u>40-yr cumulative incidence (95% CI):</u> 10.7% (1.4-19.9) <u>Relative risk (95% CI) for breast cancer from multivariable regression analysis:</u> - Chest radiation yes vs. no: 1.3 (0.4-5.9) - >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 *P for trend* = 0.06 <u>Excess relative risk per Gy to the breasts (95% CI):</u> 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. Of the 222 patients that underwent surgical or radiologic castration none developed breast cancer (p=0.01)

Who needs breast cancer surveillance? **Breast cancer risk after 1-9 and 10-19 Gy chest radiation, alkylating agents, pelvic radiation and menopausal status**				
Travis et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465-475.* [29]				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Population-based nested case-control study 1965-1994 <u>Follow-up:</u> Median 18 (range 7-30) yr	3,817 female 1-yr Hodgkin lymphoma survivors aged ≤30 yr at diagnosis 105 survivors with breast cancer matched to 266 survivors without breast cancer <u>Age at diagnosis:</u> Median 22 (range 13-30) yr <u>Age at follow-up:</u> Median 41.0 (range 27-57) yr breast cancer cases	<u>Chest radiation:</u> - 104/105 (99%) cases - 256/266 (96%) controls <u>Absorbed radiation dose:</u> - Mean 37.7 ± 4.7 Gy cases - Mean 37.3 ± 4.1 Gy controls <u>Alkylating agents:</u> - 31/105 (30%) cases - 104/266 (39%) controls <u>Pelvic radiation:</u> - <3.0 Gy: 94/105 (89.5%) cases - <3.0 Gy: 214/266 (80.5%) controls - 3.0-4.9 Gy: 4/105 (3.8%) cases - 3.0-4.9 Gy: 13/266 (4.9%) controls - ≥5.0 Gy: 7/105 (6.7%) cases - ≥5.0 Gy: 39/266 (14.7%) controls	<u>Relative breast cancer risk (95% CI) from multivariable regression analysis:</u> - Chest radiation only vs. none: 3.2 (1.4-8.2) - Chest radiation 4.6 (4.0-6.9) Gy vs. 3.2 (0-3.9) Gy: 1.8 (0.7-4.5) - Chest radiation 21.0 (7.0-23.1) Gy vs. 3.2 (0-3.9) Gy: 4.1 (1.4-12.3) - Chest radiation 24.5 (23.2-27.9) Gy vs. 3.2 (0-3.9) Gy: 2.0 (0.7-5.9) - Chest radiation 35.2 (28.0-37.1) Gy vs. 3.2 (0-3.9) Gy: 6.8 (2.3-22.3) - Chest radiation 39.8 (37.2-40.4) Gy vs. 3.2 (0-3.9) Gy: 4.0 (1.3-13.4) - Chest radiation 41.7 (40.5-61.3) Gy vs. 3.2 (0-3.9) Gy: 8.0 (2.6-26.4) *P for trend* <0.001 - 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) *P for trend* = 0.003 - Pelvic radiation 3.0-4.9 Gy vs. <3.0 Gy: 1.2 (0.3-3.9) - Pelvic radiation ≥5.0 Gy vs. <3.0 Gy: 0.4 (0.1-1.1)	Analysis on chest radiation were adjusted for number of alkylating agent cycles and radiation dose delivered to the ovaries. Analysis on alkylating agents were adjusted for radiation dose delivered to the breasts and ovaries. Analysis on pelvic radiation were adjusted for radiation dose delivered to the breasts and number of alkylating agent cycles. Two controls were selected for each case matched on registry, calendar year of Hodgkin disease diagnosis, age at Hodgkin disease diagnosis, and length of survival without a second cancer at least as long as the interval between the diagnoses of Hodgkin disease and breast cancer in the case.

			- Premenopausal women: 3.5 (1.6-8.3) - Postmenopausal women: 1.9 (0.5-12.9) <u>Excess relative risk per Gy to the breasts (95% CI):</u> 0.15 (95% CI: 0.04-0.73) <u>Detailed estimation relative risk (95% CI):**</u> - 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)	

* Same cohort as Travis 2005.

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

Who needs breast cancer surveillance? **Breast cancer risk after alkylating agents**				
Travis et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Nat Cancer Inst 2005;97:1428-1437.[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 105 survivors with breast cancer matched to 266 survivors without breast cancer <u>Age at diagnosis:</u> Median 22 (range 13-30) yr <u>Age at follow-up:</u> Median 41.0 (range 27-57) yr breast cancer cases	<u>Chest radiation:</u> - 104/105 (99%) survivors with breast cancer - 256/266 (96%) survivors without breast cancer <u>Absorbed radiation dose:</u> - Mean 37.7 ± 4.7 Gy survivors with breast cancer - Mean 37.3 ± 4.1 Gy survivors without breast cancer <u>Alkylating agents:</u> - 31/105 (30%) survivors with breast cancer - 104/266 (39%) survivors without breast cancer	<u>Breast cancer:</u> 105/3817 (2.8%) <u>Relative risk (95% CI) with reference category ≥40 Gy mediastinal radiation without alkylating agents:</u> - Alkylating agents, no mediastinal radiation: 0.07 (0.02-0.36) - 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, no mediastinal radiation: 0.16 (0.47-0.72) - No alkylating agents with 20-<40 Gy mediastinal radiation: 0.82 (0.47-1.43) <u>Relative risk (95% CI) with reference category general population:</u> - Alkylating agents, no mediastinal radiation: 0.8 (0.3-2.6) - 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, no mediastinal radiation: 1.7 (0.6-5.2) - 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.[29]

Who needs breast cancer surveillance? **Breast cancer risk after 1-9 and 10-19 Gy chest radiation, alkylating agents, pelvic radiation, menopausal status and oral contraceptive use**				
van Leeuwen et al. Roles of radiation dose, chemotherapy and hormonal factors in breast cancer following Hodgkin's disease. J Nat Cancer Inst 2003;95:971-980.[30]*				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Population-based nested case-control study 1965-1988 <u>Follow-up:</u> Median 18.7 yr	650 female 5-yr Hodgkin lymphoma survivors aged ≤40 yr at diagnosis (80% <30 yr) 48 survivors with breast cancer matched to 175 survivors without breast cancer <u>Age at diagnosis:</u> - Median 25 (range 15-40) yr cases - Median 24 (range 13-40) yr controls <u>Age at follow-up:</u> Not reported (Median age breast cancer diagnosis 44 yr)	<u>Chest radiation:</u> - 48/48 (100%) cases - 172/175 (98%)controls <u>Absorbed radiation dose:</u> - Mean 38.5 Gy cases - Mean 37.6 Gy controls <u>Alkylating agents:</u> - 12/48 (25%) cases - 92/175 (53%) control <u>Ovarian radiation:</u> - <5 Gy: 47/48 (97.9%) cases - <5 Gy: 151/175 (86.3%) controls - ≥5 Gy: 1/48 (2.1%) cases - ≥5 Gy: 24/175 (13.7%) controls	<u>Relative breast cancer risk (95% CI) from multivariable regression analysis:</u> - Chest radiation 15.5 (4-23.2) Gy vs. 3.6 (0.26-3.9) Gy: 1.11 (0.32-3.58) - Chest radiation 30.2 (24-38.2) Gy vs. 3.6 (0.26-3.9) Gy: 4.20 (0.99-17.8) - Chest radiation 40.7 (38.5-56) Gy vs. 3.6 (0.26-3.9) Gy: 5.16 (1.27-21.0) - <6 cycles alkylating agents vs. no chemotherapy: 0.31 (0.09-1.05) - ≥6 cycles alkylating agents vs. no chemotherapy: 0.33 (0.13-0.86) - Non-alkylating single agents vs. no chemotherapy: 1.26 (0.42-3.82) - Ovarian radiation ≥5 Gy vs. <5 Gy: 0.13 (0.02-1.08) - Postmenopausal vs. premenopausal survivors: 0.30 (0.12-0.75) - Age at menopause 19-30 yr vs. no menopause: 0.06 (0.01-0.45) - Age at menopause 36-45 yr vs. no menopause: 0.80 (0.26-2.40) - Age at menopause (continuous per year): 1.12 (1.02-1.23) - Time from HL treatment to menopause ≥15 yr vs. premenopausal: 0.91 (0.26-3.18) - Time from HL treatment to menopause 5-14 yr vs. premenopausal: 0.24 (0.06-0.96)	Analysis on chest radiation were adjusted for ovarian radiation dose and chemotherapy. Analysis on alkylating agents were adjusted for radiation dose delivered to the breasts and ovaries. Analysis on ovarian radiation were adjusted for chest radiation dose and chemotherapy. Analysis on menopause were adjusted for chest radiation dose. Analysis on oral contraceptive and hormonal replacement use were adjusted for chest radiation dose, and menopausal age and status.

			- Time from HL treatment to menopause <5 yr vs. premenopausal: 0.15 (0.03-0.60) - No. premenopausal yrs after HL (continuous per year): 1.11 (1.00-1.22) - Oral contraceptive use <7.7 yr vs. none: 1.11 (0.47-2.62) - Oral contraceptive use ≥7.7 yr vs. none: 1.50 (0.61-3.65) - Hormonal replacement therapy ≥3 yr vs. <3 yr/none: 2.16 (0.36-12.9) <u>Excess relative risk per Gy (95% CI):</u> 0.06 (0.01-0.13)	

* This cohort was also included in the cohort of Travis 2003[29] and Travis 2005.[37]

Who needs breast cancer surveillance? **Breast cancer risk after 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;111:939-944. [35]				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter cohort study 1969-2000 <u>Follow-up:</u> Median 9.9 (range 7.0-32.2) yr	3,337 female 5-yr HCT survivors aged ≤70 yr at treatment (50% <30 yr) <u>Age at treatment:</u> Median 28.1 (range 0.2-70.3) yr <u>Age at follow-up:</u> Not reported (Median age breast cancer diagnosis 47.5 (range 25.5-65.8) yr	<u>TBI:</u> - 2,162 (64.8%) - 47/52 (90.4%) survivors with breast cancer - 2,115/3,285 (64.4%) survivors without breast cancer <u>TBI dose:</u> - 8-15.75 Gy fractionated - 9.2-10 Gy single fraction <u>Alkylating agents:</u> Not reported	<u>Breast cancer:</u> 52/3,337 (1.6%) <u>10-yr cumulative incidence (95% CI):</u> - No TBI: 0.1% (0.02-0.8) - TBI: 1.1% (0.6-1.7) <u>20-yr cumulative incidence (95% CI):</u> - No TBI: 1.3% (0.4-3.3) - TBI: 6.1% (3.9-8.9) <u>25-yr cumulative incidence (95% CI):</u> - No TBI: 2.8% (0.7-7.4) - TBI: 16.9% (9.4-26.2) <u>Hazard ratio (95% CI) in multivariable Cox regression analysis:</u> - TBI yes vs. no: 4.0 (1.6-10.3) - HCT at <18 yr vs. ≥40 yr: 9.5 (1.8-51.0) - HCT at 18-39 yr vs. ≥40 yr: 1.6 (0.7-3.8)	No TBI group may not be an appropriate reference category, since patients in the 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 it is 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.

Who needs breast cancer surveillance? Breast cancer risk after alkylating agents				
Kenney et al. Breast cancer after childhood cancer: A report from the Childhood Cancer Survivor Study. Ann Int Med 2004;141:590-597.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study 1970-1986 <u>Follow-up:</u> Median 19 (range 6-29) yr	6,068 5-yr female childhood cancer survivors aged ≤21 yr at diagnosis <u>Age at diagnosis:</u> - Median 16 (range 5-20) yr breast cancer cases - Median 6 (range 0-20) yr non-breast cancer survivors <u>Age at follow-up:</u> - Median 39 (range 26-50) yr breast cancer cases - median 27 (range 5-51) yr non breast cancer survivors	<u>Chest radiation:</u> - 1,258 (20.7%) - 73/95 (77%) survivors with breast cancer - 1,185/5,973 (20%) survivors without breast cancer <u>Radiation dose:</u> Not reported <u>Alkylating agents:</u> - 2,986 (49.2%) - 47/95 (50%) survivors with breast cancer - 2,939/5,973 (49%) survivors without breast cancer <u>Pelvic radiation:</u> Not reported	<u>Breast cancer:</u> 95/6,068 (1.6%) <u>Cumulative incidence (95% CI) at age 40 yr for Hodgkin lymphoma survivors treated with chest radiation:</u> 12.9% (9.3-16.5) <u>Standardized incidence ratio (95% CI) for survivors treated with chest radiation:</u> 24.7 (19.3-31.0) <u>Standardized incidence ratio (95% CI) for survivors treated without chest radiation:</u> 4.8 (2.9-7.4) <u>Relative breast cancer rate (95% CI) adjusted for chest radiation:</u> - 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) *P trend* >0.2 - Pelvic radiation yes vs. no: 0.6 (0.4-0.9)	Analyses were adjusted for chest radiation. Alkylating agent score accounts for exposure to various alkylating agents and range of doses.

Who needs breast cancer surveillance? **Breast cancer risk after alkylating agents**				
Bhatia et al. High riks of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. J Clin Oncol 2003;21:4386-4394. [38]				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multicenter 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 Age at diagnosis: Median 11.7 (range 0.3-16.9) yr Age at follow-up: Not reported (Median age at breast cancer 32.0 (range 16.3-42.7) yr)	Chest radiation: Not reported (30/30 (100%) survivors with breast cancer) Prescribed radiation dose: Median 35 (range 26-46) Gy in survivors with breast cancer Alkylating agents: Number of patients not reported	Breast cancer: 30/1,380 (2.2%); 42 breast cancers in 30 patients (29 females, 1 male) 10-yr cumulative incidence (95% CI) females: 5.6% (2.8-8.3) 20-yr cumulative incidence (95% CI) females: 16.9% (9.4-24.5) Standardized incidence ratio (95% CI) females: 55.5 (39.5-75.9) Absolute excess risk females per 1,000 person-years: 5.3 Relative risk (95% CI) in multiple regression analysis females: 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.

Who needs breast cancer surveillance? **Breast cancer risk after alkylating agents**				
de Bruin et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol 2009;27:4239-4246. [36]				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Population-based cohort study 1965-1995 <u>Follow-up:</u> Median 17.8 (range 5-40) yr	1,122 female 5-yr Hodgkin lymphoma survivors aged ≤50 yr at diagnosis (66% ≤30 yr) <u>Age at diagnosis:</u> Median 26.3 (range 5-50) yr <u>Age at follow-up:</u> Not reported	<u>Chest radiation:</u> - 932 (83.1%) - 119/120 (99.2%) survivors with breast cancer - 813/1,002 (81.1%) survivors without breast cancer <u>Radiation dose:</u> Prescribed radiation dose not reported (patients usually received 40 Gy (36-44 Gy)) <u>Alkylating agents:</u> - 481 (42.9%) - 33/120 (27.5%) survivors with breast cancer - 448/1,002 (44.7%) survivors without breast cancer <u>Pelvic radiation:</u> - 161/1122 (14.3%) - 6/120 (5.0%) survivors with breast cancer - 155/1002 (15.5%) survivors without breast cancer	<u>Breast cancer:</u> 120/1,222 (9.8%) <u>30-yr cumulative incidence (95% CI):</u> 19% (16-23) <u>Standardized incidence ratio (95% CI):</u> 5.6 (4.6-6.8) <u>Absolute excess risk (95% CI) per 10,000 person-years:</u> 57.0 (45.0-72.0) <u>Hazard ratio (95% CI) in multivariable regression analysis:</u> - Mantle field radiation vs. mediastinal field radiation: 2.7 (1.1-6.9) - ≤8.4 g/m^2 procarbazine vs. no alkylating agents: 0.6 (0.3-0.9) - >8.4 g/m^2 procarbazine vs. no alkylating agents: 0.4 (0.1-1.3) - Pelvic radiation yes vs. no: 0.4 (0.1-1.4) - 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) - Chest radiation and non-alkylating	Analyses were based on 782 women treated with mantle field, axillary, or mediastinal radiation before age 41. Analyses on cancer treatment were adjusted for chest radiation, alkylating agent chemotherapy, pelvic radiation, age at first radiation to the breast and time since first radiation to the breast. Analyses on premature menopause were adjusted for chest radiation, years intact ovarian function, lifestyle factors (BMI, smoking) and hormone factors (nulilparity, oral contraceptives). Analyses on years intact ovarian function were adjusted for chest radiation, premature menopause, lifestyle factors (BMI, smoking) and hormone factors (nulliparity, oral contraceptives). Analyses on oral contraceptive use were adjusted for chest radiation, premature menopause, years intact ovarian function, lifestyle factors (BMI, smoking)

			chemotherapy vs. chest radiation only: 2.0 (0.9-4.5) - Menopause at age <41 yr vs. ≥41 yr: 0.4 (0.2-0.8) - Years of intact ovarian function <10 yr vs. 10-20 yr: 0.3 (0.2-0.6) - Years of intact ovarian function >20 yr vs. 10-20 yr: 5.3 (2.9-9.9) - Oral contraceptive use yes vs. no/unknown: 1.4 (0.8-2.3)	and nulliparity.

What breast cancer surveillance modality should be used? **Additional value of screening with a mammogram in CAYA 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.[48]				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Single-center prospective cohort study 1995-1999 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	90 female 8-yr Hodgkin lymphoma survivors treated with mantle radiation Age at diagnosis: Median 20 (range 13-30) yr Prescribed radiation dose: median 37.5 (range 30.0-41.5) Gy Age at study: Median 38 (range 24-51) yr; 40% <35 yr	Mammogram: - 79/90 (87.8%) at baseline - 84/90 (93.3%) during study Breast cancer: 12/90 (13.3%) in 10 women; 10 invasive, 2 DCIS	Baseline mammogram: 10/79 (12.7%) abnormal mammogram Recalls after baseline mammogram: - 5/79 (6.3%) women further imaging - 2/79 (2.5%) women biopsy for malignant lesions - 3/79 (3.8%) women biopsy for benign lesions - 7/12 (58.3%) breast cancers initially detected by mammogram - 12/12 (100%) detectable by mammogram	In total, 90 of 167 (53.9%) eligible patients were included in the study. 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.

DCIS = ductal carcinoma-in-situ.

What breast cancer surveillance modality should be used? **Additional value of screening with a mammogram in CAYA 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.[49]				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Single-center prospective cohort study 2002 <u>Follow-up:</u> Median 16.9 (range 4.5-32.5) yr after radiation No follow-up years during study, only baseline examinations	115 female Hodgkin lymphoma survivors treated with chest radiation <u>Age at diagnosis:</u> Median 24 (range 13-36) yr <u>Prescribed radiation dose:</u> 15-≥44 Gy <u>Age at study:</u> Mean 40.4 (range 26-55) yr	<u>Mammogram:</u> 99/115 (86.1%) <u>Breast cancer:</u> 4/115 (3.5%); 2 invasive, 2 DCIS	<u>Baseline mammogram:</u> 17/99 (17.2%) abnormal mammogram <u>Recalls after baseline mammogram:</u> - 10/99 (10.1%) women further imaging - 1/99 (1.0%) women biopsy for malignant lesions - 6/99 (6.1%) women biopsy for benign lesions - 3/4 (75.0%) breast cancers initially detected by mammogram - 4/4 (100%) detectable by mammogram	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.

DCIS = ductal carcinoma-in-situ.

What breast cancer surveillance modality should be used? **Additional value of screening with a mammogram in CAYA 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.[66]				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Population-based retrospective cohort study 2003-2007 <u>Follow-up:</u> 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 <u>Age at diagnosis:</u> Mean 25.5 ± 5.3 yr <u>Prescribed radiation dose:</u> - 35.2 ± 4.6 Gy in breast cancer cases - 33.92 ± 4.8 Gy in controls <u>Age at study:</u> Mean 40.3 ± 9.09 yr (none aged <30 yr)	<u>Mammogram:</u> 171/243 (70.4%) <u>Screening rounds:</u> Mean 2.2 per patient <u>Screening examinations:</u> 370 <u>Breast cancer:</u> 28/243 (11.5%) in 23 women; 25 invasive, 3 DCIS	<u>Mammogram within screening program:</u> 39/370 (10.5%) screening examinations abnormal <u>Recalls within screening program:</u> - 31/171 (18.1%) women further imaging - 5/171 (2.9%) women biopsy for malignant lesions - 3/171 (1.8%) women biopsy for benign lesions - 10/28 (35.7%) breast cancers initially detected by mammogram	Of the 210 patients referred for screening, 9 (4.3%) subsequently declined and no evidence of screening could be found for 30 (14.3%) patients.

DCIS = ductal carcinoma-in-situ.

What breast cancer surveillance modality should be used? **Additional value of screening with a mammogram in CAYA cancer survivors**				
Lee et al. Screening mammography for young women treated with supradiaphragmatic radiation for Hodgkin's lymphoma. Ann Oncol 2008; 19: 62–7.[50]				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Single-center prospective cohort study 1997-2006 <u>Follow-up:</u> 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 <u>Age at diagnosis:</u> Median 22 (range 9-31) yr <u>Prescribed radiation dose:</u> Median 35 (range 15-60) Gy <u>Age at study:</u> Median 35 (range 24-55) yr	<u>Mammogram only:</u> 82/115 (71.3%) <u>Mammogram + MRI:</u> 12/115 (10.4%) <u>Mammogram + ultrasound:</u> 3/115 (2.6%) <u>MRI only:</u> 1/115 (0.7%) <u>Breast cancer:</u> 12/115 (10.4%); 7 invasive, 5 DCIS	<u>Recalls:</u> Not reported - 5/12 (41.7%) breast cancers initially detected by mammogram - 11/12 (91.7%) detectable by mammogram	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.

What breast cancer surveillance modality should be used? Additional value of screening with a mammogram in CAYA cancer survivors				
Dershaw et al. Breast carcinoma in women previously treated for Hodgkin disease: mammographic evaluation. Radiology 1992; 184: 421–3.[65]				
Study design Study years Years of follow-up	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center retrospective cohort study Study years not reported <u>Follow-up:</u> Mean 18 (range 8-34) yr after diagnosis	27 female Hodgkin lymphoma survivors treated with chest radiation with 29 secondary breast cancers <u>Age at diagnosis:</u> Not reported <u>Prescribed radiation dose:</u> 20-50 Gy <u>Age at study:</u> Mean 48 (range 33-75) yr at breast cancer diagnosis; 9/29 (31.0%) aged 33-39 yr	Mammogram, physical findings	26/29 (89.7%) breast cancers detectable by mammogram 11/29 (37.9%) breast cancers only detected by mammogram 18/29 (62.1%) breast cancers detected by physical findings	Interpretation of the results is limited by the retrospective study design and small number of cases.

What breast cancer surveillance modality should be used? Additional value of screening with a mammogram in CAYA cancer survivors				
Wolden et al. Management of breast cancer after Hodgkin's disease. J Clin Oncol 2000; 18: 765–72.[46]				
Study design Study years Years of follow-up	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center retrospective cohort study Until 1997 <u>Follow-up:</u> Median 17.4 (range 1.5-32.7) yr after diagnosis	65 female Hodgkin lymphoma survivors treated with chest radiation with 71 secondary breast cancers <u>Age at diagnosis:</u> Median 24.6 (range13.3-71.8) yr <u>Prescribed radiation dose:</u> mean 43.3 (range 24.0-51.0) Gy <u>Age at study:</u> Median 42.6 (range 23.0-79.1) yr at breast cancer diagnosis	Self-examination, clinical breast exam, mammogram	19/71 (26.8%) breast cancers detected by mammogram, of which 4 detected in women aged 33-38 yr 7/71 (9.9%) breast cancers detected by clinical breast exam 45/71 (63.3%) breast cancers detected by self-examination	Interpretation of the results is limited by the retrospective study design.

What breast cancer surveillance modality should be used? Diagnostic value mammogram vs. MRI in younger vs. older age group				
Kriege et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004; 351: 427–37.[72]				
Study design Study years Years of follow-up	**Participants**	**Diagnostic test Breast cancer**	**Main outcomes**	**Additional remarks**
Multi-center 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	Diagnostic test: Mammogram, MRI Screening examinations: 4134 Breast cancer: 45/1779 (2.5%); 39 invasive, 6 DCIS Cases of interval cancer: 4/45 (8.9%)	Sensitivity mammogram; odds ratio (95% CI): - ≥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 Sensitivity MRI; odds ratio (95% CI): - ≥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 Positive predictive value mammogram: - ≥50 yr: 7.8% - 40-49 yr: 7.4% - <40 yr: 9.6% - *P* = 0.89 Positive predictive value MRI: - ≥50 yr: 5.7% - 40-49 yr: 8.2% - <40 yr: 8.2% - *P* = 0.60 False positive rate mammogram; odds ratio (95% CI): - ≥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 False positive rate MRI; odds ratio (95% CI): - ≥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)	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.

			- *P* = 0.009 <u>Discriminating capacity MRI vs. mammogram – AUC difference:</u> - ≥50 yr: 0.114 (*P* = 0.53) - 40-49 yr: 0.227 (*P* = 0.02) - <40 yr: 0.068 (*P* = 0.47)	

BI-RADS = Breast Imaging-Reporting and Data System.

What breast cancer surveillance modality should be used? **Diagnostic value mammogram vs. MRI in younger vs. older 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). Invest Radiol 2011;46:94-105. [73]				
Study design **Study years** **Years of follow-up**	**Participants**	**Diagnostic test** **Breast cancer**	**Main outcomes**	**Additional remarks**
Multi-center prospective cohort study 2000-2007 Follow-up: Not reported	501 women with a high familial risk of breast cancer; 44% prior history of breast and/or ovarian cancer Age at study: Median 45.0 (range 22-79) yr	Diagnostic test: Mammogram, MRI, ultrasound, clinical breast exam Screening examinations: 1592; mean 3.2 per patient Breast cancer: - 52/501 (10.4%); 44 invasive, 8 DCIS - 2/52 (3.8%) breast cancers in women aged 20-29 yr - 9/52 (17.3%) breast cancers in women aged 30-39 yr Cases of interval cancer: 3/52 (5.8%)	Cancer detection rate per woman-year (95% CI): 3.1 (2.3-4.0) Sensitivity (95% CI) mammogram: - <50 yr: 45.5% (24.5-67.8) - ≥50 yr: 53.6% (33.9-72.5) Sensitivity (95% CI) MRI: - <50 yr: 88.9% (65.3-98.6) - ≥50 yr: 92.9% (76.5-99.1) Specificity (95% CI) mammogram: - <50 yr: 98.7% (97.5-99.5) - ≥50 yr: 99.5% (98.2-99.9) Specificity (95% CI) MRI: - <50 yr: 96.6% (94.8-97.9) - ≥50 yr: 96.9% (94.6-98.4) Positive predictive value (95% CI) mammogram: - <50 yr: 55.6% (30.8-78.5) - ≥50 yr: 88.2% (63.6-98.5) Positive predictive value (95% CI) MRI: - <50 yr: 43.2% (27.1-60.5) - ≥50 yr: 68.4% (51.3-82.5) Negative predictive value (95% CI) mammogram: - <50 yr: 98.1% (96.7-99.0)	Screening exam was defined positive if BI-RADS score was 4 or 5. Results were blinded so that the two examinations were not linked.

			- ≥50 yr: 96.9% (94.8-98.3) <u>Negative predictive value (95% CI) MRI:</u> - <50 yr: 99.7% (98.8-100) - ≥50 yr: 99.5% (98.1-99.9)	

BI-RADS = Breast Imaging-Reporting and Data System.