Conclusions of evidence tables breast cancer surveillance

Who needs breast cancer surveillance?

1. What is the risk of breast cancer in childhood and young adult cancer survivors treated with 1-9 and 10-19 Gy chest radiation?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors, **higher chest radiation dose** was **significantly** associated with an **increased breast cancer risk** (OR per 10 Gy: 3.9 (2.5-6.5)). In female childhood cancer survivors, <5 Gy **chest radiation** was borderline significantly associated with an **increased breast cancer risk** as compared to **no chest radiation** adjusted for adjusted for type of first cancer, calendar year of follow-up, family history of breast or ovarian cancer, and chemotherapy (OR: 1.7 (1.0-3.0))	*Veiga 2019#*
In female childhood cancer survivors, **>0-<10 Gy chest radiation** was **non-significantly** associated with **breast cancer risk** as compared to **no chest radiation** adjusted for age at primary childhood cancer diagnosis, pathogenic/likely pathogenic mutation, alkylating agents, pelvic radiation and anthracyclines (HR 0.7 (0.2-2.8)). In female childhood cancer survivors, **10-<20 Gy chest radiation** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no chest radiation** adjusted for age at primary childhood cancer diagnosis, pathogenic/likely pathogenic mutation, alkylating agents, pelvic radiation and anthracyclines (HR 2.4 (0.4-15.0)). In female childhood cancer survivors without pathogenic/likely pathogenic mutations, **>0-<10 Gy chest radiation** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no chest radiation** adjusted for age at primary childhood cancer diagnosis, alkylating agents, pelvic radiation and anthracyclines (HR 1.2 (0.3-5.0)). In female childhood cancer survivors without pathogenic/likely pathogenic mutations, **10-<20 Gy chest radiation** was **significantly** associated with an **increased breast cancer risk** as compared to **no chest radiation** adjusted for age at primary childhood cancer diagnosis, alkylating agents, pelvic radiation and anthracyclines (HR 8.0 (1.1-56.3)).	*Ehrhardt 2019*
In female childhood cancer survivors with breast cancer, **17 (14.0%**) and **19 (15.7%)** were treated with **<10 Gy** and **10-20 Gy chest radiation**, respectively.	*Demoor-Goldschmidt 2017*
In female childhood cancer survivors, **10-19 Gy chest radiation** was s**ignificantly** associated with an **increased breast cancer risk** as compared to the **general population** (SIR: 30.6 (18.4-50.7)). in female childhood cancer survivors, **2-20 Gy (median 14 Gy) whole lung radiation** was **significantly** associated with an **increased breast cancer risk after** as compared to the **general population** (SIR: 43.6 (27.1-70.1)). In female childhood cancer survivors, **whole lung radiation (median 14 Gy (range 2-20 Gy))** was **significantly** associated with an **increased breast cancer risk** compared to **mediastinal radiation (median 30 Gy (range 3-54 Gy))** adjusted for radiation dose (incidence rate ratio: 3.4 (1.6-7.2)). In female childhood cancer survivors, **whole lung radiation (median 14 Gy (range 2-20 Gy))** was **non-significantly** associated with an **increased breast cancer risk** as compared to **mantle radiation (median 40 Gy (range 5-54 Gy))** adjusted for radiation dose (incidence rate ratio: 1.8 (0.9-3.7)).	*Moskowitz 2014#*
In female Wilms tumor survivors, **1-12 Gy and >12 Gy chest radiation** were associated with an **increased breast cancer risk** as compared to the **general population** (SIR: 46.8 and 18.9, respectively) (unclear if significant as 95% CI not reported).	*Lange 2014*

In female Wilms tumor survivors, **higher chest radiation dose** was **significantly** associated with an **increased breast cancer risk** as compared to lower chest radiation dose adjusted for flank radiation dose, doxorubicin and age at Wilms tumor diagnosis (HR: 1.96 (1.45-2.69)).	
In female retinoblastoma survivors **very low dose chest radiation (0.01-≥0.50 Gy)** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no chest radiation** in univariate analysis (OR 0.01-0.24 Gy vs. 0 Gy: 1.79 (0.55-∞); OR 0.25-0.49 Gy vs. 0 Gy: 1.98 (0.61-∞); OR ≥0.50 Gy vs. 0 Gy: 0.92 (0.24-∞); OR ≥0.01 Gy vs. 0 Gy: 1.49 (0.68-∞)).	*Little 2014*
In female childhood cancer survivors, **1.30-11.39 Gy chest radiation** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no chest radiation** adjusted for primary cancer diagnosis and follow-up years (OR 1.30-11.39 Gy: 1.9 (0.7-5.0)). In female childhood cancer survivors, **11.40-29.99 Gy chest radiation** was **significantly** associated with an **increased breast cancer risk** as compared to **no chest radiation** adjusted for primary cancer diagnosis and follow-up years (OR 11.40-29.99 Gy: 7.1 (2.9-17.0)). (Recalculated odds ratios: non-significant increased breast cancer risk after 1.3-9.9 Gy (OR: 1.9 (0.7-5.4)) and significant increased breast cancer risk after 10-19.9 Gy OR: 6.5 (2.3-18.5)) compared to no chest radiation.	*Inskip 2009#*
In female childhood cancer survivors, **1-9.9 Gy and 10-19.9 Gy chest radiation** were **non-significantly** associated with an **increased breast cancer risk** as compared to **no chest radiation** adjusted for age at childhood cancer, attained age, castration, chemotherapy, and primary cancer diagnosis (RR 1-9.9 Gy: 1.5 (0.3-8.1); RR 10-19.9 Gy: 3.7 (0.6-24.2)). Note that this study has a methodological limitation which may have resulted in an underestimation of risk.	*Guibout 2005*
In Wilms tumor survivors there was a **significantly increased breast cancer risk** as compared to the **general population** (SIR: 5.8 (2.6-11.0)). It is unclear whether or not breast cancer was secondary to low dose chest radiation (10-19 Gy), the high abdominal fields, or a combination (likely the latter).	*Taylor 2008*
Hodgkin lymphoma survivors	
In female Hodgkin lymphoma survivors, **3.0-7.9 Gy (median 4.9 Gy) chest radiation** was **non-significantly** associated with an **increased breast cancer risk** as compared to **0-2.9 Gy (median 1.2 Gy) chest radiation** adjusted for duration of post-radiation intact ovarian function (OR: 1.33 (0.64-2.77)). In female Hodgkin lymphoma survivors, **8.0-27.9 Gy (median 17.5 Gy) chest radiation** was **significantly** associated with an **increased breast cancer risk** as compared to **0-2.9 Gy (median 1.2 Gy) chest radiation** adjusted for duration of post-radiation intact ovarian function (OR: 2.21 (1.09-4.46)).	*Krul 2017§*
In female Hodgkin lymphoma survivors, **4-6.9 Gy chest radiation** was **non-significantly** associated with an **increased breast cancer risk** as compared to **0-3.9 Gy chest radiation** adjusted for number of alkylating agent cycles and radiation dose delivered to the ovaries (RR 4-6.9 Gy: 1.8 (0.7-4.5)). In Hodgkin lymphoma survivors, **7-23.1 Gy chest radiation** was **significantly** associated with an **increased breast cancer risk** as compared to **0-3.9 Gy chest radiation** adjusted for number of alkylating agent cycles and radiation dose delivered to the ovaries (RR 7-23.1 Gy: 4.1 (1.4-12.3)). (Estimated RR based on post hoc analysis for 19 Gy vs. 0 Gy: 3.85)	*Travis 2003**
In female Hodgkin lymphoma survivors, **4-23.2 Gy chest radiation** was **non-significantly** associated with an **increased breast cancer risk** as compared to **0.3-3.9 Gy chest radiation** adjusted for ovarian radiation dose and chemotherapy (RR: 1.11 (0.32-3.58)).	*van Leeuwen 2003§**
Overall conclusion	
Risk after moderate dose (10-19 Gy) chest radiation: There is high quality evidence that female childhood, adolescent and young adult cancer survivors treated with moderate dose chest radiation (10-19 Gy) have an increased risk of breast cancer.	*7 studies* **Level A**
Risk after low dose (1-9 Gy) chest radiation: There is moderate quality evidence that female childhood, adolescent and young adult cancer survivors treated with low dose chest radiation (1-9 Gy) do not have a significantly increased breast cancer risk. It is known that there is a linear dose response, implicating lower excess risks at these comparatively low doses compared to doses >10 Gy.	*7 studies* **Level B**

*§ # Overlap in included patients

Breast cancer risk after 10-19 Gy chest radiation		
<u>Childhood cancer survivors</u>		
Veiga 2019	Per 10 Gy	**OR 3.9 (2.5-6.5)**
Ehrhardt 2019	10-<20 Gy vs. 0 Gy:	HR 2.4 (0.4-15.0)
	Survivors without pathogenic/likely pathogenic mutations	
	10-<20 Gy: vs. 0 Gy:	**HR 8.0 (1.1-56.3)**
Demoor-Goldschmidt 2017	10-20 Gy	19 (15.7%)
Moskowitz 2014	10-19 Gy	**SIR 30.6 (18.4-50.7)**
	2-20 Gy (median 14 Gy) whole lung radiation	**SIR 43.6 (27.1-70.1)**
	whole lung radiation (2-20 Gy (median 14 Gy)) vs. mediastinal radiation (3-54 Gy (median 30 Gy))	**Incidence rate ratio 3.4 (1.6-7.2)**
	whole lung radiation (2-20 Gy (median 14 Gy)) vs. mantle radiation (5-54 Gy (median 40 Gy))	Incidence rate ratio 1.8 (0.9-3.7)
Lange 2014	1-12 Gy	SIR 46.8
	>12 Gy	SIR 18.9
Inskip 2009	11.4-29.99 Gy vs. 0 Gy	**OR 7.1 (2.9-17.0)**
Recalculated data (unpublished)	10-19.9 Gy vs. 0 Gy	**OR 6.5 (2.3-18.5)**
Guibout 2005	10-19.9 Gy vs. 0 Gy	RR 3.7 (0.6-24.2)
Taylor 2008	Wilms tumor survivors	SIR 5.8 (2.6-11.0) (4/8 breast cancers 12-15 Gy chest radiation)

Breast cancer risk after 1-9 Gy chest radiation		
<u>Childhood cancer survivors</u>		
Veiga 2019	<5 Gy vs. 0 Gy	OR 1.7 (1.0-3.0)
Ehrhardt 2019	>0-<10 Gy vs. 0 Gy	HR 0.7 (0.2-2.8)
	Survivors without pathogenic/likely pathogenic mutations	
	>0-<10 Gy vs. 0 Gy	HR 1.2 (0.3-5.0)
Demoor-Goldschmidt 2017	<10 Gy	17 (14.0%)
Little 2014	0.01-0.24 Gy vs. 0 Gy	OR 1.79 (0.55-∞)
	0.25-0.49 Gy vs. 0 Gy	OR 1.98 (0.61-∞)
	≥0.50 Gy vs. 0 Gy	OR 0.92 (0.24-∞)
Inskip 2009	1.3-11.39 Gy vs. 0 Gy	OR 1.9 (0.7-5.0)
Recalculated data (unpublished)	1.3-9.9 Gy vs. 0 Gy	OR 1.9 (0.7-5.4)
Guibout 2005	1-9.9 Gy vs. 0 Gy	RR 1.5 (0.3-8.1)
<u>Hodgkin lymphoma survivors</u>		
Krul 2017	3.0-7.9 Gy vs. 0-2.9 Gy	OR 1.33 (0.64-2.77)

Travis 2003	4-6.9 Gy vs. 0-3.9 Gy	RR 1.8 (0.7-4.5)

2. What is the risk of breast cancer in childhood and young adult cancer survivors treated with TBI?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors, **TBI** (median 12 (range 4-16) Gy) was **significantly** associated with an **increased breast cancer risk** as compared to the **general population** (SIR: 19.3 (7.3-51.5)).	*Moskowitz 2014*
In female childhood cancer survivors, **TBI** (median 7.5 (range 1.6-12) Gy) was **significantly** associated with an **increased breast cancer risk** as compared to **no TBI** adjusted for chest radiation, ifosfamide and doxorubicin (HR: 10.6 (3.7-30.2)).	*Teepen 2017*
In female childhood cancer survivors with breast cancer, **5 (4.1%)** were treated with **TBI**.	*Demoor-Goldschmidt 2017*
Hematopoietic cell transplantation survivors (any age)	
In female hematopoietic cell transplant survivors (median age at transplant 28.1 (range 0.2-70.3) years), **TBI** (range 8-15.8 Gy) was **significantly** associated with an **increased breast cancer risk** as compared to **no TBI** (i.e. women treated with other cytoreduction regimens) (HR: 4.0 (1.6-10.3)). Note that this study has a methodological limitation which may have resulted in an overestimation. The comparison group is highly likely to have ovarian failure and so may not be an appropriate comparison population for breast cancer risk.	*Friedman 2008*
Overall conclusion	
Risk after TBI: There is moderate quality evidence that female childhood, adolescent and young adult cancer survivors treated with TBI have an increased risk of breast cancer as compared to no TBI.	*3 studies* **Level B**
Risk after TBI <10 Gy: There is low quality evidence that female childhood, adolescent and young adult cancer survivors treated with a median TBI dose <10 Gy (median 7.5 Gy, range 1.6-12 Gy) have an increased risk of breast cancer as compared to no TBI.	*1 study* **Level C**

Breast cancer risk after TBI		
Childhood cancer survivors		
Moskowitz 2014	TBI (median 12 Gy, range 4-16)	**SIR 19.3 (7.3-51.5)**
Teepen 2017	TBI (median 7.5 Gy, range 1.6-12) vs. no TBI	**HR 10.6 (3.7-30.2)**
Demoor-Goldschmidt 2017	TBI	5 (4.1%)
HSCT survivors (any age)		
Friedman 2008	TBI (range 8-15.8 Gy) vs. no TBI	**HR 4.0 (1.6-10.3)**

3. What is the risk of breast cancer in childhood and young adult cancer survivors treated with upper abdominal radiation exposing breast tissue?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors with breast cancer, **16 (13.2%)** were treated with **abdominal field radiation**.	*Demoor-Goldschmidt 2017*
In female childhood cancer survivors treated with chest radiation, **high abdominal field radiation** (median 20 (range 4-40) Gy) was **significantly** associated with an **increased breast cancer risk** as compared to the **general population** (SIR: 10.8 (2.7-43.2)).	*Moskowitz 2014*
In female Wilms tumor survivors (15% treated with chest radiation), **abdominal field radiation** was **significantly** associated with an **increased breast cancer risk** as compared to the **general population** (SIR: 6.0 (2.9-11.0)). In female Wilms tumor survivors, **whole abdominal radiation and flank radiation** were associated with an **increased breast cancer risk** as compared to the **general population** (SIR: 7.2 and 5.8, respectively) (unclear if significant as 95% CI not reported). In female Wilms tumor survivors, **higher flank radiation dose** was **non-significantly** associated with an **increased breast cancer risk** as compared to lower flank radiation dose adjusted for chest radiation dose, doxorubicin and age at Wilms tumor diagnosis (HR: 1.09 (0.88-1.35)).	*Lange 2014*
In Wilms tumor survivors there was a **significantly increased breast cancer risk** as compared to the **general population** (SIR: 5.8 (2.6-11.0)). It is unclear whether or not breast cancer was secondary to low dose chest radiation (10-19 Gy), the high abdominal fields, or a combination (likely the latter).	*Taylor 2008*
Overall conclusion	
Risk after upper abdominal radiation exposing breast tissue: There is moderate quality evidence that female childhood, adolescent and young adult cancer survivors treated with upper abdominal radiation exposing breast tissue have an increased risk of breast cancer as compared to no high abdominal field radiation.	*3 studies* **Level B**

Breast cancer risk after upper abdominal radiation exposing breast tissue		
Childhood cancer survivors		
Demoor-Goldschmidt 2017	Abdominal field radiation	16 (13.2%)
Moskowitz 2014	High abdominal field RT (4-40 Gy) + chest RT	**SIR 10.8 (2.7-43.2)**
Lange 2014	Abdominal field RT (dose not mentioned)	**SIR 6.0 (2.9-11.0)**
	Whole abdominal field RT	SIR 7.2
	Flank RT	SIR 5.8
	Flank RT dose	HR 1.09 (0.88-1.35)
Taylor 2008	Wilms tumor survivors	**SIR 5.8 (2.6-11.0)**
	Abdominal RT (20-35 Gy)	Unclear whether breast cancer was secondary to low dose chest radiation, the high abdominal fields, or a combination

4. Does radiotherapy to volumes exposing the ovaries decrease the risk of breast cancer in CAYA cancer survivors treated with chest radiation and to what extent?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors, **ovarian radiation** was **significantly** associated with a **decreased breast cancer risk** adjusted for type of first cancer, calendar year of follow-up, family history of breast or ovarian cancer and chemotherapy (OR ovarian radiation any dose per 10 Gy chest radiation: 3.9 (2.5-6.9), OR ovarian radiation <1 Gy per 10 Gy chest radiation: 6.3 (3.6-12.0), OR ovarian radiation ≥1 Gy per 10 Gy chest radiation: 2.8 (1.8-5.2)).	*Veiga 2019#*
In female childhood cancer survivors, **pelvic radiation** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no pelvic radiation** adjusted for age at primary childhood cancer diagnosis, pathogenic/likely pathogenic mutation, chest radiation, alkylating agents, and anthracyclines (HR 1.8 (0.9-3.9)).	*Ehrhardt 2019*
In female childhood cancer survivors treated with chest radiation, **ovarian radiation** was associated with a **decreased breast cancer risk** as compared to **no ovarian radiation** in univariate analysis (SIR ovaries irradiated: 8.8 (4.7-16.4); SIR ovaries not irradiated: 23.7 (20.6-27.3); (unclear if significant difference)).	*Moskowitz 2014#*
In female childhood cancer survivors treated with chest radiation, **ovarian radiation** was **significantly** associated with a **decreased breast cancer risk** as compared to **no ovarian radiation** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR: 0.35 (0.18-0.69)).	*Moskowitz 2017#*
In female childhood cancer survivors (74.5% treated with chest radiation), **≥5 Gy ovarian radiation** was **significantly** associated with a **decreased breast cancer risk** as compared to **<5 Gy ovarian radiation** in univariate analysis (Excess odds ratio per Gy to the breasts <5 Gy vs. ≥5 Gy: 0.36 (0.14-0.93) vs. 0.06 (-0.06-0.27) (*P* = 0.002)).	*Inskip 2009#*
In female childhood Hodgkin lymphoma survivors treated with chest radiation, **pelvic radiation** was associated with a **decreased breast cancer risk** as compared to **no pelvic radiation** in univariate analysis (breast cancer in females treated with vs. without pelvic radiation: 1/98 (1.0%) vs. 28/272 (10.3%); p = 0.0032).	*Constine 2008*
In female childhood cancer survivors, **pelvic radiation** was **significantly** associated with a **decreased breast cancer risk** as compared to **no pelvic radiation** adjusted for chest radiation (OR: 0.6 (0.4-0.9)).	*Kenney 2004#*
Hodgkin lymphoma survivors	
In female Hodgkin lymphoma survivors, **pelvic radiation** was **significantly** associated with a **decreased breast cancer risk** as compared to **no pelvic radiation** adjusted for chest radiation field and dose and alkylating agents (OR: 0.33 (0.13-0.84)).	*Krul 2017**
In female Hodgkin lymphoma survivors, a **≥5 Gy pelvic radiation** was associated with a **decreased breast cancer risk** as compared to **no pelvic radiation** in univariate analysis (SIR supradiaphragmatic radiation and ≥5 Gy pelvic radiation: 1.4 (0.5-4.4); SIR supradiaphragmatic radiation and alkylating agents and ≥5 Gy pelvic radiation: 3.8 (2.4-6.1); SIR supradiaphragmatic radiation: 6.0 (5.2-7.0); (unclear if significant difference)).	*Swerdlow 2012*
In female Hodgkin lymphoma survivors, **≥5 Gy ovarian radiation or alkylating agents** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **<5 Gy ovarian radiation or no alkylating agents** in univariate analysis (SIR 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); SIR 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)).	*Hill 2005*
In female Hodgkin lymphoma survivors, **pelvic radiation** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no pelvic radiation** adjusted for chest radiation, alkylating agent chemotherapy, age at first radiation to the breast and time since first radiation to the breast (HR: 0.4 (0.1-1.4)).	*de Bruin 2009**

In female Hodgkin lymphoma survivors, **3.0-4.9 Gy pelvic radiation** was **non-significantly** associated with an **increased breast cancer risk** as compared to **<3 Gy pelvic radiation** adjusted for chest radiation dose and number of alkylating agent cycles (RR: 1.2 (0.3-3.9)). In female Hodgkin lymphoma survivors, **≥5 Gy pelvic radiation** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **<3 Gy pelvic radiation** adjusted for chest radiation dose and number of alkylating agent cycles (RR: 0.4 (0.1-1.1)).	*Travis 2003**
In female Hodgkin lymphoma survivors, **≥5 Gy ovarian radiation** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **<5 Gy ovarian radiation** adjusted for chest radiation dose and chemotherapy (RR: 0.13 (0.02-1.08)).	*van Leeuwen 2003**
Overall conclusion	
Risk after pelvic radiation in childhood cancer survivors treated at younger ages: There is moderate quality evidence that childhood cancer survivors treated with pelvic radiation at younger ages (<21 year) have a decreased risk of breast cancer after chest radiation compared to chest radiation but no pelvic radiation.	*7 studies from 3 cohorts* **Level A**
Risk after pelvic radiation in Hodgkin lymphoma survivors treated at older ages: There is low quality evidence that Hodgkin lymphoma survivors treated with pelvic radiation at older ages (21-49 year) have a decreased risk of breast cancer after chest radiation compared to chest radiation but no pelvic radiation.	*6 studies from 3 cohorts* **Level C**

*Overlap in included patients

Breast cancer risk after radiotherapy to volumes exposing the ovaries		
Childhood cancer survivors		
Veiga 2019	Ovarian radiation any dose per 10 Gy chest radiation Ovarian radiation <1 Gy per 10 Gy chest radiation Ovarian radiation ≥1 Gy per 10 Gy chest radiation	**OR 3.9 (2.5-6.9)** **OR 6.3 (3.6-12.0)** **OR 2.8 (1.8-5.2)** ***P* = 0.01**
Ehrhardt 2019	Pelvic radiation yes vs. no	HR 1.8 (0.9-3.9)
Moskowitz 2014	Ovarian radiation No ovarian radiation	**SIR 8.8 (4.7-16.4)** **SIR 23.7 (20.6-27.3)**
Moskowitz 2017	Ovarian radiation yes vs. no	**HR 0.35 (0.18-0.69)**
Inskip 2009	Ovarian radiation <5 Gy Ovarian radiation ≥5 Gy	**Excess odds ratio per Gy to the breasts: 0.36 (0.14-0.93)** **Excess odds ratio per Gy to the breasts: 0.06 (-0.06-0.27); *P* = 0.002**
Constine 2008	Pelvic radiation yes vs. no	**Breast cancer in 10.3% vs. 1.0%, *P* = 0.0032**
Kenney 2004	Pelvic radiation yes vs. no	**OR 0.6 (0.4-0.9)**
Hodgkin lymphoma survivors		
Krul 2017	Pelvic radiation yes vs. no	**OR 0.33 (0.13-0.84)**
Swerdlow 2012	Supradiaphragmatic radiation and ≥5 Gy pelvic radiation Supradiaphragmatic radiation and alkylating agents and ≥5 Gy pelvic	**SIR 1.4 (0.5-4.4)** **SIR 3.8 (2.4-6.1)**

	radiation Supradiaphragmatic radiation	**SIR 6.0 (5.2-7.0)**
Hill 2005	≥5 Gy ovarian radiation or alkylating agents vs. <5 Gy ovarian radiation or no alkylating agents	SIR premenopausal women 0.7 (0.3-1.5) SIR postmenopausal women 0.2 (0.1-1.3)
de Bruin 2009	Pelvic radiation yes vs. no	HR 0.4 (0.1-1.4)
Travis 2003	Pelvic radiation 3.0-4.9 Gy vs. <3 Gy Pelvic radiation ≥5 Gy vs. <3 Gy	RR 1.2 (0.3-3.9) RR 0.4 (0.1-1.1)
van Leeuwen 2003	Ovarian radiation ≥5 Gy vs. <5 Gy	RR 0.13 (0.02-1.08)

5. Does alkylating agent chemotherapy decrease the risk of breast cancer in CAYA cancer survivors treated with chest radiation and to what extent?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors, **<0 - 5,999 mg/m^2 alkylating agent chemotherapy** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agents** adjusted for age at primary childhood cancer diagnosis, pathogenic/likely pathogenic mutation, chest radiation, pelvic radiation, and anthracyclines (HR 1.0 (0.4-2.6)). In female childhood cancer survivors, **≥6,000 mg/m^2 alkylating agent chemotherapy** was **significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agents** adjusted for age at primary childhood cancer diagnosis, pathogenic/likely pathogenic mutation, chest radiation, pelvic radiation, and anthracyclines (HR 0.4 (0.2-0.9)).	*Ehrhardt 2019*
In female childhood Hodgkin lymphoma survivors, **alkylating agent score ≥**2 was **significantly** associated with a **decreased breast cancer risk** as compared to **alkylating agent score 0 or 1** adjusted for chest radiation, age at primary childhood cancer diagnosis and anthracyclines (HR 0.5 (0.3-0.9)).	*Holmqvist 2019*
In female childhood cancer survivors treated with chest radiation, **alkylating agent chemotherapy** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no alkylating agent chemotherapy** adjusted for chest radiation dose (incidence rate ratio: 1.1 (0.8-1.4)).	*Moskowitz 2014#*
In female childhood cancer survivors treated with chest radiation, a **cyclophosphamide equivalence dose of <14,000 mg/m2** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agents** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR: 0.86 (0.61-1.20)). In female childhood cancer survivors treated with chest radiation, a **cyclophosphamide equivalence dose of ≥14,000 mg/m2** was **significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agents** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR: 0.41 (0.21-0.79); HR <40yr at breast cancer diagnosis: 0.50 (0.23-1.08); HR +40 yr at breast cancer diagnosis: 0.26 (0.08-0.87)). In female childhood cancer survivors treated with chest radiation, **1-4,200, 4,201-7,036 mg/m^2 and ≥7,037 mg/m^2 procarbazine** were **non-significantly** associated with a **decreased breast cancer risk** as compared to **no procarbazine** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR 1-4,200 mg/m^2: 0.97 (0.61-1.54); HR 4,201-7,036 mg/m^2: 1.03 (0.66-1.62); HR ≥7,037 mg/m^2: 0.58 (0.31-1.11)).	*Moskowitz 2017#*
In female childhood cancer survivors (74.5% treated with chest radiation), **alkylating agent chemotherapy** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agent chemotherapy** adjusted for chest radiation dose, ovarian radiation dose and	*Inskip 2009#*

primary cancer diagnosis (OR alkylating agents vs. no alkylating agents: 0.93 (0.56-1.55); OR alkylating agent score 1 vs. 0: 0.67 (0.30-1.51); OR alkylating agent score 2 vs. 0: 1.40 (0.58-3.39); OR alkylating agent score 3 vs. 0: 1.15 (0.55-2.41)).	
In female childhood Hodgkin lymphoma survivors treated with supradiaphragmatic radiation, **alkylating agent chemotherapy** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agent chemotherapy** in univariate analysis (RR: 0.49 (0.18-1.33)).	*Taylor 2007*
In female childhood Hodgkin lymphoma survivors, **3-9 cycles alkylating agent chemotherapy** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **<3 cycles alkylating agent chemotherapy** adjusted for age at diagnosis, clinical stage, treatment groups (radiotherapy, chemotherapy, both) and recurrence of Hodgkin lymphoma (RR: 0.62 (0.09-2.48)).	*Bhatia 2003*
Hodgkin lymphoma survivors	
In female Hodgkin lymphoma survivors, **≤4.2 g/m^2 and >4.2 g/m^2 procarbazine** were **non-significantly** associated with a **decreased breast cancer risk** as compared to **chest radiation only** adjusted for radiation dose to breast tumor location (OR ≤4.2 g/m^2: 0.95 (0.53-1.70), OR >4.2 g/m^2: 0.62 (0.38-1.00))	*Krul 2017**
In female Hodgkin lymphoma survivors, **≤4.2 g/m^2 and 4.3-8.4 g/m^2 procarbazine** were **non-significantly** associated with a **decreased breast cancer risk** as compared to **no chemotherapy** adjusted for chest radiation (HR ≤4.2 g/m^2 procarbazine vs. 0: 0.84 (0.52-1.36); HR 4.3-8.4 g/m^2 procarbazine vs. 0: 0.71 (0.47-1.07)). In Hodgkin lymphoma survivors, **>8.4 g/m^2 procarbazine** was **significantly** associated with a **decreased breast cancer risk** as compared to **no chemotherapy** adjusted for chest radiation (HR: 0.33 (0.16-0.68)).	*Schaapveld 2015**
In female Hodgkin lymphoma survivors treated with chest radiation, a **higher number of alkylating agent chemotherapy cycles** was **significantly** associated with a **decreased breast cancer risk** as compared to a **lower number of alkylating agent chemotherapy cycles** in univariate analysis (SIR 0 alkylating agent cycles: 5.6 (4.8-6.6); SIR 1-5 alkylating agent cycles: 4.9 (3.5-7.1); SIR 6 alkylating agent cycles: 4.7 (3.6-6.1); SIR 7-12 alkylating agent cycles: 4.1 (2.9-5.8); SIR ≥13 alkylating agent cycles: 1.4 (0.2-10.4) (*P* for trend 0.027). The decreased breast cancer risk was especially seen in older patients aged ≥20 years at primary cancer treatment.	*Swerdlow 2012*
In female Hodgkin lymphoma survivors, **≤8.4 g/m^2 procarbazine** was **significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agent chemotherapy** adjusted for chest radiation, pelvic radiation, age at first radiation to the breast and time since first radiation to the breast (HR: 0.6 (0.3-0.9)). In female Hodgkin lymphoma survivors, **>8.4 g/m^2 procarbazine** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agent chemotherapy** adjusted for chest radiation, pelvic radiation, age at first radiation to the breast and time since first radiation to the breast (HR: 0.4 (0.1-1.3)).	*de Bruin 2009**
In female Hodgkin lymphoma survivors, **alkylating agent chemotherapy** was **significantly** associated with a **decreased breast cancer risk** as compared to **≥40 Gy chest radiation** (RR alkylating agents, no mediastinal radiation vs. ≥40 Gy mediastinal radiation: 0.07 (0.02-0.36); RR alkylating agents with 20-<40 Gy mediastinal radiation vs. ≥40 Gy mediastinal radiation: 0.38 (0.19-0.77); RR alkylating agents with ≥40 Gy mediastinal radiation vs. ≥40 Gy mediastinal radiation: 0.47 (0.27-0.79)).	*Travis 2005**
In female Hodgkin lymphoma survivors, **alkylating agent chemotherapy, 1-4 alkylating agent cycles and 5-8 alkylating agent cycles** were **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agent chemotherapy** adjusted for chest and ovarian radiation dose (RR alkylating agent chemotherapy vs. none: 0.6 (0.0-2.0); RR 1-4 alkylating agent cycles vs. 0: 0.7 (0.3-1.7); RR 5-8 alkylating agent cycles vs. 0: 0.6 (0.3-1.1)). In female Hodgkin lymphoma survivors, **≥9 cycles alkylating agent chemotherapy** was **significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agent chemotherapy** adjusted for chest and ovarian radiation dose (RR: 0.2 (0.1-0.7)).	*Travis 2003**
In female Hodgkin lymphoma survivors, **<6 cycles alkylating agent chemotherapy** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **chest radiation only** adjusted for chest radiation dose and ovarian radiation dose (RR: 0.31 (0.09-1.05)).	*van Leeuwen 2003**

In female Hodgkin lymphoma survivors, **≥6 cycles alkylating agent chemotherapy** was **significantly** associated with a **decreased breast cancer risk** as compared to **chest radiation only** adjusted for chest radiation dose and ovarian radiation dose (RR: 0.33 (0.13-0.86)).	
Overall conclusion	
Risk after alkylating agent chemotherapy in childhood cancer survivors treated with chest radiation at younger ages: There is low quality evidence that childhood cancer survivors treated with higher doses of alkylating agent chemotherapy and chest radiation at younger ages (<21 year) have a decreased risk of breast cancer (especially for survivors with a breast cancer diagnosis at age ≥40 years) as compared to chest radiation but no alkylating agents.	*7 studies from 5 cohorts* **Level C**
Risk after alkylating agent chemotherapy in Hodgkin lymphoma survivors treated with chest radiation at older ages: There is high quality evidence that Hodgkin lymphoma survivors treated with higher doses of alkylating agent chemotherapy and chest radiation at older ages (21-49 year) have a decreased risk of breast cancer as compared to chest radiation but no alkylating agents. This difference could be explained by an age-related sensitivity of the ovarian follicles to alkylating agent chemotherapy.	*7 studies from 3 cohorts* **Level A**

*#Overlap in included patients

Breast cancer risk after alkylating agents		
Childhood cancer survivors		
Ehrhardt 2019	Alkylating agents <0 - 5,999 mg/m²	HR 1.0 (0.4-2.6)
	Alkylating agents ≥6,000 mg/m²	**HR 0.4 (0.2-0.9)**
Holmqvist 2019	Alkylating agent score ≥2 vs. 0 or 1	**HR 0.5 (0.3-0.9)**
Moskowitz 2014	Alkylating agents yes vs. no	IRR 1.1 (0.8-1.4)
Moskowitz 2017	Cyclophosphamide equivalence dose <14,000 mg/m² vs. none	HR 0.86 (0.61-1.20)
	Cyclophosphamide equivalence dose ≥14,000 mg/m² vs. none	**HR 0.41 (0.21-0.79)**
	<40 yr at breast cancer diagnosis	HR 0.50 (0.23-1.08)
	≥40 yr at breast cancer diagnosis	**HR 0.26 (0.08-0.87)**
	Procarbazine 1-4,200 mg/m² vs. none	HR 0.97 (0.61-1.54)
	Procarbazine 4,201-7,036 mg/m² vs. none	HR 1.03 (0.66-1.62)
	Procarbazine ≥7,037 mg/m² vs. none	HR 0.58 (0.31-1.11)
Taylor 2007	Alkylating agents yes vs. no	RR 0.49 (0.18-1.33)
Inskip 2009	Alkylating agents yes vs. no	OR 0.93 (0.56-1.55)
	Alkylating agent score 1 vs. 0	OR 0.67 (0.30-1.51)
	Alkylating agent score 2 vs. 0	OR 1.40 (0.58-3.39)
	Alkylating agent score 3 vs. 0	OR 1.15 (0.55-2.41)
Bhatia 2003	Alkylating agents 3-9 cycles vs. <3 cycles	RR 0.62 (0.09-2.48)
Hodgkin lymphoma survivors		
Krul 2017	Procarbazine ≤4.2 g/m² vs. chest radiation only	OR 0.95 (0.53-1.70)
	Procarbazine >4.2 g/m² vs. chest radiation only	OR 0.62 (0.38-1.00)
Schaapveld 2015	Procarbazine ≤4.2 g/m² vs. no chemotherapy	HR 0.84 (0.52-1.36)
	Procarbazine ≤ 4.3-8.4 g/m² vs. no chemotherapy	HR 0.71 (0.47-1.07)
	Procarbazine >8.4 g/m² vs. no chemotherapy	**HR 0.33 (0.16-0.68)**
Swerdlow 2012	0 alkylating agent cycles	**SIR 5.6 (4.8-6.6)**

	1-5 alkylating agent cycles	**SIR 4.9 (3.5-7.1)**
	6 alkylating agent cycles	**SIR 4.7 (3.6-6.1)**
	7-12 alkylating agent cycles	**SIR 4.1 (2.9-5.8)**
	≥13 alkylating agent cycles	**SIR 1.4 (0.2-10.4); *P* trend 0.027**
de Bruin 2009	Procarbazine ≤8.4 g/m^2 vs. no	**HR 0.6 (0.3-0.9)**
	Procarbazine >8.4 g/m^2 vs. no	HR 0.4 (0.1-1.3)
Travis 2005	Alkylating agents, no mediastinal radiation vs. ≥40 Gy mediastinal radiation	**RR 0.07 (0.02-0.36)**
	Alkylating agents with 20-<40 Gy mediastinal radiation vs. ≥40 Gy mediastinal radiation	**RR 0.38 (0.19-0.77)**
	Alkylating agents with ≥40 Gy mediastinal radiation vs. ≥40 Gy mediastinal radiation	**RR 0.47 (0.27-0.79)**
Travis 2003	Alkylating agents yes vs. no	RR 0.6 (0.0-2.0)
	1-4 alkylating agent cycles vs. 0	RR 0.7 (0.3-1.7)
	5-8 alkylating agent cycles vs. 0	RR 0.6 (0.3-1.1)
	≥9 alkylating agent cycles vs. 0	**RR 0.2 (0.1-0.7)**
van Leeuwen 2003	<6 alkylating agent cycles vs. chest radiation only	RR 0.31 (0.09-1.05)
	≥6 alkylating agent cycles vs. chest radiation only	**RR 0.33 (0.13-0.86)**

6.1 What is the influence of age at menopause on the risk of breast cancer in CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors treated with chest radiation, **menopause at age <20 years, 20-39 years and ≥40 years** were **non-significantly** associated with a **decreased breast cancer risk** as compared to **still menstruating** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR <20 yr: 0.60 (0.32-1.13), HR 20-39 yr: 0.82 (0.49-1.36), HR ≥40 yr: 0.87 (0.43-1.80)). In female childhood cancer survivors treated with chest radiation there was a strong **significant** trend of **decreasing breast cancer risk** with **decreasing age at menopause** (P trend = 0.014).	*Moskowitz 2017*
Hodgkin lymphoma survivors	
In female Hodgkin lymphoma survivors, **menopause at age <40 yr** was **significantly** associated with a **decreased breast cancer risk** as compared to **premenopausal at age ≥40 yr** adjusted for chest radiation dose (OR: 0.43 (0.25-0.75)). In female Hodgkin lymphoma survivors, **menopause at age 18-29 yr** was **significantly** associated with a **decreased breast cancer risk** as compared to **menopause at age ≥50 yr** adjusted for chest radiation dose (OR: 0.13 (0.03-0.51)). In female Hodgkin lymphoma survivors, **menopause at age 30-39 yr and 40-49 yr** were **non-significantly** associated with a **decreased breast cancer risk** as compared to **menopause at age ≥50 yr** adjusted for chest radiation dose (OR 30-39 yr: 0.48 (0.20-1.15), OR 40-49 yr: 0.61 (0.27-1.36)).	*Krul 2017**
In female Hodgkin lymphoma survivors, **menopause at age <40 yr** was **significantly** associated with a **decreased breast cancer risk** as compared to **menopause at age ≥40 yr** adjusted for age and year of treatment, duration between treatment and questionnaire completion, calendar year of birth and chest radiation field (OR: 0.65 (0.44-0.94)).	*Cooke 2013*
In female Hodgkin lymphoma survivors, **menopause at age <41 years** was **significantly** associated with a **decreased breast cancer risk** as compared to **menopause at age ≥41 years** adjusted for chest radiation (HR: 0.4 (0.2-0.8)).	*de Bruin 2009**
In female Hodgkin lymphoma survivors, **menopause at age 19-30 years** was **significantly** associated with a **decreased breast cancer risk** as compared to **no menopause** adjusted for chest radiation dose (RR: 0.06 (0.01-0.45)). In female Hodgkin lymphoma survivors, **menopause at age 36-45 years** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no menopause** adjusted for chest radiation dose (RR: 0.80 (0.26-2.40)). In female Hodgkin lymphoma survivors, **older age at menopause** was **significantly** associated with an **increased breast cancer risk** as compared to **younger age at menopause** adjusted for chest radiation dose (RR: 1.12 (1.02-1.23) (continuous variable)).	*van Leeuwen 2003**
Overall conclusion	
There is high quality evidence that female childhood, adolescent and young adult cancer survivors treated with chest radiation with a younger age at menopause have a decreased risk of breast cancer as compared to older age at menopause.	*5 studies from 3 cohorts* **Level A**

*Overlap in included patients

Breast cancer risk by age at menopause		
Childhood cancer survivors		
Moskowitz 2017	Age at menopause <20 yr vs. still menstruating	HR 0.60 (0.32-1.13)
	Age at menopause 20-39 yr vs. still menstruating	HR 0.82 (0.49-1.36)
	Age at menopause ≥40 yr vs. still menstruating	HR 0.87 (0.43-1.80)
		***P* trend = 0.014**

Hodgkin lymphoma survivors		
Krul 2017	Menopause at age <40 yr vs. menopause ≥40 yr/premenopausal ≥40 yr	**OR 0.43 (0.25-0.75)**
	Age at menopause 18-29 yr vs. ≥50 yr	**OR 0.13 (0.03-0.51)**
	Age at menopause 30-39 yr vs. ≥50 yr	OR 0.48 (0.20-1.15)
	Age at menopause 40-49 yr vs. ≥50 yr	OR 0.61 (0.27-1.36)
Cooke 2013	Menopause at age < 40 yr vs. ≥ 40 yr	**OR 0.65 (0.44-0.94)**
de Bruin 2009	Menopause at age <41 yr vs. ≥41 yr	**HR 0.4 (0.2-0.8)**
van Leeuwen 2003	Menopause at age 19-30 yr vs. no menopause	**RR 0.06 (0.01-0.45)**
	Menopause at age 36-45 yr vs. no menopause	**RR 0.80 (0.26-2.40)**
	Age at menopause (continuous per year)	**RR 1.12 (1.02-1.23)**

6.2 What is the influence of duration of intact ovarian function after chest radiation on the risk of breast cancer in CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors treated with chest radiation, **≥10 years of ovarian function after chest radiation** was **significantly** associated with an **increased breast cancer risk** as compared to **<10 years of ovarian function after chest radiation** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR: 2.89 (1.56-5.35)). In female childhood cancer survivors treated with chest radiation, **no menarche** was **significantly** associated with a **decreased breast cancer risk** as compared to **still menstruating** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR: 0.12 (0.02-0.89)).	*Moskowitz 2017*
Hodgkin lymphoma survivors	
In female Hodgkin lymphoma survivors, **5-9 yr and 10-14 yr of post-radiation intact ovarian function** were **non-significantly** associated with an **increased breast cancer risk** as compared to **<5 yr of post-radiation intact ovarian function** adjusted for chest radiation dose (OR 5-9 yr: 1.53 (0.63-3.72), OR 10-14 yr: 1.45 (0.62-3.37)). In female Hodgkin lymphoma survivors, **15-19 yr, 20-24 yr and ≥25 yr of post-radiation intact ovarian function** were **significantly** associated with an **increased breast cancer risk** as compared to **<5 yr of post-radiation intact ovarian function** adjusted for chest radiation dose (OR 15-19 yr: 2.69 (1.20-6.05), OR 20-24 yr: 4.42 (1.80-10.9), OR ≥25 yr: 3.82 (1.27-11.5)).	*Krul 2017**
In female Hodgkin lymphoma survivors, **menopause within 5 yr of start of treatment** was **significantly** associated with a **decreased breast cancer risk** as compared to **no menopause** adjusted for age and year of treatment, duration between treatment and questionnaire completion, calendar year of birth and chest radiation field (OR: 0.55 (0.35-0.85)). In female Hodgkin lymphoma survivors, there was a strong **significant** trend of **increasing breast cancer risk** with **increasing premenopausal years after start of cancer treatment** (OR 1-4 vs. <1: 0.96 (0.34-2.69), OR 5-9 vs. <1: 1.02 (0.36-2.87), OR 10-14 vs. <1: 1.49 (0.63-3.55), OR 15-24 vs. <1: 1.62 (0.76-3.44), OR ≥25 vs. <1: 3.56 (1.50-8.45), P trend = 0.003).	*Cooke 2013*
In female Hodgkin lymphoma survivors, **<10 yr of intact ovarian function** was **significantly** associated with a **decreased breast cancer risk** as compared to **10-20 yr of intact ovarian function** adjusted for chest radiation, premature menopause, BMI, smoking, nulliparity and oral contraceptives (HR 0.3 (0.2-0.6)). In female Hodgkin lymphoma survivors, **>20 yr of intact ovarian function** was **significantly** associated with an **increased breast cancer risk** as compared to **10-20 yr of intact ovarian function** adjusted for chest radiation, premature menopause, BMI, smoking, nulliparity and oral contraceptives (HR 5.3 (2.9-9.9)).	*de Bruin 2009**
In female Hodgkin lymphoma survivors, **<5 yr** and **5-14 yr from treatment to menopause** were **significantly** associated with a **decreased breast cancer risk** as compared to **being premenopausal** adjusted for chest radiation dose (RR <5 yr: 0.15 (0.03-0.60), RR 5-14 yr: 0.24 (0.06-0.96)). In female Hodgkin lymphoma survivors, **≥15 yr from treatment to menopause** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **being premenopausal** adjusted for chest radiation dose (RR 0.91 (0.26-3.18)). In female Hodgkin lymphoma survivors, **increasing premenopausal years after cancer treatment** was **significantly** associated with an **increased breast cancer risk** as compared to **decreasing premenopausal years after cancer treatment** adjusted for chest radiation dose (RR: 1.11 (1.00-1.22) (continuous variable)).	*van Leeuwen 2003**
Overall conclusion	
There is high quality evidence that female childhood, adolescent and young adult cancer survivors with a **shorter duration of intact ovarian function** after chest radiation have a **decreased breast cancer risk** as compared to females with a longer duration of intact ovarian function after	*5 studies from 3 cohorts*

chest radiation.	**Level A**

Breast cancer risk by duration of intact ovarian function after chest radiation		
Childhood cancer survivors		
Moskowitz 2017	Years of ovarian function after chest radiation ≥10 yr vs. <10 yr	**HR 2.89 (1.56-5.35)**
	No menarche vs. still menstruating	**HR 0.12 (0.02-0.89)**
Hodgkin lymphoma survivors		
Krul 2017	Duration of post-radiation intact ovarian function 5-9 yr vs. <5 yr	OR 1.53 (0.63-3.72)
	Duration of post-radiation intact ovarian function 10-14 yr vs. <5 yr	OR 1.45 (0.62-3.37)
	Duration of post-radiation intact ovarian function 15-19 yr vs. <5 yr	**OR 2.69 (1.20-6.05)**
	Duration of post-radiation intact ovarian function 20-24 yr vs. <5 yr	**OR 4.42 (1.80-10.9)**
	Duration of post-radiation intact ovarian function ≥25 yr vs. <5 yr	**OR 3.82 (1.27-11.5)**
Cooke 2013	Menopause within 5 yr of start of treatment vs. no menopause	**OR 0.55 (0.35-0.85)**
	Premenopausal yrs after start of treatment 1-4 vs. <1	OR 0.96 (0.34-2.69)
	Premenopausal yrs after start of treatment 5-9 vs. <1	OR 1.02 (0.36-2.87)
	Premenopausal yrs after start of treatment 10-14 vs. <1	OR 1.49 (0.63-3.55)
	Premenopausal yrs after start of treatment 15-24 vs. <1	OR 1.62 (0.76-3.44)
	Premenopausal yrs after start of treatment ≥25 vs. <1	**OR 3.56 (1.50-8.45)** ***P trend* = 0.003**
de Bruin 2009	Years of intact ovarian function <10 yr vs. 10-20 yr	**HR 0.3 (0.2-0.6)**
	Years of intact ovarian function >20 yr vs. 10-20 yr	**HR 5.3 (2.9-9.9)**
van Leeuwen 2003	Time from HL treatment to menopause ≥15 yr vs. premenopausal	RR 0.91 (0.26-3.18)
	Time from HL treatment to menopause 5-14 yr vs. premenopausal	**RR 0.24 (0.06-0.96)**
	Time from HL treatment to menopause <5 yr vs. premenopausal	**RR 0.15 (0.03-0.60)**
	No. premenopausal yrs after HL (continuous per year)	**RR 1.11 (1.00-122)**

6.3 What is the influence of time between menarche and chest radiation on the risk of breast cancer in CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors treated with chest radiation, **radiotherapy given within 1 yr of menarche** was **significantly** associated with an **increased breast cancer risk** as compared to **≥1 yr from menarche** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR: 1.80 (1.19-2.72). In female childhood cancer survivors treated with chest radiation, **radiotherapy given within 1 yr of menarche** was **significantly** associated with an **increased breast cancer risk** as compared to **≥3 yr after menarche** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR: 2.04 (1.18-3.53)). In female childhood cancer survivors treated with chest radiation, **no menarche, chest radiation >3 yr before menarche, 1-3 yr before menarche, 1-2 yr after menarche and 2-3 yr after menarche** were **non-significantly** associated with an **increased breast cancer risk** as compared to **chest radiation >3 yr after menarche** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR no menarche: 0.16 (0.02-1.18), HR >3 yr before menarche: 1.31 (0.53-3.29), HR 1-3 yr before menarche: 1.08 (0.45-2.56), HR 1-2 yr after menarche: 1.42 (0.78-2.57), HR 2-3 yr after menarche: 1.49 (0.89-2.47).	*Moskowitz 2017*
Hodgkin lymphoma survivors	
In female Hodgkin lymphoma survivors, **time between menarche and cancer treatment** was **non-significantly** associated with an **increased breast cancer risk** as compared to **≥15 yr between menarche and cancer treatment** adjusted for radiation dose to breast tumor location, intact ovarian function, and age at menarche (OR 10-14 yr: 1.16 (0.48-2.85), OR 5-9 yr: 1.13 (0.43-3.01), OR 2-4 yr: 1.25 (0.38-4.15), OR <2 yr: 0.94 (0.16-5.71))	*Krul 2017*
In female Hodgkin lymphoma survivors, **chest radiation given 2-5 yr before menarche, 0.5-2 yr before menarche, within 0.5 yr of menarche, 0.5-2 yr after menarche and 2-5 yr after menarche** were **significantly** associated with an **increased breast cancer risk** as compared to **chest radiation given ≥10 yr after menarche** adjusted for age and year of treatment, duration between treatment and questionnaire completion, calendar year of birth, chest radiation field and ovarian-toxic treatment (OR 2-5 yr before menarche: 4.08 (1.27-13.14), OR 0.5-2 yr before menarche: 4.90 (1.60-14.98), OR within 0.5 yr of menarche: 5.52 (1.97-5.46), OR 0.5-2 yr after menarche: 3.47 (1.40-8.58), OR 2-5 yr after menarche: 2.38 (1.43-3.97)). In female Hodgkin lymphoma survivors, **chest radiation given** ≥5 yr before menarche, 5-10 yr after menarche and no menarche were **non-significantly** associated with an **increased breast cancer risk** as compared to **chest radiation given ≥10 yr after menarche** adjusted for age and year of treatment, duration between treatment and questionnaire completion, calendar year of birth, chest radiation field and ovarian-toxic treatment (OR ≥5 yr before menarche: 0.94 (0.10-8.46), OR 5-10 yr after menarche: 1.33 (0.89-1.98), OR no menarche: 2.14 (0.20-22.56)). In female Hodgkin lymphoma survivors there was a strong **significant** trend of **increasing breast cancer risk** with **decreasing time between menarche and chest radiation** (P trend <0.001).	*Cooke 2013*
Overall conclusion	
There is moderate quality evidence that female childhood, adolescent and young adult cancer survivors who received chest radiation close to menarche have an increased breast cancer risk as compared to chest radiation that was given a longer time from menarche.	*3 studies* **Level B**

Breast cancer risk by time between menarche and chest radiation		
Childhood cancer survivors		
Moskowitz 2017	Chest radiation <1 yr of menarche vs. ≥1 yr from menarche	**HR 1.80 (1.19-2.72)**

	No menarche vs. chest radiation >3 yr after menarche	HR 0.16 (0.02-1.18)
	Chest radiation >3 yr before menarche vs. >3 yr after menarche	HR 1.31 (0.53-3.29)
	Chest radiation 1-3 yr before menarche vs. >3 yr after menarche	HR 1.08 (0.45-2.56)
	Chest radiation ± 1 yr of menarche vs. >3 yr after menarche	**HR 2.04 (1.18-3.53)**
	Chest radiation 1-2 yr after menarche vs. >3 yr after menarche	HR 1.42 (0.78-2.57)
	Chest radiation 2-3 yr after menarche vs. >3 yr after menarche	HR 1.49 (0.89-2.47)
Hodgkin lymphoma survivors		
Krul 2017	Time between menarche and HL treatment 10-14 yr vs. ≥15 yr	OR 1.16 (0.48-2.85)
	Time between menarche and HL treatment 5-9 yr vs. ≥15 yr	OR 1.13 (0.43-3.01)
	Time between menarche and HL treatment 2-4 yr vs. ≥15 yr	OR 1.25 (0.38-4.15)
	Time between menarche and HL treatment <2 yr before or <2 yr after HL treatment vs. ≥15 yr:	OR 0.94 (0.16-5.71)
Cooke 2013	Chest radiation ≥5 yr before menarche vs. ≥10 yr after menarche	OR 0.94 (0.10-8.46)
	Chest radiation 2-5 yr before menarche vs. ≥10 yr after menarche	**OR 4.08 (1.27-13.14)**
	Chest radiation 0.5-2 yr before menarche vs. ≥10 yr after menarche	**OR 4.90 (1.60-14.98)**
	Chest radiation within 0.5 yr of menarche vs. ≥10 yr after menarche	**OR 5.52 (1.97-5.46)**
	Chest radiation 0.5-2 yr after menarche vs. ≥10 yr after menarche	**OR 3.47 (1.40-8.58)**
	Chest radiation 2-5 yr after menarche vs. ≥10 yr after menarche	**OR 2.38 (1.43-3.97)**
	Chest radiation 5-10 yr after menarche vs. ≥10 yr after menarche	OR 1.33 (0.89-1.98)
	No menarche vs. chest radiation ≥10 yr after menarche	OR 2.14 (0.20-22.56) ***P trend* <0.001**

7. What is the influence of treatment of early menopause on the risk of breast cancer in CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors treated with chest radiation, **combined estrogen and progestin use** was **non-significantly** associated with an **increased breast cancer risk** as compared to **none** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis, anthracyclines and age at menopause (HR: 1.54 (0.70-3.40)). In female childhood cancer survivors treated with chest radiation, **≥10 years of gonadal hormone exposure** was **non-significantly** associated with an **increased breast cancer risk** as compared to **<10 years of gonadal hormone exposure** adjusted for chest radiation field and dose, age at primary childhood cancer diagnosis and anthracyclines (HR: 1.59 (0.88-2.90)).	*Moskowitz 2017*
Hodgkin lymphoma survivors	
In female Hodgkin lymphoma survivors, hormone replacement therapy was **non-significantly** associated with a **decreased breast cancer risk** as compared to **none** adjusted for chest radiation dose and duration of post-radiation intact ovarian function (OR yes vs. no: 0.82 (0.48-1.39), OR <5 yr hormone replacement therapy vs. none: 0.93 (0.49-1.77), OR 5-9 yr hormone replacement therapy vs. none: 0.91 (0.34-2.46), OR ≥10 yr hormone replacement therapy vs. none: 0.84 (0.30-2.32)).	*Krul 2017**
In female Hodgkin lymphoma survivors, **≥3 years hormonal replacement therapy** was **non-significantly** associated with an **increased breast cancer risk** as compared to **<3 years hormonal replacement therapy or none** adjusted for chest radiation dose (RR: 2.16 (0.36-12.9)).	*van Leeuwen 2003**
Overall conclusion	
There is moderate quality evidence that there is no significant effect of treatment of early menopause on the risk of breast cancer in female childhood, adolescent and young adult cancer survivors.	*3 studies from 2 cohorts* **Level B**

*Overlap in included patients

Breast cancer risk by treatment of early menopasue		
Childhood cancer survivors		
Moskowitz 2017	Combined estrogen and progestin use yes vs. no	HR 1.54 (0.70-3.40)
	Gonadal hormone exposure ≥10 yr vs. <10 yr	HR 1.59 (0.88-2.90)
Hodgkin lymphoma survivors		
Krul 2017	Hormone replacement therapy yes vs. no	OR 0.82 (0.48-1.39)
	<5 yr hormone replacement therapy vs. none	OR 0.93 (0.49-1.77)
	5-9 yr hormone replacement therapy vs. none	OR 0.91 (0.34-2.46)
	≥10 yr hormone replacement therapy vs. none	OR 0.84 (0.30-2.32)
van Leeuwen 2003	Hormonal replacement therapy ≥3 yr vs. <3 yr or none	RR 2.16 (0.36-12.9)

8.1 Do other certain types of chemotherapy affect the risk of breast cancer in CAYA cancer survivors treated without chest radiation?	
Conclusion single studies	
Anthracyclines	
In female childhood cancer survivors, **increasing doses of anthracyclines** were **significantly** associated with an **increased breast cancer risk** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR per 100 mg/m^2: 1.23 (1.09-1.39)). In female childhood cancer survivors, **1-223 mg/m^2, 224-343 mg/m^2 and 224-343 mg/m^2 anthracyclines** were **significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR 1-223 mg/m^2: 2.3 (1.3-4.2), OR 224-343 mg/m^2: 2.4 (1.3-4.6), OR >455 mg/m^2: 3.8 (1.8-8.2)). In female childhood cancer survivors, **344-455 mg/m^2 anthracyclines** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR 1.5 (0.7-3.2)). In female childhood cancer survivors, **>0-279 mg/m^2 and ≥424 mg/m^2 doxorubicin** were **significantly** associated with an **increased breast cancer risk** as compared to **no doxorubicin** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR >0-279 mg/m^2: 2.0 (1.1-3.5), OR ≥424 mg/m^2: 2.7 (1.3-5.8)). In female childhood cancer survivors, 279-<424 mg/m^2 **doxorubicin** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no doxorubicin** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR 279-<424 mg/m^2: 1.8 (0.9-3.6)). In female childhood cancer survivors, **daunorubicin** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no daunorubicin** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR 1.1 (0.5-2.6)). In female childhood leukemia, CNS tumor and non-Ewing sarcoma survivors (Li-Fraumeni syndrome associated childhood cancer types) **increasing doses of anthracyclines** were **significantly** associated with an **increased breast cancer risk** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR per 100 mg/m^2: 1.31 (1.1-1.5)). In female survivors of non-Li-Fraumeni syndrome associated childhood cancer types **increasing doses of anthracyclines** were **significantly** associated with an **increased breast cancer risk** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR per 100 mg/m^2: 1.16 (1.0-1.4)). In female childhood cancer survivors, there is a **significant additive interaction** between **chest radiation** and **anthracyclines** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and alkylating agents (OR: no anthracyclines and 1-<10 Gy chest radiation vs. 0-<1 Gy chest radiation: 2.1 (0.9-4.8), OR no anthracyclines and ≥10 Gy chest radiation vs. 0-<1 Gy chest radiation: 9.6 (4.4-20.7), OR anthracyclines and 1-<10 Gy chest radiation vs. 0-<1 Gy chest radiation: 3.7 (1.4-10.3), OR anthracyclines and ≥10 Gy chest radiation vs. 0-<1 Gy chest radiation: 19.1 (7.6-48.0)).	*Veiga 2019**

In female childhood cancer survivors treated without chest radiation, **increasing doses of anthracyclines** were **significantly** associated with an **increased breast cancer risk** adjusted for age at primary cancer diagnosis, treatment era, history of splenectomy, cyclophosphamide equivalent dose, epipodophyllotoxins and platinum agents (RR per 100 mg/m^2 RR 1.3 (1.2-1.6)). In female childhood cancer survivors treated without chest radiation, **0-100 mg/m^2 and 101-300 mg/m^2 anthracyclines** were **non-significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for age at primary cancer diagnosis, treatment era, history of splenectomy, cyclophosphamide equivalent dose, epipodophyllotoxins and platinum agents (RR 0-100 mg/m^2: 0.9 (0.1-9.1), RR 101-300 mg/m^2: 1.8 (0.6-6.0)). In female childhood cancer survivors treated without chest radiation, **301-600 mg/m^2 and 600 mg/m^2 anthracyclines** were **significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for age at primary cancer diagnosis, treatment era, history of splenectomy, cyclophosphamide equivalent dose, epipodophyllotoxins and platinum agents (RR 301-600 mg/m^2: 3.7 (1.3-10.8), RR >600 mg/m^2: 8.1 (1.2-56.0)).	*Turcotte 2019**
In female childhood cancer survivors treated without ≥10 Gy chest radiation and without pathogenic/likely pathogenic mutations, **1-249 mg/m^2 anthracyclines** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for age at primary childhood cancer diagnosis, alkylating agents and pelvic radiation (HR 2.1 (0.2-27.0)). In female childhood cancer survivors treated without ≥10 Gy chest radiation and without pathogenic/likely pathogenic mutations, **≥250 mg/m^2 anthracyclines** was **significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for age at primary childhood cancer diagnosis, alkylating agents and pelvic radiation (HR 16.9 (2.2-126.6)). In female childhood cancer survivors, **1-249 mg/m^2 anthracyclines** was **significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for age at primary childhood cancer diagnosis, pathogenic/likely pathogenic mutation, chest radiation, alkylating agents and pelvic radiation (HR 2.6 (1.1-6.2)). In female childhood cancer survivors, **≥250 mg/m^2 anthracyclines** was **significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for age at primary childhood cancer diagnosis, pathogenic/likely pathogenic mutation, chest radiation, alkylating agents and pelvic radiation (HR 13.4 (5.5-13.4)).	*Ehrhardt 2019*

In female childhood cancer survivors treated without chest radiation, **≤270 mg/m² doxorubicin** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no doxorubicin** adjusted for ifosfamide (HR: 1.3 (0.3-6.1)). In female childhood cancer survivors treated without chest radiation, **271-443 mg/m² and >443 mg/m² doxorubicin** were **significantly** associated with an **increased breast cancer risk** as compared to **no doxorubicin** adjusted for ifosfamide (HR 271-443 mg/m²: 5.6 (1.9-16.2), HR >443 mg/m²: 9.9 (4.2-23.8)). In female childhood cancer survivors treated without chest radiation, there was a strong **significant** trend of **increasing breast cancer risk** with **increasing doxorubicin dose** (P for trend 0.002). In female childhood leukemia, CNS tumor and non-Ewing sarcoma survivors (Li-Fraumeni syndrome associated childhood cancer types) (7.6% treated with chest radiation), **≤270 mg/m² doxorubicin** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no doxorubicin** adjusted for chest radiation, TBI and ifosfamide (HR: 0.6 (0.1-3.2)). In female childhood leukemia, CNS tumor and non-Ewing sarcoma survivors (Li-Fraumeni syndrome associated childhood cancer types) (7.6% treated with chest radiation), **271-443 mg/m² and >443 mg/m² doxorubicin** were **significantly** associated with an **increased breast cancer risk** as compared to **no doxorubicin** adjusted for chest radiation, TBI and ifosfamide (HR 271-443 mg/m²: 9.1 (2.5-32.8), HR >443 mg/m²: 14.8 (5.1-43.2)). In female childhood leukemia, CNS tumor and non-Ewing sarcoma survivors (Li-Fraumeni syndrome associated childhood cancer types) (7.6% treated with chest radiation), there was a strong **significant** trend of **increasing breast cancer risk** with **increasing doxorubicin dose** (P for trend <0.001). In female survivors of non-Li-Fraumeni syndrome associated childhood cancer types (13.4% treated with chest radiation), **≤270 mg/m², 271-443 mg/m² and >443 mg/m² doxorubicin** were **non-significantly** associated with an **increased breast cancer risk** as compared to **no doxorubicin** adjusted for chest radiation, TBI and ifosfamide (HR ≤270 mg/m²: 1.9 (0.6-6.2), HR 271-443 mg/m²: 1.1 (0.2-4.9), HR >443 mg/m²: 2.4 (0.7-8.4)). In female survivors of non-Li-Fraumeni syndrome associated childhood cancer types (13.4% treated with chest radiation), there was **no significant** trend of increasing breast cancer risk with increasing doxorubicin dose (P for trend=0.94)).	*Teepen 2017*
In female childhood cancer survivors treated without chest radiation, **1-249 mg/m² anthracyclines** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for cyclophosphamide, age at primary cancer diagnosis, ethnicity and current age (Relative SIR: 2.6 (0.8-8.7)). In female childhood cancer survivors treated without chest radiation, **≥250 mg/m² anthracyclines** was **significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for cyclophosphamide, age at primary cancer diagnosis, ethnicity and current age (Relative SIR: 3.8 (1.7-8.3)). In female childhood cancer survivors treated without chest radiation there was a strong **significant** trend of **increasing breast cancer risk** with **increasing anthracycline dose** (P for trend =0.004). In female childhood leukemia and sarcoma survivors treated without chest radiation, **1-249 mg/m² and ≥250 mg/m² anthracyclines** were **significantly** associated with an **increased breast cancer risk** as compared to **no anthracyclines** adjusted for cyclophosphamide, age at primary cancer diagnosis, ethnicity and current age (Relative SIR 1-249 mg/m²: 4.3 (1.1-16.6), Relative SIR ≥250 mg/m²: 5.1 (1.9-13.7)). In female childhood leukemia and sarcoma survivors treated without chest radiation there was a strong **significant** trend of **increasing breast cancer risk** with **increasing anthracycline dose** (P for trend =0.005).	*Henderson 2016**
Overall conclusion	
Risk after anthracyclines without chest radiation: There is high quality evidence that female childhood, adolescent and young adult cancer survivors treated with anthracyclines have an increased risk of breast cancer in a dose-response relationship. However, the threshold dose for survivors at low, moderate and high risk is difficult to	*5 studies from 3 cohorts* **Level A**

determine.	
There is moderate quality evidence that survivors of Li-Fraumeni syndrome-associated childhood cancer types (leukemia, CNS tumor and non-Ewing sarcoma) treated without chest radiation have an increased breast cancer risk as compared to no anthracyclines and no chest radiation.	*3 studies from 2 cohorts* **Level B**

* Overlap in included patients

Study	Effect estimate per 100 mg/m²
Veiga 2019 CCSS case-control study	**OR 1.23 (1.09-1.39)**
Non-LFS-associated	**OR 1.16 (1.0-1.4)**
LFS-associated[1]	**OR 1.31 (1.1-1.5)**
Turcotte 2019 CCSS cohort study Treated without chest RT	**RR 1.3 (1.2-1.6)**

[1] Childhood leukemia, CNS tumor and non-Ewing sarcoma survivors

Study	Low risk Estimate RR <2	Medium risk Estimate RR 2-4	High risk Estimate RR ≥4
Veiga 2019[1] CCSS case-control study	344-455 mg/m² vs. 0: OR 1.5 (0.7-3.2)	**1-223 mg/m² vs. 0: OR 2.3 (1.3-4.2)** **224-343 mg/m² vs. 0: OR 2.4 (1.3-4.6)** **>455 mg/m² vs. 0: OR 3.8 (1.8-8.2)**	
	Doxorubicin 279-<424 mg/m² vs. 0: OR 1.8 (0.9-3.6)	**Doxorubicin** **>0-279 mg/m² vs. 0: OR 2.0 (1.1-3.5)** **≥424 mg/m² vs. 0: OR 2.7 (1.3-5.8)**	
Turcotte 2019 CCSS cohort study Treated without chest RT	0-100 mg/m² vs. 0: RR 0.9 (0.1-9.1) 101-300 mg/m² vs. 0: RR 1.8 (0.6-6.0)	**301-600 mg/m² vs. 0: RR 3.7 (1.3-10.8)**	**>600 mg/m² vs. 0: RR 8.1 (1.2-56.0)**
Ehrhardt 2019 StJudeLIFE cohort study		**1-249 mg/m² vs. 0: HR 2.6 (1.1-6.2)**	**≥250 mg/m² vs. 0: HR 13.4 (5.5-13.4)**
Treated without ≥10 Gy chest RT, without (likely) pathogenic mutations		1-249 mg/m² vs. 0: HR 2.1 (0.2-27.0)	**≥250 mg/m² vs. 0: HR 16.9 (2.2-126.6)**
Teepen 2017 DCOG-LATER cohort study	Doxorubicin ≤270 mg/m² vs. 0: HR 1.3 (0.3-6.1)		Doxorubicin **271-443 mg/m² vs. 0: HR 5.6 (1.9-16.2)** **>443 mg/m² vs. 0: HR 9.9 (4.2-23.8)**
Treated without chest RT Non-LFS-associated (13.4% chest RT)	Doxorubicin ≤270 mg/m² vs. 0: HR 1.9 (0.6-6.2) 271-443 mg/m² vs. 0: HR 1.1 (0.2-4.9)	Doxorubicin >443 mg/m² vs. 0: HR 2.4 (0.7-8.4)	
LFS-associated[2] (7.6% chest RT)	Doxorubicin ≤270 mg/m² vs. 0: HR 0.6 (0.1-3.2)		Doxorubicin **271-443 mg/m² vs. 0: HR 9.1 (2.5-32.8)** **>443 mg/m² vs. 0: HR 14.8 (5.1-43.2)**

<u>Henderson 2016</u> CCSS cohort study Treated without chest RT		1-249 mg/m^2 vs. 0: Relative SIR 2.6 (0.8-8.7) **≥250 mg/m^2 vs. 0: Relative SIR 3.8 (1.7-8.3)**	
LFS-associated[3] Treated without chest RT			**1-249 mg/m^2 vs. 0: Relative SIR 4.3 (1.1-16.6)** **≥250 mg/m^2 vs. 0: Relative SIR 5.1 (1.9-13.7)**

[1] Daunorubicin yes vs. no: 1.1 (0.5-2.6); Additive interaction between radiotherapy and anthracyclines (p=0.04)
[2] Childhood leukemia, CNS tumor and non-Ewing sarcoma survivors
[3] Childhood leukemia and sarcoma survivors

8.2 Do other certain types of chemotherapy affect the risk of breast cancer in CAYA cancer survivors treated without chest radiation?	
Conclusion single studies	
Alkylating agents	
In female childhood cancer survivors, **alkylating agents** was **non-significantly** associated with **breast cancer risk** as compared to **no alkylating agents** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and anthracyclines (OR 1.1 (0.8-1.5)). In female childhood cancer survivors, a **cyclophosphamide equivalent dose of >0-<5,201 mg/m^2, 5,201-<9,435 mg/m^2, 9,435-<13,955 mg/m^2, and ≥13,955 mg/m^2** were **non-significantly** associated with **breast cancer risk** as compared to **no alkylating agents** adjusted for type of first cancer, categories of breast radiation dose, calendar year of follow-up, family history of breast or ovarian cancer and anthracyclines (OR >0-<5,201 mg/m^2: 0.8 (0.4-1.4), OR 5,201-<9,435 mg/m^2: 1.4 (0.8-2.3), OR 9,435-<13,955 mg/m^2: 1.1 (0.7-1.9), OR ≥13,955 mg/m^2: 0.9 (0.5-1.5)).	*Veiga 2019*
In female childhood cancer survivors treated without chest radiation, a **cyclophosphamide equivalent dose of 1-2,000 mg/m^2, 2,001-4,000 mg/m^2, 4,001-7,000 mg/m^2, 7,001-10,000 mg/m^2 and >10,000 mg/m^2** were **non-significantly** associated with **breast cancer risk** as compared to **no alkylating agents** adjusted for age at primary cancer diagnosis, treatment era, history of splenectomy, anthracyclines, epipodophyllotoxins and platinum agents (RR 1-2,000 mg/m^2: 0.8 (0.1-6.9), RR 2,001-4,000 mg/m^2: 0.5 (0.1-3.8), RR 4,001-7,000 mg/m^2: 2.6 (0.9-7.4), RR 7,001-10,000 mg/m^2: 1.5 (0.5-5.3), RR >10,000 mg/m^2: 1.4 (0.5-4.3)).	*Turcotte 2019*
In female childhood cancer survivors treated without chest radiation, **ifosfamide** was **non-significantly** associated with an **increased breast cancer risk** as compared to **no ifosfamide** adjusted for doxorubicin (HR: 2.3 (0.6-8.0)). In female childhood cancer survivors (6.4% treated with chest radiation), a **cyclophosphamide equivalent dose of <6,000 mg/m^2, 6,000-17,999 mg/m^2 and ≥18,000 mg/m^2** were **non-significantly** associated with an **increased breast cancer risk** as compared to **no alkylating agents** adjusted for chest radiation, TBI and anthracyclines (HR <6,000 mg/m^2: 2.0 (0.9-4.8); HR 6,000-17,999 mg/m^2: 1.7 (0.7-3.9); HR ≥18,000 mg/m^2: 1.0 (0.2-4.5); *P trend* = 0.99).	*Teepen 2017*
In female childhood cancer survivors treated without chest radiation, **cyclophosphamide equivalent doses of 1-5,999 mg/m^2 and 6,000-17,999 mg/m^2** were **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agents** adjusted for anthracyclines, age at primary cancer diagnosis, ethnicity and current age (Relative SIR 1-5,999 mg/m^2: 0.6 (0.2-2.0); Relative SIR 6,000-17,999 mg/m^2: 1.6 (0.7-3.5)). In female childhood cancer survivors treated without chest radiation, a **cyclophosphamide equivalent dose of ≥18,000 mg/m^2** was **significantly** associated with an **increased breast cancer risk** as compared to **no alkylating agents** adjusted for anthracyclines, age at primary cancer diagnosis, ethnicity and current age (Relative SIR: 3.0 (1.2-7.7)). In female childhood cancer survivors treated without chest radiation there was a **significant** trend of **increasing breast cancer risk** with **increasing cyclophosphamide equivalent dose** (P for trend = 0.044). In female childhood leukemia and sarcoma survivors treated without chest radiation, **cyclophosphamide equivalent doses of 1-5,999 mg/m^2 and 6,000-17,999 mg/m^2** were **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agents** adjusted for anthracyclines, age at primary cancer diagnosis, ethnicity and current age (Relative SIR 1-5,999 mg/m^2: 0.7 (0.2-2.3); Relative SIR 6,000-17,999 mg/m^2: 1.9 (0.8-4.5)). In female childhood leukemia and sarcoma survivors treated without chest radiation, a **cyclophosphamide equivalent dose of ≥18,000 mg/m^2** was **significantly** associated with an **increased breast cancer risk** as compared to **no alkylating agents** adjusted for anthracyclines, age at primary cancer diagnosis, ethnicity and current age (Relative SIR: 3.4 (1.2-9.7)). In female childhood leukemia and sarcoma survivors treated without chest radiation there was a **significant** trend of **increasing breast cancer risk**	*Henderson 2016*

with **increasing cyclophosphamide equivalent dose** (P for trend =0.045).	
In female childhood cancer survivors (20.7% treated with chest radiation), **alkylating agent chemotherapy** was **non-significantly** associated with a **decreased breast cancer risk** as compared to **no alkylating agent chemotherapy** adjusted for chest radiation (OR alkylating agent score 1-2 vs. 0: 0.8 (0.4-1.6); OR alkylating agent score 3-4 vs. 0: 0.8 (0.4-1.4); OR alkylating agent score ≥5 vs. 0: 1.11 (0.6-2.0) (*P* for trend >0.2)).	*Kenney 2004*
Overall conclusion	
Risk after alkylating agents without or independent of chest radiation: There is low quality evidence that female childhood, adolescent and young adult cancer survivors treated with higher doses of alkylating agents (≥18,000 mg/m^2) without chest radiation have an increased risk of breast cancer as compared to no alkylating agents and no chest radiation.	*5 studies* **Level C**

Breast cancer risk after alkylating agents in patients treated without chest radiation		
Childhood cancer survivors		
Veiga 2019	Alkylating agents yes vs. no:	OR 1.1 (0.8-1.5)
	CED >0- <5,201 mg/m^2 vs. none:	OR 0.8 (0.4-1.4)
	CED 5,201 -<9,435 mg/m^2 vs. none:	OR 1.4 (0.8-2.3)
	CED 9,435- <13,955 mg/m^2 vs. none:	OR 1.1 (0.7-1.9)
	CED ≥13,955 mg/m^2 vs. none:	OR 0.9 (0.5-1.5)
Turcotte 2019	CED 1-2,000 mg/m^2 vs. none:	RR 0.8 (0.1-6.9)
	CED 2,001-4,000 mg/m^2 vs. none:	RR 0.5 (0.1-3.8)
	CED 4,001-7,000 mg/m^2 vs. none:	RR 2.6 (0.9-7.4)
	CED 7,001-10,000 mg/m^2 vs. none:	RR 1.5 (0.5-5.3)
	CED >10,000 mg/m^2 vs. none	RR 1.4 (0.5-4.3)
Teepen 2017	*Childhood cancer survivors treated without chest radiation*	
	Ifosfamide yes vs. no	HR 2.3 (0.6-8.0)
	All childhood cancer survivors (6.4% treated with chest radiation)	
	CED <6,000 mg/m^2 vs. none	HR 2.0 (0.9-4.8)
	CED 6,000-17,999 mg/m^2 vs. none	HR 1.7 (0.7-3.9)
	CED ≥18,000 mg/m^2 vs. none	HR 1.0 (0.2-4.5)
		P trend = 0.99
Henderson 2016	*All childhood cancer survivors treated without chest radiation*	
	CED 1-5,999 mg/m^2 vs. no	Relative SIR 0.6 (0.2-2.0)
	CED 6,000-17,999 mg/m^2 vs. no	Relative SIR 1.6 (0.7-3.5)
	CED ≥18,000 mg/m^2 vs. no	**Relative SIR 3.0 (1.2-7.7)**; ***P* trend = 0.044**
	Childhood leukemia and sarcoma survivors treated without chest radiation	
	CED 1-5,999 mg/m^2 vs. no	Relative SIR 0.7 (0.2-2.3)
	CED 6,000-17,999 mg/m^2 vs. no	Relative SIR: 1.9 (0.8-4.5)
	CED ≥18,000 mg/m^2 vs. no	**Relative SIR: 3.4 (1.2-9.7)** ***P* trend = 0.045**
Kenney 2004	*All childhood cancer (20.7% treated with chest radiation)*	
	Alkylating agent score 1-2 vs. 0	OR 0.8 (0.4-1.6)
	Alkylating agent score 3-4 vs. 0	OR 0.8 (0.4-1.4)
	Alkylating agent score ≥5 vs. 0	OR 1.11 (0.6-2.0)

At what age should continuation of intensive breast cancer surveillance be stopped?

9 What is the risk of breast cancer in childhood and young adult cancer survivors treated with chest radiation with an attained age >50 years?	
Conclusion single studies	
Childhood cancer survivors	
In female childhood cancer survivors treated with chest radiation ≥10 Gy, there is an **increased breast cancer risk by age 50 years** (cumulative incidence childhood cancer survivors: 41%).	*Ehrhardt 2019*
In female childhood Hodgkin lymphoma survivors treated with chest radiation, there is an **increased breast cancer risk by age 50 years** (cumulative incidence childhood cancer survivors: 23.5% (16.9-30.7)).	*Holmqvist 2019*
In female childhood cancer survivors treated with chest radiation (81% treated with ≥20 Gy), there is an **increased breast cancer risk by age 50 years** (cumulative incidence childhood cancer survivors: 30% (25-34); cumulative incidence Hodgkin lymphoma survivors: 35% (29-40); cumulative incidence BRCA1 mutation carriers: 31% (15-48); cumulative incidence BRCA2 mutation carriers: 10% (1-23); cumulative incidence continues to increase by age 55 years (no effect measures reported).	*Moskowitz 2014*
Hodgkin lymphoma survivors	
In female Hodgkin lymphoma survivors treated with chest radiation (on average, 36 Gy for mantle and 31 to 33 Gy for mediastinum, axilla, and neck/clavicle), there is a **significantly increased breast cancer risk by age ≥50 years** as compared to the **general population** (SIR 50-59 year: 3.8 (3.1-4.7); SIR ≥60 year: 2.7 (1.7-4.3)).	*Swerdlow 2012*
In female Hodgkin lymphoma survivors treated with and without chest radiation (on average, 40 Gy (range 36 to 44 Gy), there is a **significantly increased breast cancer risk by age ≥50 years** as compared to the **general population** (SIR 50-59 years, 15-24 years at HL: 8.6 (5.1-13.4); SIR ≥60 years, 15-24 years at HL: 7.4 (1.5-21.7) SIR 50-59 years, 25-34 years at HL: 4.0 (2.4-6.3); SIR ≥60 years, 25-34 years at HL: 2.7 (0.7-6.9)).	*Schaapveld 2015*
Overall conclusion	
Risk among survivors previously treated with chest radiation by age >50 years: There is high quality evidence that female childhood, adolescent and young adult cancer survivors previously treated with (high-dose) chest radiation with an attained age of 50-60 years have an increased risk of breast cancer.	*5 studies* **Level A**
There is low quality evidence that female childhood, adolescent and young adult cancer survivors previously treated with (high-dose) chest radiation with an attained age of ≥60 years have an increased risk of breast cancer.	*2 studies* **Level C**

Breast cancer risk in survivors aged >50 years		
Childhood cancer survivors		
Ehrhardt 2019	Breast cancer risk after chest radiation by age 50 years	Cumulative incidence: 41%
Holmqvist 2019	Breast cancer risk after chest radiation by age 50 years	Cumulative incidence: 23.5% (16.9-30.7)
Moskowitz 2014	Breast cancer risk after chest radiation by age 50 years	Cumulative incidence childhood cancer survivors: 30% (25-34) Cumulative incidence Hodgkin lymphoma survivors: 35% (29-40) Cumulative incidence BRCA1 mutation carriers: 31% (15-48) Cumulative incidence BRCA2 mutation carriers: 10% (1-23)

		Cumulative incidence continues to increase by age 55 years
<u>Hodgkin lymphoma survivors</u>		
Swerdlow 2012	Breast cancer risk after chest radiation by age ≥50 years	**SIR 50-59 years: 3.8 (3.1-4.7)** **SIR ≥60 years: 2.7 (1.7-4.3)**
Schaapveld 2015	Breast cancer risk by age ≥50 years in patients treated with and without chest radiation	**SIR 50-59 years, 15-24 years at HL diagnosis: 8.6 (5.1-13.4)** **SIR ≥60 years, 15-24 years at HL diagnosis: 7.4 (1.5-21.7)** **SIR 50-59 years, 25-34 years at HL diagnosis: 4.0 (2.4-6.3)** SIR ≥60 years, 25-34 years at HL diagnosis: 2.7 (0.7-6.9)

What breast cancer surveillance modality should be used?

10 What is the diagnostic value of a breast MRI and a mammogram compared to a breast MRI alone (additional value of mammogram) or mammogram alone (additional value of MRI) to detect breast cancer in an early stage in CAYA cancer survivors? **11 What is the diagnostic value of a breast MRI and a mammogram compared to a breast MRI (additional value of a mammogram) to detect breast cancer in an early stage in women aged 25-35 years?**	
Conclusion single studies	
In female childhood cancer survivors treated with chest radiation, the **sensitivity** of **mammogram, MRI, and both** to detect breast cancer was **53.8% (26.8% -80.9%), 69.2% (44.1%-94.3%) and 85.8% (72.4%-99.2%)**, respectively. In female childhood cancer survivors treated with chest radiation, the **specificity** of **mammogram, MRI, and both** to detect breast cancer was **96.3% (94.1%-98.4%), 91.4% (88.1%-94.6%) and 99.7% (99.3%-100.0%)**, respectively. (Mean age at screening: 36.9 ± 7.8 yr)	*Ehrhardt 2019*
In female Hodgkin lymphoma survivors treated with chest radiation, the **sensitivity** of **mammogram, MRI, and both** to detect breast cancer was **68%, 67% and 94%**, respectively. In female Hodgkin lymphoma survivors treated with chest radiation, the **specificity** of **mammogram, MRI, and both** to detect breast cancer was **93%, 94% and 90%**, respectively. (Median age at screening: 43 (range 22-65) yr)	*Ng 2013*
In female Hodgkin lymphoma survivors treated with chest radiation, the **sensitivity** of **mammogram, MRI, and both** to detect breast cancer was **70.0%, 80.0% and 100%**, respectively. In female Hodgkin lymphoma survivors treated with chest radiation, the **specificity** of **mammogram, MRI, and both** to detect breast cancer was **95.0%, 93.5% and 88.6%**, respectively. (Median age at screening: 30 (range 19-59) yr)	*Tieu 2014*
In female young adult cancer survivors treated with chest radiation, the **added cancer yield per patient** of **mammogram and MRI** to detect breast cancer was **1 (0.2-5.6) and 4.1 (1.6-10)** (*P* = 0.175), respectively. In female young adult cancer survivors treated with chest radiation, the **sensitivity** of **mammogram and MRI** to detect breast cancer was **69% (60-78%) and 100% (93-100%)** (*P* = 0.375), respectively. In female young adult cancer survivors treated with chest radiation, the **specificity** of **mammogram and MRI** to detect breast cancer was **98% (93-99%) and 94% (87-97%)** (*P* = 0.375), respectively. In female young adult cancer survivors treated with chest radiation, the **positive predictive value (PPV)** of **mammogram and MRI** to detect breast cancer was **82% (74-89%) and 71% (62-79%)** (*P* = 0.945), respectively. In female young adult cancer survivors treated with chest radiation, the **negative predictive value (NPV)** of **mammogram and MRI** to detect breast cancer was **95% (89-98%) and 99% (94-99%)** (*P* = 0.950), respectively. (Mean age at screening: 37 (range 19-65) yr)	*Freitas 2013*
In female childhood cancer survivors treated with chest radiation, the **sensitivity** of **mammogram and MRI** to detect breast cancer was **73% (39-94%) and 100% (93-100%)**, respectively. In female childhood cancer survivors treated with chest radiation, the **specificity** of **mammogram and MRI** to detect breast cancer was **99% (98-100%) and 80% (68-88%)**, respectively. (Median age at screening: 25 (range 14-45) yr)	*Terenziani 2013*

In female CAYA cancer survivors treated with chest radiation, the **sensitivity** of **mammogram and MRI** to detect breast cancer was **66.7% (29.9-92.5%) and 66.7% (29.9-92.5%)**, respectively. In female CAYA cancer survivors treated with chest radiation, the **specificity** of **mammogram and MRI** to detect breast cancer was **93.2% (84.9-97.8%) and 81.7% (71.6-89.4%)**, respectively. In female CAYA cancer survivors treated with chest radiation, the **positive predictive value (PPV)** of **mammogram and MRI** to detect breast cancer was **54.5% (23.4-83.3%) and 28.6% (11.3-52.1%)**, respectively. In female CAYA cancer survivors treated with chest radiation, the **negative predictive value (NPV)** of **mammogram and MRI** to detect breast cancer was **95.8% (88.3-99.1%) and 95.7% (88.8-99.1%)**, respectively. In female CAYA cancer survivors treated with chest radiation, the **accuracy** of **mammogram and MRI** to detect breast cancer was **90.4% (81.9-95.8%) and 80.2% (70.6-87.8%)**, respectively. (Median age at screening 40 (range 18-62) yr)	*Sung 2011*
In female Hodgkin lymphoma survivors treated with chest radiation, there were **34 true-positive findings, 23 false-positive findings and 1 false-negative finding in 117 survivors with mammogram** screening. In addition, there were **no true-positive findings, 2 false-positive findings and 1 false-negative finding and 39 survivors with MRI** screening.	*Horst 2016*
In female Hodgkin lymphoma survivors treated with chest radiation, **58.3%** of **breast cancers** were initially **detected by mammogram** screening.	*Diller 2000*
In female Hodgkin lymphoma survivors treated with chest radiation, **75.0%** of **breast cancers** were initially **detected by mammogram** screening.	*Kwong 2008*
In female Hodgkin lymphoma survivors treated with chest radiation, **35.7%** of **breast cancers** were initially **detected by mammogram** screening.	*Howell 2009*
In female Hodgkin lymphoma survivors treated with chest radiation, **41.7%** of **breast cancers** were initially **detected by mammogram** screening.	*Lee 2008*
In female Hodgkin lymphoma survivors treated with chest radiation, **37.9%** of **breast cancers** were initially **detected by mammogram** screening.	*Dershaw 1992*
In female Hodgkin lymphoma survivors treated with chest radiation, **26.8%** of **breast cancers** were initially **detected by mammogram** screening.	*Wolden 2000*
Overall conclusion	
Diagnostic value breast MRI in CAYA cancer survivors: There is moderate quality evidence that the diagnostic value of a breast MRI to detect breast cancer in CAYA cancer survivors is moderate (sensitivity ranged from 67% to 100%, specificity ranged from 80% to 94%).	*6 studies* **Level B**
Diagnostic value mammogram in CAYA cancer survivors: There is high quality evidence that the diagnostic value of a mammogram to detect breast cancer in CAYA cancer survivors is moderate (sensitivity ranged from 54% to 73%, specificity ranged from 93% to 99%).	*6 studies* **Level A**
Diagnostic value breast MRI and mammogram compared to breast MRI or mammogram alone in CAYA cancer survivors: There is moderate quality evidence that the diagnostic value of a breast MRI and mammogram is better than either test alone to detect breast cancer in CAYA cancer survivors (sensitivity ranged from 86% to 100%, specificity ranged from 89% to 99.7%).	*3 studies* **Level B**
Mammography in Hodgkin lymphoma survivors: There is moderate quality evidence that 26.8% to 75.0% of breast cancers in Hodgkin lymphoma survivors treated with chest radiation are initially detected by mammogram screening.	*6 studies* **Level B**
Diagnostic value breast MRI and mammogram compared to breast MRI alone in women aged 25-35 years: There are no studies that reported the diagnostic value of a breast MRI and a mammogram compared to a breast MRI to detect breast cancer in an early stage in women aged 25-35 years. Thus, it is unclear what the additional value is of a mammogram to a breast MRI (or visa versa) for younger women.	*0 studies* **No studies**

Diagnostic value mammogram and breast MRI in CAYA cancer survivors							
		Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**	**Added cancer yield per patient**
Ehrhardt 2019	Mammogram	53.8% (26.8 -80.9%)	96.3% (94.1-98.4%)	-	-	-	-
Mean age at screening:	MRI	69.2% (44.1-94.3%)	91.4% (88.1-94.6%)	-	-	-	-
36.9 ± 7.8 yr	Both	85.8% (72.4-99.2%)	99.7% (99.3-100%)	-	-	-	-
Ng 2013	Mammogram	68%	93%	-	-	-	-
Median age at screening:	MRI	67%	94%	-	-	-	-
43 (range 22-65) yr	Both	94%	90%	-	-	-	-
Tieu 2014	Mammogram	70%	95.0%	-	-	-	-
Median age at screening:	MRI	80%	93.5%	-	-	-	-
30 (range 19-59) yr	Both	100%	88.6%	-	-	-	-
Freitas 2013	Mammogram	69% (60-78%)	98% (93-99%)	82% (74-89%)	95% (89-98%)	-	1 (0.2-5.6)
Mean age at screening: 37 (range 19-65) yr	MRI	100% (93-100%)	94% (87-97%)	71% (62-79%)	99% (94-99%)	-	4.1 (1.6-10)
Terenziani 2013	Mammogram	73% (39-94%)	99% (98-100%)	-	-	-	-
Median age at screening:	MRI	100% (93-100%)	80% (68-88%)	-	-	-	-
25 (range 14-45) yr							
Sung 2011	Mammogram	66.7% (29.9-92.5%)	93.2% (84.9-97.8%)	54.5% (23.4-83.3%)	95.8% (88.3-99.1%)	90.4% (81.9-95.8%)	-
Median age at screening:	MRI	66.7% (29.9-92.5%)	81.7% (71.6-89.4%)	28.6% (11.3-52.1%)	95.7% (88.8-99.1%)	80.2% (70.6-87.8%)	-
40 (range 18-62) yr							

12 What is the diagnostic value of a mammogram, compared to a breast MRI, to detect breast cancer in an early stage in women in a young age group compared to an older age group?	
Conclusion single studies	
Women with an inherited susceptibility to breast cancer	
Suggested decreased sensitivity of a mammogram and breast MRI in women with an inherited susceptibility to breast cancer aged <40 yr compared to women aged ≥50 yr (sensitivity mammogram: 33.3% vs. 55.6%; sensitivity MRI: 61.6% vs. 66.7%). Suggested decreased discriminating capacity of a breast MRI versus a mammogram in women with an inherited susceptibility to breast cancer aged <40 yr compared to women aged ≥50 yr (AUC difference: 0.068 vs. 0.114).	*Kriege 2006*
Suggested decreased sensitivity of a mammogram and breast MRI in women with an inherited susceptibility to breast cancer aged <50 yr compared to women aged ≥50 yr (sensitivity mammogram: 45.5% vs. 53.6%; sensitivity MRI: 88.9% vs. 92.9%). No suggested difference in specificity of a mammogram and breast MRI in women with an inherited susceptibility to breast cancer aged <50 yr compared to women aged ≥50 yr (specificity mammogram: 98.7% vs. 99.5%; specificity MRI: 96.6% vs. 96.9%).	*Sardanelli 2008*
Overall conclusion	
Diagnostic value mammogram compared to breast MRI in women in a young age group compared to an older age group: There is moderate quality evidence that in women with an inherited susceptibility to breast cancer aged <40 yr or <50 yr there is a lower sensitivity compared to women aged ≥50 yr. There is no difference in the discriminating capacity of a breast MRI versus a mammogram for women aged <40 yr and ≥50 yr.	*2 studies* **Level B**

13 What is the diagnostic value of a clinical breast exam to detect breast cancer in an early stage in women aged <25 years?
No studies reported on the diagnostic value of a clinical breast exam to detect breast cancer in an early stage in women aged <25 years.