Conclusions of evidence tables from the systematic literature search for POI surveillance in female CAYA cancer survivors.

What is the risk of POI in female CAYA cancer survivors treated with alkylating agents? after higher doses? What is the additive effect (combination of therapy)?	What is the risk
Conclusion single studies	
Childhood cancer survivors	
In female survivors of childhood cancer aged 21-25 years, **alkylating agents** were **significantly** associated with amenorrhea compared to menstruating siblings **(RR 9.17, 95% 2.67-31.49)**.	*Byrne 1992*
In female survivors of childhood cancer, **high doses of alkylating agents** were **significantly** associated with menopause compared to survivors treated with non-sterilizing surgery in multivariate analyses **(AA-score ≥21: RR 3.08, 95% CI 1.15-8.21).**	*Chiarelli 1999*
In female survivors of childhood cancer, **low to median doses of alkylating agents** were **non-significantly** associated with menopause compared to survivors treated with non-sterilizing surgery only in multivariate analyses **(AA-score 1-13: RR 1.13, 95% CI 0.41-3.09)**.	
In female survivors of childhood cancer, **cyclophosphamide** was **significantly** associated with AOF in children diagnosed with cancer between **13-20 years** of age as compared to survivors treated without cyclophosphamide **(OR 4.9 95%CI 2.8-9.2)** in multivariate analyses.	*Chemaitilly 2006*
In female survivors of childhood cancer, **cyclophosphamide** was **non-significantly** associated with AOF in children diagnosed with cancer between **0-12 years** of age as compared to survivors treated without cyclophosphamide **(OR 1.2 95% CI 0.7-2.1)** in multivariate analyses.	
In female survivors of childhood cancer **procarbazine** was **significantly** associated with AOF in children diagnosed with cancer between **0-12 years of age** as compared to survivors treated without procarbazine **(OR 3.2 (1.3-7.3)** in multivariate analyses.	
In female survivors of childhood cancer **procarbazine** was **significantly** associated with AOF in children diagnosed with cancer between **13-20 years** of age as compared to survivors treated without procarbazine **(OR 2.6 (1.4-4.7)** in multivariate analyses.	
In female survivors of childhood cancer, **alkylating agents scores** were **significantly** associated with premature menopause as compared to survivors treated without alkylating agents in multivariate analyses.	*Sklar 2006*
In female survivors of childhood cancer, **higher alkylating agents scores** were **significantly** associated with a higher risk of premature menopause as compared to survivors treated without and lower alkylating agent scores in multivariate analyses **(AA score 1-2: RR 2.30, 95% CI 1.08-4.90; AA score 3: RR 5.78, 95% CI 2.90-11.55).**	
In female survivors of childhood cancer, **higher alkylating agent scores** were **significantly** associated with **higher** (but not necessarily abnormal) **FSH** values compared to survivors treated without and with lower alkylating agent scores in a multivariate regression analysis **(β 0.91 mIU/ml FSH, p=0.016).**	*Gracia 2012*
Overall conclusion	
Risk after alkylating agents vs. no alkylating agents: There is evidence that female CAYA cancer survivors treated with alkylating agents have an increased risk of premature ovarian insufficiency.	*4 studies* **Level A**
Risk after higher alkylating agent dose vs. lower dose: There is evidence that female CAYA cancer survivors treated with higher doses of alkylating agents have a higher risk of premature ovarian insufficiency. There is evidence that a higher dose is associated with a higher risk of POI, but no threshold dose is known. There no evidence for a linear or exponential dose relationship.	*3 studies* **Level A**
Risk after cyclophosphamide vs. no cyclophosphamide: Some evidence suggests that female CAYA cancer survivors treated with cyclophosphamide have an increased risk of premature ovarian insufficiency.	*1 study* **Level C**
Risk after higher cyclophosphamide dose vs. lower dose	*0 studies*

No studies reported on the effect of cyclophosphamide dose on POI in female childhood cancer survivors.	**No studies**
Risk after procarbazine vs. no procarbazine:	*1 study*
Some evidence suggests that female CAYA cancer survivors treated with procarbazine have an increased risk of premature ovarian insufficiency.	**Level C**
Risk after higher procarbazine dose vs. lower dose:	*0 studies*
No studies reported on the effect of procarbazine dose on POI in female childhood cancer survivors.	**No studies**
Risk after multiple alkylating agents and other chemotherapeutic agents vs. single alkylating agents:	*0 studies*
No studies reported on the risk of premature ovarian insufficiency in female CAYA cancer survivors treated with a combination of alkylating agents and other chemotherapeutic agents as compared to single alkylating agents.	**No studies**

What is the risk of POI in female CAYA cancer survivors treated with radiotherapy possibly exposing the ovaries? **What is the risk after higher doses?** **What is the additive effect (combination of therapy)?**	
Conclusion single studies	
Childhood cancer survivors	
In female survivors of childhood cancer aged 21-30, **radiotherapy below diaphragm alone** is **significantly** associated with **amenorrhea** compared to menstruating siblings **(21-25 RR 3.66, 95% CI 1.34-9.99; 26-30 RR 2.41 p<0.05).**	*Byrne 1992*
In female survivors of childhood cancer, **high doses abdominal-pelvic radiotherapy (≥ 3500 cGy**) were **significantly** associated with menopause compared to survivors treated with non-sterilizing surgery in multivariate analyses **(RR 3.27, 95% CI 1.57-6.81).**	*Chiarelli 1999*
In female survivors of childhood cancer, <**2000 cGy to 3499 cGy abdominal-pelvic radiotherapy** were **non-significantly** associated with menopause compared to survivors treated with non-sterilizing surgery, in multivariate analyses **(<2000 cGy: RR 1.02, 95% CI 0.29- 3.59; 2000-3499 cGy: RR 1.36, 95% CI 0.57-3.25).**	
In female survivors of childhood cancer, **alkylating agents combined with abdominal-pelvic radiotherapy** was **significantly** associated with menopause compared to survivors treated with non-sterilizing surgery in multivariate analyses **(RR 2.58, 95% CI 1.14-5.80).**	
In female survivors of childhood cancer, a dose of **1.99 Gy to the abdomen** is required to destroy 50% of the oocytes based on the Faddy-Gosden mathematical model.	*Wallace 2003*
In female survivors of childhood cancer, a dose of **20.3 Gy to the ovaries at birth** is associated with POI in 97.5% of the patients, based on the Faddy-Gosden mathematical model.	*Wallace 2005*
In female survivors of childhood cancer, a dose of **18.4 Gy to the ovaries at 10 years** of age is associated with POI in 97.5% of the patients, based on the Faddy-Gosden mathematical model.	
In female survivors of childhood cancer, a dose of **16.5 Gy to the ovaries at 20 years** of age is associated with POI in 97.5% of the patients, based on the Faddy-Gosden mathematical model.	
In female survivors of childhood cancer, **radiation to the ovaries** (1-2000 cGy) was **significantly** associated with AOF as compared to survivors treated without radiation to the ovaries in multivariate analyses.	*Chemaitilly 2006*
In female survivors of childhood cancer, **higher doses of radiation to the ovaries** were **significantly** associated with a higher risk of AOF **(0-12 yr: 1-99cGy: OR 3.7 (1.6-10.2); 100-999: OR 9.0 (3.4-26.5); 1000-1999: OR 55.3 (22.3-157.8); ≥2000: OR 950.1 (352.9-3043.2); 13-20 yr: 1-99 cGy: OR 2.9 (1.2-8.3); 100-999: OR 17.2 (6.8-49.5); 1000-1999: OR 90.9 (29.1-323.5); ≥2000: OR 171.2 (55.8-609.8))** in multivariate analysis.	
In female survivors of childhood cancer, **radiotherapy to the ovaries** was **significantly** associated with premature menopause compared to survivors treated without radiation to the ovaries in multivariate analysis.	*Sklar 2006*

In female survivors of childhood cancer, **higher doses of radiation to the ovaries** were **significantly** associated with a higher risk of premature menopause (**1-99 cGy: RR 4.30, 95% CI 1.20-15.47; 100-999 cGy: RR 5.70, 95% CI 1.12-28.99; ≥1000 cGy: RR 109.59, 95% CI 28.15-426.70).** In female survivors of Hodgkin lymphoma, **radiotherapy to the ovaries** was **significantly** associated with a higher risk of premature menopause compared to Hodgkin lymphoma survivors treated without radiation to the ovaries in multivariate analysis, and increased with dosage (no ovarian RT but diagnosed with HL compared to other diagnoses: RR 9.18, 95% CI 1.52-55.24; 1-99 cGy: RR 12.26, 95% CI 3.41-44.14; 100-999 cGy: RR 11.41, 95% CI 2.75-47.26; ≥1000 cGy: RR 6.74, 95% CI 0.63-71.74). In female survivors of childhood cancer, the **cumulative incidence** of non-surgical premature menopause was **higher** among childhood cancer survivors treated with **abdominopelvic radiation combined with alkylating agents as compared to alkylating agents only or abdominopelvic radiation only** (cumulative incidence AA+RT ±30%, AA only ±15%, RT only ±5%).	
In female survivors of childhood cancer treated with a bone marrow transplantation (conditioning: TBI and/or alkylating agents), **TBI** was **significantly** associated with ovarian failure in multivariate analyses **(p=0.014).**	*Jadoul 2011*
In female survivors of childhood cancer, **pelvic radiation** was **significantly** associated with **higher** (but not necessarily abnormal) **FSH** values compared to post-menarchal controls **(FSH 28.4 versus 9.4, p<0.001).**	*Gracia 2012*
Overall conclusion	
Risk after radiotherapy possibly exposing the ovaries vs. no radiotherapy: There is evidence that female CAYA cancer survivors treated with radiation potentially exposing ovaries have an increased risk of premature ovarian insufficiency.	*8 studies* **Level A**
Risk after higher dose of radiotherapy possibly exposing the ovaries vs. lower dose: There is evidence that female CAYA cancer survivors treated with higher doses of radiation potentially exposing the ovaries have a higher risk of premature ovarian insufficiency, but no specific threshold dose can be determined. There is a suggestion for an exponential dose-relationship.	*4 studies* **Level A**
Risk after radiotherapy possibly exposing the ovaries and other chemotherapeutic agents vs. either treatment in the same dose alone: Some evidence suggests that female CAYA cancer survivors treated with a combination of radiation potentially exposing the ovaries and alkylating agents have an increased risk of POI compared to either treatment alone.	*1 study* **Level C**

What is the influence of age at treatment on the risk of POI in female CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors	
In female survivors of childhood cancer, **aged 13-19 at diagnosis** (and aged 21-30 at follow-up) was significantly associated with **amenorrhea** as compared to female survivors **aged 0-12 at diagnosis** (and aged 21-30 at follow-up) **(13-19: RR 2.32, 95% CI 1.63-3.291; 0-12: RR 0.62, p>0.05).**	*Byrne 1992*
In female survivors of childhood cancer, **age at diagnosis** was **not associated** with premature menopause in multivariate analyses (effect measure not reported).	*Sklar 2006*
In female survivors of childhood cancer treated with a bone marrow transplantation (conditioning: TBI and alkylating agents), **older age at transplantation** was **significantly** associated with ovarian failure/ POI in multivariate analysis (**p=0.004**).	*Jadoul 2011*
Overall conclusion	
Older age at diagnosis vs. younger age: Evidence suggests that female CAYA cancer survivors who are older at cancer diagnosis have an increased risk of premature ovarian insufficiency, while other studies did not observe this association.	*3 studies* **Level B**

What is the risk of POI in female CAYA cancer survivors treated with platinum agents?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of POI in female CAYA cancer survivors treated with unilateral oophorectomy?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is diagnostic value of antral follicle count to detect POI female CAYA cancer survivors?
No studies identified in childhood, adolescent and young adult cancer survivors.

diagnostic value of anti-Müllerian hormone to detect POI in female CAYA cancer survivors treated with platinum agents?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is prognostic value of follicle stimulating hormone to predict POI in female CAYA cancer survivors?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is prognostic value of oestradiol to predict POI in female CAYA cancer survivors?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is prognostic value of anti-Müllerian hormone to predict POI in female CAYA cancer survivors?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is prognostic value of antral follicle count to predict POI in female CAYA cancer survivors?
No studies identified in childhood, adolescent and young adult cancer survivors.

Is there a change in POI risk (deterioration or recovery of gonadal function) during the fertile life span in female CAYA cancer survivors?
No studies identified in childhood, adolescent and young adult cancer survivors.