Working Group 1: Who is at risk of spontaneous abortion/miscarriage, terminations and still birth. What is the risk, what should be done?

Index:

What is the risk of spontaneous abortion/miscarriage in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis: 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up: Not reported.	Threatened abortion, <20 weeks of gestation (n=76, 4%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group - 15-19 at diagnosis: 0.76 (0.42-1.68) - 20-29 at diagnosis: 1.15 (0.58-3.98)	SB: low AB: low DB: unclear CF: low RB: low
Lantinga 2006	41 CAYA cancer survivors with 75 pregnancies	Age at diagnosis: Median 7.0 (range 0-19) yrs Age at follow-up Median 27.0 (range 18-45) yrs	Spontaneous abortion/miscarriage not further specified (n=17, 22.7%)	-	- Miscarriages 22.7% (95% CI 14-34) in all pregnancies (assumed in general population 10-15%) - Miscarriage in 19.5% (95% CI 9-35) of the first pregnancies. - Recurrent miscarriage 7.3% (95% CI 2-20) (assumed in general population 0.5-1.0%).	SB: low AB: low DB: unclear CF: high RB: high
Nielsen 2013	46 CCS with 85 pregnancies	Age at diagnosis: range 0-15 yr Age at follow-up: median 35.1 (28.4-48.6) yrs	Spontaneous abortion/miscarriage not further specified (n=11, 12.9%)	-	Miscarriage in 11 of 85 (7.7%) pregnancies	SB: low AB: low DB: unclear CF: high RB: high
Reinmuth 2008	44 CCS achieved 69 pregnancies, 50 in female CCS	Mean age at diagnosis: 10.9 Mean age at follow-up: 24.3	Spontaneous abortion/miscarriage not further specified (n=3, 6.0%)	-	Miscarriage in 3 of 50 (6%) pregnancies	SB: low AB: high DB: unclear CF: high RB: high
Sudour 2010	28 CAYA cancer survivors with 67 pregnancies	Age at diagnosis Median 11.3 yrs (range: 10 mths-17.6 yrs) Age at follow-up Median 27.1 (range 18-45) yrs	Spontaneous abortion/miscarriage not further specified (n=18, 26.9%)	-	Miscarriage in 18 of 67 (26.9%) pregnancies	SB: high AB: low DB: unclear CF: high RB: high

Winther 2008	1688 CAYA cancer survivors with 1479 pregnancies	Age at diagnosis Younger than 20 years Age at follow-up At least 15 yrs	Spontaneous abortion/miscarriage (n=109, 7.4%)	adjusted for maternal age and calendar time	Adjusted PR (95% CI) compared to control group: 1.23 (1.00-1.52)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 5/6, high in 1/6; Attrition bias low in 5/6, high in 1/6; Detection bias low in 2/6, high in 3/6, unclear in 1/6; Confounding low in 2/6, high in 4/6;
Consistency:	0	No important inconsistency, 2 studies did not show a significant increased risk. 4 studies reported mainly descriptive data.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	Four studies are too small (<100) to expect sufficient power, two are large cohorts
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect, prevalence ranging from 4.0 – 26.9%
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant increased risk of miscarriage in CAYA cancer survivors as compared to controls. (3.650 pregnancies; 595 miscarriages) The prevalence of miscarriages among CAYA cancer survivors ranged from 4.0-31.8%

Abbreviations: AB, attrition bias; AYA, adolescent and young adult; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; yr, year; RR, relative risk; PR, proportion ratio; RB, report bias.

What is the risk of spontaneous abortion/miscarriage in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Spontaneous abortion/miscarriage not further specified (n=326)	-	RR (95% CI), compared with siblings control group Treatment – Radiation only: RR 1.73 (1.49-2.00) – Sugery+radiation: RR 1.32 (0.98-1.78)	SB: high AB: high DB: unclear CF: high
Van de Loo 2018	110 CCS with 47 pregnancies, 14 after RT	Not specified. RT-group 44 (80%) diagnosed before menarche	Miscarriage (self-reported), not further specified (n=4)	Parity and maternal education	OR of abdominopelvic RT-exposed CCS vs population controls, – 1.99 (0.45-8.79), p=0.34	SB: high AB: unclear DB: unclear CF: high
Hawkins 1991	1037 CCS with 944 completed pregnancies	Not specified	Spontaneous abortion/miscarriage not further specified (n=67)	-	Frequencies (compared to unexposed to specific treatment) Exposed to RT on gonads or alkylating agents: – First pregnancies: 15 vs 8%, p=0.073 – Subsequent pregnancies: 14 vs 10 %, p=0.147 Exposed to RT to the abdomen or gonads only: – First pregnancy: 19 vs 8 %, p=0.018 – Subsequent pregnancies: 16 vs 10%, p=0.098 – All pregnancies: 17 vs 9%, p=0.006	SB: low AB: low DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis: 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up: Not reported.	Threatened abortion, >20 weeks of gestation (76, 4%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group - RT only: 1.98 (1.38-2.59)	SB: low AB: low DB: unclear CF: low

Lantinga 2006	41 CAYA cancer survivors with 75 pregnancies	Age at diagnosis: Median 7.0 (range 0-19) yrs Age at follow-up Median 27.0 (range 18-45) yrs	Spontaneous abortion/miscarriage not further specified (n=17, 22.7%)	-	"No association between miscarriages and infra-diaphragmatic irradiation not including the ovaries or any of the specific cytostatic drugs."	SB: low AB: low DB: unclear CF: high
Nielsen 2013	46 CCS with 85 pregnancies	Age at diagnosis: range 0-15 yr Age at follow-up: median 35.1 (28.4-48.6) yrs	Spontaneous abortion/miscarriage not further specified (n=11, 12.9%)	-	- 11/85 miscarriages, with highest incidence with increasing gonadotoxic treatment (no alkylating agents/alkylating agents/RT to abdomen). - Second-trimester abortions complicated by severe uterine bleeding (2) in survivors treated with RT on ovaries (n=26)	SB: low AB: low DB: unclear CF: high
Reulen 2009	4113 CCS with singleton pregnancies	Age at diagnosis: 0-14 yr, age at follow-up not specified	Pregnancy ending before gestational week 24 without the fetus surviving (n=607)	Types of childhood cancer adjusted for maternal age and birth order. Chemotherapy RR adjusted for treatment with radiotherapy, maternal age, and birth order. Radiotherapy adjusted for chemotherapy, maternal age and birth order.	RR (95% CI), compared to no radiotherapy - Nonbrain/nonabdominal: 1.0 (0.7-1.3) - Brain: 0.9 (0.7-1.2) - Abdominal: 1.4 (1.0-1.9) - Abdominal non Wilms: 1.5 (0.9-2.3) - Abdominal Wilms only: 1.4 (0.9-2.1) - P-value for heterogeneity: 0.151	SB: low AB: unclear DB: unclear CF: low
Sudour 2010	28 CAYA cancer survivors with 67 pregnancies	Age at diagnosis Median 11.3 yrs (range: 10 mths-17.6 yrs) Age at follow-up Median 27.1 (range 18-45) yrs	Spontaneous abortion/miscarriage not further specified (n=18, 26.9%)	-	18/67 of pregnancies: miscarriage - Abdominal RT excluding the pelvis: 53 pregnancies with 14 miscarriages - Abdominal RT including the pelvis : 14 pregnancies with 4 miscarriages	SB: high AB: low DB: unclear CF: high
Winther 2008	1688 CAYA cancer survivors with 1479 pregnancies	Age at diagnosis Younger than 20 years Age at follow-up At least 15 yrs	Spontaneous abortion/miscarriage (n=109, 7.4%)	adjusted for maternal age and calendar time	Adjusted PR (95% CI) compared to control group Radiotherapy: - No: PR 1.06 (0.82-1.36) - Yes: PR 1.58 (1.15-2.17)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 6/9, high in 3/9; Attrition bias low in 6/9, high in 1/9, unclear in 2/9; Detection bias unclear in 9/9; Confounding low in 3/9, high in 6/9.
Consistency:	0	No important inconsistency, 4 studies show significant effect of RT on uterus and ovaries, 3 studies show non-significant effects (including two relatively small cohorts). Two studies reported mainly descriptive data.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals, although three studies are too small (<100) to expect sufficient power
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		Statistically significant effect of (abdominal) radiotherapy on the risk of miscarriage in CAYA cancer survivors. (4 studies significant effect, 3 studies non-significant effect, 2 studies are mainly descriptive; 13,295 pregnancies; 1596 miscarriages, 4 multivariable analyses)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; yr, year; RR, relative risk; PR, proportion ratio; OR, odds ratio.

What is the risk of spontaneous abortion/miscarriage in CAYA cancer survivors by dose of radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Fetal loss after 4 weeks and before 20 weeks of gestation (n=112, 18.9%)	adjusted for age at pregnancy	OR (95% CI) compared with treated with surgery: - abd-Pelvic radiation: 0.91 (0.48-1.70) - CT with AA and Abd-Pelvic: 0.76 (0.34-1.72) - low dose (<2500 cGy) abd-Pelvic: 1.31 (0.68-2.53) - high dose (>2500 cGy) abd-Pelvic: 0.48 (0.21-1.11)	SB: high AB: low DB: unclear CF: low RB: high
Winther 2008	1688 CAYA cancer survivors with 1479 pregnancies	Age at diagnosis Younger than 20 years Age at follow-up At least 15 yrs	Spontaneous abortion/miscarriage (n=109, 7.4%)	adjusted for maternal age and calendar time	Adjusted PR (95% CI) compared to control group Level of irradiation - Low dose (<1 Gy) RT on ovary, uterus and (<0.1 Gy) on pituitary gland: PR 0.8 (0.3-1.7) - Low dose RT (<1 Gy) on ovary and uterus and high dose (~5-50 Gy) on pituitary gland: PR 1.8 (1.1-3.0) - High dose RT (~1-40 Gy) on ovary and uterus and low dose (<0.1 Gy) on pituitary gland: PR 2.8 (1.7-4.7)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 1/2, high 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	-1	Substantial inconsistency, 1 study suggests a dose relationship, 1 study does not suggest a dose relationship
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, moderate total number of events and narrow confidence intervals, but the 95% CI of the high dose PR overlaps the 95% CI of the low dose PR, so it is not entirely clear that there is a statistically significant dose relationship.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect

Dose-response:	0	Conflicting evidence of dose response, PR and 95% are different but no p-value for heterogeneity is given.
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Increased risk of miscarriage with increasing doses of abdominal and pituitary radiotherapy in CAYA cancer survivors (unclear if statistically significant, 2073 pregnancies, 582 miscarriages, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of spontaneous abortion/miscarriage in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Fetal loss after 4 weeks and before 20 weeks of gestation (n=112, 18.9%)	adjusted for age at pregnancy	OR (95% CI) compared with treated with surgery: - CT with AA: 1.06 (0.59-1.90)	SB: high AB: low DB: unclear CF: low RB: high
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Spontaneous abortion/miscarriage not further specified (n=326)	-	RR (95% CI), compared to siblings control group - Chemotherapy only: RR 1.07 (0.61-1.85) - Chemo+surgery: RR 0.90 (0.67-1.21)	SB: high AB: high DB: unclear CF: high RB: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis: 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up: Not reported.	Threatened abortion, <20 weeks of gestation (76, 4%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group - Chemo only: 1.48 (0.87-2.34)	SB: low AB: low DB: unclear CF: low RB: low
Nielsen 2013	46 CCS with 85 pregnancies	Age at diagnosis: range 0-15 yr Age at follow-up: median 35.1 (28.4-48.6) yrs	Spontaneous abortion/miscarriage not further specified (n=11, 12.9%)	-	11/85 miscarriages, with highest incidence with increasing gonadotoxic treatment (no alkylating agents/alkylating agents/alkylating agents and RT to abdomen).	SB: low AB: low DB: unclear CF: high RB: high
Reulen 2009	4113 CCS with	Age at diagnosis: 0-14 yr, age at	Pregnancy ending before gestational week 24 without the	Types of childhood cancer adjusted for maternal age and birth order.	RR (95% CI) compared with no chemotherapy received: - Chemotherapy: RR 1.2 (0.9-1.7)	SB: low AB: unclear

	singleton pregnancies	follow-up not specified	fetus surviving (n=607)	Chemotherapy RR adjusted for treatment with radiotherapy, maternal age, and birth order. Radiotherapy adjusted for chemotherapy, maternal age and birth order.	DB: unclear CF: low RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/5, high in 2/5; Attrition bias low in 3/5, high in 1/5, unclear in 1/5; Detection bias unclear in 5/5; Confounding low in 3/5, high in 2/5.
Consistency:	0	No important inconsistency for effect chemotherapy only, 4 studies show no significant effect of chemotherapy only;
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, one study is too small (<100) to expect sufficient power
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant effect of chemotherapy on the risk of miscarriage in CAYA cancer survivors. (4 studies non-significant effect, 1 descriptive study, 10,715 pregnancies, 1132 miscarriages, 3 multivariable analyses)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, report bias. RR, relative risk; PR, proportion ratio; OR, odds ratio; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of spontaneous abortion/miscarriage in CAYA cancer survivors treated with radiotherapy and chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Fetal loss after 4 weeks and before 20 weeks of gestation (n=112, 18.9%)	adjusted for age at pregnancy	OR (95% CI) compared with treated with surgery: - CT with AA and Abd-Pelvic RT: 0.76 (0.34-1.72)	SB: high AB: low DB: unclear CF: low RB: high
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Spontaneous abortion/miscarriage not further specified (n=326)	-	RR (95% CI), compared with siblings control group Treatment - Chemo+radiation: RR 1.42 (1.03-1.97) - Chemo+surgery+radiation: RR 1.19 (0.96-1.49)	SB: high AB: high DB: unclear CF: high RB: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis: 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up: Not reported.	Threatened abortion, <20 weeks of gestation (n=76, 4%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group - Chemoradiation: 1.08 (0.54-1.87)	SB: low AB: low DB: unclear CF: low RB: low
Lantinga 2006	41 CAYA cancer survivors with 75 pregnancies	Age at diagnosis: Median 7.0 (range 0-19) yrs Age at follow-up Median 27.0 (range 18-45) yrs	Spontaneous abortion/miscarriage not further specified (n=17, 22.7%)	-	"No association between miscarriages and infra-diaphragmatic irradiation not including the ovaries or any of the specific cytostatic drugs."	SB: low AB: low DB: unclear CF: high RB: high
Nielsen 2013	46 CCS with 85 pregnancies	Age at diagnosis: range 0-15 yr Age at follow-up: median35.1 (28.4-48.6) yrs	Spontaneous abortion/miscarriage not further specified (n=11, 12.9%)	-	11/85 miscarriages, with highest incidence with increasing gonadotoxic treatment (no alkylating agents/alkylating agents/alkylating agents and RT to abdomen).	SB: low AB: low DB: unclear CF: high RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/5, high in 2/5; Attrition bias low in 4/5, high in 1/5; Detection bias unclear in 5/5; Confounding low in 2/5, high in 3/5.
Consistency:	-1	Moderate inconsistency for effect chemotherapy and radiotherapy, 1 study shows significant effect of the combination of chemotherapy with radiotherapy on uterus and ovaries, 3 studies show non-significant effects for this combination, 1 study is mainly descriptive
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals, although two studies are too small (<100) to expect sufficient power
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		The found association was not adjusted for confounders
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of chemotherapy and radiotherapy (no specific field) on the risk of miscarriage in CAYA cancer as compared to sibling controls treated with surgery only. (1 study significant effect, 2 studies non-significant effect, 2 studies descriptive, 4563 pregnancies, 542 miscarriages, 2 multivariable analyses)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of spontaneous abortion/miscarriage in CAYA by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors with 1894 pregnancies	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Threatened abortion, <20 weeks of gestation (n=76, 4%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group By age at diagnosis (yrs) - 15-19: 0.76 (0.42-1.68) - 20-29: 1.15 (0.58-3.98)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only one study with medium total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Small magnitude of effect;
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of age at diagnosis on the risk of miscarriage in CAYA cancer survivors who were diagnosed after 15 yrs of age, compared to controls. (1 study non-significant effect, 1894 pregnancies; 76 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of terminations in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reinmuth 2008	44 CAYA cancer survivors achieved 69 pregnancies, 50 in female CCS	Mean age at diagnosis: 10.9 Mean age at follow-up: 24.3	Terminations not further specified (n=13)	-	13 of 50 (26.0%) pregnancies: abortion	SB: low AB: high DB: unclear CF: high RB: high
Winther 2008	1688 CAYA cancer survivors with 1479 pregnancies	Age at diagnosis: Younger than 20 years Age at follow-up: At least 15 yrs	Induced abortion (n=292, 19.7%)	adjusted for maternal age and calendar time	Adjusted RR (95% CI) compared to control group - Survivors: PR 1.08 (0.96 – 1.22)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2.
Consistency:	0	No important inconsistency, 1 study shows no increased risk on terminations and 1 study is mainly descriptive.
Directness:	-1	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, only one study investigated the risk compared to siblings and one small study reported the prevalence of abortions
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		The nature of the outcome may have given rise to report bias.
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant increased risk for medical induced terminations of pregnancy in CAYA cancer survivors as compared to controls. (1 study non-significant effect, 1 study mainly descriptive; 1,479 pregnancies; 1 multivariable analysis) The prevalence of medical induced terminations of pregnancy among CAYA cancer survivors was 26.0% in 1 study. (1 study; 69 pregnancies;13 terminations)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of terminations in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Terminations not further specified (n=695)	-	RR (95% CI), compared with siblings - Radiation only: RR 1.81 (1.53-2.13) - Sugery+radiation: RR 1.48 (1.09-2.02)	SB: high AB: high DB: unclear CF: high RB: high
Reulen 2009	4113 CCS singleton pregnancies	Age at diagnosis: 0-14 yr, age at follow-up not specified	Medically induced abortions (n=485)	Types of childhood cancer adjusted for maternal age and birth order. Chemotherapy RR adjusted for treatment with radiotherapy, maternal age, and birth order. Radiotherapy adjusted for chemotherapy, maternal age and birth order.	RR (95% CI), compared with no radiotherapy received - Brain: 0.8 (0.6-1.2) - Nonbrain/nonabdominal: 1.1 (0.8-1.5) - Abdominal: 1.1 (0.7-1.7) - Abdominal non Wilms: 0.9 (0.5-1.6) - Abdominal Wilms only: 1.4 (0.8-2.4) - P-value for heterogeneity: 0.457	SB: low AB: unclear DB: unclear CF: low RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	Moderate inconsistency, 1 study showed a significant increased risk after radiation, 1 study showed a non-significant increased risk after radiation of any radiation field
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, high total number of events and narrow confidence intervals, but only two studies of which one a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Different methodologies hinder comparability, both data from questionnaire
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of radiotherapy (no specific field) on the risk of terminations in CAYA cancer survivors as compared to sibling controls or no treated without RT. (1 study significant effect, 1 study non-significant effect; 6028 pregnancies; 1180 terminations; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of terminations in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Terminations not further specified (n=695)	-	RR (95% CI), compared with siblings - Chemotherapy only: RR 2.47 (1.58-3.88) - Chemo+surgery: RR 2.04 (1.56-2.68)	SB: high AB: high DB: unclear CF: high RB: high
Reulen 2009	4113 CCS singleton pregnancies	Age at diagnosis: 0-14 yr, age at follow-up not specified	Medically induced abortions (n=485)	Types of childhood cancer adjusted for maternal age and birth order. Chemotherapy RR adjusted for treatment with radiotherapy, maternal age, and birth order. Radiotherapy adjusted for chemotherapy, maternal age and birth order.	RR (95% CI), compared with no chemotherapy: - Chemotherapy: RR 0.8 (0.6-1.3)	SB: low AB: unclear DB: unclear CF: low RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias high in 1/2, unclear in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Some inconsistency, 1 study showed a significant increased risk after chemotherapy, 1 study showed no increased risk after chemotherapy
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, high total number of events and narrow confidence intervals, but only two studies of which one a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Different methodologies hinder comparability, both data from questionnaire
Quality of evidence:		⊕⊖⊖⊖ **Very low**

Conclusion:	Statistically significant effect of chemotherapy on the risk of terminations in CAYA cancer survivors as compared to siblings or treatment without chemotherapy. (1 study significant effect, 1 study non-significant effect ; 8142 pregnancies; 1180 terminations; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias.; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of terminations in CAYA cancer survivors treated with radiotherapy and chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Terminations not further specified (n=695)	-	RR (95% CI), compared with siblings - Chemo+radiation: RR 1.63 (1.14-2.31) - Chemo+surgery+radiation: RR 1.49 (1.18-1.89)	SB: high AB: high DB: unclear CF: high RB: high
Hawkins 1991	1037 CCS with 944 completed pregnancies	Not specified	Terminations not further specified (n=99)	-	Frequencies (compared to unexposed to specific treatment) Exposed to RT on gonads or alkylating agents: - First pregnancies: 30 vs 15%, p=0.006 - Subsequent pregnancies: 8 vs 8%	SB: low AB: low DB: unclear CF: high RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-2	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding high in 2/2
Consistency:	0	Very moderate inconsistency, 1 study showed a significant increased risk after the combination of radiation with chemotherapy, 1 study showed a significant increased risk in first but not in subsequent pregnancies
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Different methodologies hinder comparability, both data from questionnaire
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of chemotherapy and/or radiotherapy (to any field or gonadal) on the risk of terminations in CAYA cancer survivors as compared to siblings or no chemotherapy and/or radiotherapy. (2 studies significant effect; 5066 pregnancies; 794 terminations; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of still births in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Intrauterine death: Pregnancies ending with the death of the fetus in gestations week 20 or later (38, 2%); Neonatal death: death occurring within 1st week after birth (19, 1%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group Intrauterine death: - General ARR: 1.07 (0.86-1.65) Neonatal death: - General ARR: 1.03 (0.54-1.71)	SB: low AB: low DB: unclear CF: low RB: low
Winther 2008	1688 CAYA cancer survivors with 1479 pregnancies	Age at diagnosis Younger than 20 years Age at follow-up At least 15 yrs	Pregnancies ending with the death of the fetus in gestational week 28 or later (n=5)	adjusted for maternal age and calendar time	Adjusted RR (95% CI) compared to control group - Survivors: PR 1.1 (0.4 – 2.9)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	0	No inconsistencies, both studies found no increased risk of still births
Directness:	0	Results are direct, population broadly generalizable.
Precision:	-1	Some imprecision, low total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Largest publications indicate no increased risk. Outcomes are heterogeneous
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significantly increased risk of still births in CAYA cancer survivors as compared to controls. (2 studies non-significant effect; 3,373 pregnancies; 24 still births; 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of still births in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Perinatal deaths, includes stillbirths and neonatal deaths: pregnancies ending with the death of the fetus in gestational week 20 or later, or an infant death occurring before the 1st week of life (n=17)	adjusted for age at pregnancy	OR (95% CI, compared with treated with surgery: - abd-Pelvic radiation: 2.41 (0.50 – 11.5)	SB: high AB: low DB: unclear CF: low RB: high
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Still births not further specified (n=37)	-	RR (95% CI), compared with siblings control group - Radiation only: - - Surgery+radiation: RR 1.48 (0.55-3.95)	SB: high AB: high DB: unclear CF: high RB: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis: 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up: Not reported.	Intrauterine death: Pregnancies ending with the death of the fetus in gestations week 20 or later (38, 2%); Neonatal death: death occurring within 1st week after birth (19, 1%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	No significant increases in risks for intra-uterine death or neonatal death were observed across cancer diagnostic and treatment categories (data not shown).	SB: low AB: low DB: unclear CF: low RB: low
Reulen 2009	4113 CCS with singleton pregnancies	Age at diagnosis: 0-14 yr, age at follow-up not specified	Pregnancies ending with the death of the fetus in gestational week 24 or later (n=23)	Types of childhood cancer adjusted for maternal age and birth order. Chemotherapy RR adjusted for treatment with radiotherapy, maternal age, and birth order. Radiotherapy adjusted for	RR (95% CI), compared with no radiotherapy - Brain: 1.0 (0.3-3.4) - Nonbrain/nonabdominal: 2.0 (0.6-6.9) - Abdominal: 1.3 (0.2-7.2)	SB: low AB: unclear DB: unclear CF: low RB: high

				chemotherapy, maternal age and birth order.		
Winther 2012	752 female CAYA cancer survivors, 85 female CAYA cancer survivors with offspring with any genetic condition and in the sub-cohort 189 CAYA cancer survivors with offspring without genetic condition	Age at diagnosis Before 20 yrs of age Age at follow-up Above 15 yrs	Still births (n=5) and neonatal deaths (n=6) combined with congenital malformations and chromosomal abnormalities to: genetic disease (see: genetic abnormalities)		In female CCS: 5 stillbirths (4 after no ovarian or uterine RT, 1 after 0-0.50 Gy on ovaries and uterus) 6 neonatal deaths (4 after >0.50 Gy on ovaries and uterus)	SB: low AB: low DB: unclear CF: low (but for specific this outcome: high) RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Moderate limitations: Selection bias low in 3/5, high in 2/5; Attrition bias low in 3/5, high in 1/5, unclear in 1/5; Detection bias unclear in 5/5; Confounding low in 4/5, high in 1/5.
Consistency:	0	No inconsistencies. Four studies show no increased risk after radiotherapy. One study is a descriptive study.
Directness:	0	Results are direct, population broadly generalizable
Precision:	-1	Some imprecision, small total number of events and broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Largest publications indicate no increased risk. Outcomes are heterogeneous
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of radiotherapy (any field) on the risk of still births in CAYA cancer survivors. (4 studies no significant effect, 1 descriptive; 11382 pregnancies; 107 still births; 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of still births in CAYA cancer survivors by radiotherapy dose?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Perinatal deaths, includes stillbirths and neonatal deaths: pregnancies ending with the death of the fetus in gestational week 20 or later, or an infant death occurring before the 1st week of life (n=17)	adjusted for age at pregnancy	OR (95% CI, compared with treated with surgery: - low dose (<2500 cGy) abd-Pelvic RT: 1.96 (0.27 – 14.3) - high dose (>2500 cGy) abd-Pelvic RT: 4.33 (1.26 – 9.72)	SB: high AB: low DB: unclear CF: low RB: high
Signorello 2010 CCSS	1692 CAYA cancer survivors with 2942 pregnancies	Age at diagnosis: 0-4 yrs: 19% 5-9 yrs: 19% 10-14 yrs: 32% 15-20 yrs: 30% Age at follow-up At birth first child: < 20: 21% 20-24: 38% 25-29: 28% 30+: 12%	Still births and neonatal deaths combined: Still births: Pregnancies ending with the death of the fetus in gestational week 20 or later Neonatal deaths: immediately after birth or within first 28 days of life (n=60)	Calendar year of birth and maternal age	RR (95% CI), compared with no <u>radiotherapy to uterus and ovaries:</u> - 0.001-0.99 Gy: RR 0.7 (0.3-1.5) - 1.00-2.50 Gy: RR 2.4 (0.8-7.3) - 2.50-9.99 Gy: RR 1.9 (0.5-7.6) - 10 + Gy: RR 7.3 (2.3-23.0)	SB: low AB: low DB: unclear CF: low RB: high
Winther 2012	752 female CAYA cancer survivors, 85 female CAYA cancer survivors with offspring with any genetic condition and in the subcohort 189 CAYA cancer survivors	Age at diagnosis Before 20 yrs of age Age at follow-up Above 15 yrs	Still births (n=5) and neonatal deaths (n=6) combined with congenital malformations and chromosomal abnormalities to: genetic disease (see: genetic abnormalities)		In female CCS: 5 stillbirths (4 after no ovarian or uterine RT, 1 after 0-0.50 Gy on ovaries and uterus) 6 neonatal deaths (4 after >0.50 Gy on ovaries and uterus)	SB: low AB: low DB: unclear CF: low (but for specific this outcome: high)

	with offspring without genetic condition	RB: low

Quality of evidence:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 1/3.
Consistency:	0	No important inconsistencies. Two studies show increased risk after high dose radiotherapy on pelvis, one >25 Gy and one >10Gy. One study is a descriptive studies.
Directness:	0	Results are direct, population broadly generalizable
Precision:	-1	Some imprecision, small total number of events and broad confidence intervals
Publication bias:		Unlikely
Other considerations:		
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if there is a dose-response as there is not enough evidence yet
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of high-dose ovarian-abdominal radiotherapy (>10-25Gy) on the risk of still births in CAYA cancer survivors as compared to no radiotherapy. (2 studies significant effect, 1 descriptive; 4288 pregnancies; 88 still births; 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of still births in CAYA cancer survivors treated with radiotherapy, by age?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Signorello 2010 CCSS	1692 CAYA cancer survivors with 2942 pregnancies	Age at diagnosis: 0-4 yrs: 19% 5-9 yrs: 19% 10-14 yrs: 32% 15-20 yrs: 30% Age at follow-up At birth first child: < 20: 21% 20-24: 38% 25-29: 28% 30+: 12%	Still births and neonatal deaths combined: Still births: Pregnancies ending with the death of the fetus in gestational week 20 or later Neonatal deaths: immediately after birth or within first 28 days of life (n=60)	Calendar year of birth and maternal age	<u>Treatment before menarche:</u> RR (95% CI), compared to no radiotherapy to uterus and ovaries: - 0.001-0.99 Gy: RR 1.3 (0.5-3.9) - 1.00-2.50 Gy: RR 4.7 (1.2-19.0) - 2.50+ Gy: RR 12.3 (4.2-36.0) <u>Treatment after menarche:</u> RR (95% CI), compared to no radiotherapy to uterus and ovaries: - 0.001-0.99 Gy: RR 0.3 (0.1-1.0) - 1.00-2.50 Gy: RR 1.2 (0.2-6.4) - 2.50+ Gy: RR 0.2 (0.0-1.4)	SB: low AB: low DB: unclear CF: low RB: high

GRADE assessment:		
<u>Study design:</u>	+4	Retrospective cohort studies
<u>Study limitations:</u>	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
<u>Consistency:</u>	0	N/A, one study
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-2	Important imprecision, only 1 study with small number of events and wide confidence intervals
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	No evidence of dose response
<u>Plausible confounding</u>	0	No plausible confounding
<u>Other considerations:</u>		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of treatment with abdominal radiotherapy (>1.00 Gy) given before menarche on the risk of still births in CAYA cancer survivors as compared to no radiotherapy. (1 study significant effect; 2,942 pregnancies; 60 still births; 1 multivariable analysis) No statistically significant effect of treatment with abdominal radiotherapy given after menarche on the risk of still births in CAYA cancer survivors as compared to no radiotherapy. (1 study non-significant effect; 2,942 pregnancies; 60 still births; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of still births in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Perinatal deaths, includes stillbirths and neonatal deaths: pregnancies ending with the death of the fetus in gestational week 20 or later, or an infant death occurring before the 1st week of life (n=17)	adjusted for age at pregnancy	OR (95% CI, compared with treated with surgery: - CT with AA: 0.38 (0.04 – 3.80)	SB: high AB: low DB: unclear CF: low RB: high
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Still births not further specified (n=37)	-	RR (95% CI), compared with siblings - Chemotherapy only: RR 1.00 (0.13-7.71) - Chemo+surgery: RR 1.53 (0.50-4.71)	SB: high AB: high DB: unclear CF: high RB: high
Reulen 2009	4113 CCS singleton pregnancies	Age at diagnosis: 0-14 yr, age at follow-up not specified	Pregnancies ending with the death of the fetus in gestational week 24 or later (n=23)	Types of childhood cancer adjusted for maternal age and birth order. Chemotherapy RR adjusted for treatment with radiotherapy, maternal age, and birth order. Radiotherapy adjusted for chemotherapy, maternal age and birth order.	Treated with chemotherapy: - No: n=14 (0.7%) - Yes: n= 7 (0.5%) - P-value for heterogeneity: not presented	SB: low AB: unclear DB: unclear CF: low RB: high
Haggar 2014	1894 AYA cancer survivors	<u>Age at diagnosis</u> 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) <u>Age at follow-up</u>	Intrauterine death: Pregnancies ending with the death of the fetus in gestations week 20 or later (38, 2%); Neonatal death: death occurring within 1st week after birth (19, 1%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	No significant increases in risks for intra-uterine death or neonatal death were observed across cancer diagnostic and treatment categories (data not shown).	SB: low AB: low DB: unclear CF: low RB: low

	Not reported.

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 2/4, high in 1/4, unclear in 1/4; Detection bias unclear in 4/4; Confounding low in 3/4, high in 1/4.
Consistency:	0	No important inconsistency. None of the studies showed a significantly increased risk after chemotherapy.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	No important imprecision, small total number of events, although narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Outcome heterogeneous
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of chemotherapy on the risk of still births in CAYA cancer survivors. (4 studies non-significant effect; 10,630 pregnancies; 96 still births; 3 multivariable analyses)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of still births in CAYA cancer survivors treated by dose of chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Signorello 2010 CCSS	1692 CAYA cancer survivors with 2942 pregnancies	Age at diagnosis: 0-4 yrs: 19% 5-9 yrs: 19% 10-14 yrs: 32% 15-20 yrs: 30% Age at follow-up At birth first child: < 20: 21% 20-24: 38% 25-29: 28% 30+: 12%	Still births and neonatal deaths combined: Still births: Pregnancies ending with the death of the fetus in gestational week 20 or later Neonatal deaths: immediately after birth or within first 28 days of life (n=60)	Calendar year of birth and maternal age	RR (95% CI), compared to no alkylating agents: - AAD 1: 1.1 (0.5-2.5) - AAD 2: 0.8 (0.3-2.4) - AAD 3: 0.7 (0.2-2.8)	SB: low AB: low DB: unclear CF: low RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear 1/1; Confounding low in 1/1.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population broadly generalizable.
Precision:	-2	Some imprecision, only 1 study with small number of events, although narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of alkylating agent dose on the risk of still births in CAYA cancer survivors as compared to treated without alkylating agents. (1 study no significant effect; 2,942 pregnancies; 60 still births; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of still births in CAYA cancer survivors treated with radiotherapy and chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (n events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Perinatal deaths, includes stillbirths and neonatal deaths: pregnancies ending with the death of the fetus in gestational week 20 or later, or an infant death occurring before the 1st week of life (n=17)	adjusted for age at pregnancy	OR (95% CI, compared with treated with surgery: - CT with AA and Abd-Pelvic RT: 0.44 (0.44 – 17.2)	SB: high AB: low DB: unclear CF: low RB: high
Green 2002 (CCSS)	1915 CAYA cancer survivors with 4029 pregnancies	Age at diagnosis: <21 Age at follow-up: <15 - >35 yrs	Still births not further specified (n=37)	-	RR (95% CI), compared with siblings control group - Chemo+radiation: RR 1.19 (0.34-4.22) - Chemo+surgery+radiation: RR 1.49 (0.60-3.66)	SB: high AB: high DB: unclear CF: high RB: high
Hawkins 1991	1037 CCS with 944 completed pregnancies	Not specified	Still births not further specified (n=8)	-	Frequencies (compared to unexposed to specific treatment) Exposed to RT on gonads or alkylating agents: - First pregnancies: 0 vs 2% - Subsequent pregnancies: 0 vs 1%	SB: low AB: low DB: unclear CF: high RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/3, high in 2/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 1/3, high in 2/3.
Consistency:	0	No inconsistencies. Two studies show no increased risk after high dose radiotherapy on pelvis in combination with chemotherapy. One is a descriptive studies.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision, small total number of events, broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding

Other considerations: **Quality of evidence:**	Largest publications indicate no increased risk, but large confidence intervals and possibly inadequate power. Outcome heterogeneous ⊕⊕⊖⊖ **Low**
Conclusion:	No statistically significant effect of alkylating agents in combination with abdominal-pelvic radiation on the risk of still births in CAYA cancer survivors. (2 studies no significant effect, 1 descriptive; 5660 pregnancies; 62 still births; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; CNS, central nervous system; CRT, cranial radiotherapy; DB, detection bias; SB, selection bias; RB, report bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

<u>Working Group 2:</u> Who is at risk of complications during pregnancy? What is the risk, what should be done?

Index:

What is the risk of gestational hypertension in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Pregnancy-induced hypertension: not specified	-	n=4 (6%)	SB: high AB: high DB: unclear CF: high
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Pregnancy-induced hypertension: diastolic blood pressure > 90 mmHg (linearly assessed)	-	Diastolic blood pressure of full cohort: mean 81.9 mmHg (SD 12.9) p-value not significant as compared with controls (mean 81.4, SD 11.7)	SB: low AB: low DB: unclear CF: high RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Important limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only one study with small total number of included participants and large standard deviation
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant increased risk of gestational hypertension in CAYA cancer survivors as compared to controls. (1 study no significant effect, 1 study only descriptive; 111 pregnancies; no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational hypertension in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Pregnancy-induced hypertension: not specified	-	RT n=0 (0%) vs no RT n=4 (8%), p-value 0.57	SB: high AB: high DB: unclear CF: high
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Pregnancy-induced hypertension: diastolic blood pressure > 90 mmHg (linearly assessed)	-	Diastolic blood pressure after RT to abdomen (n=6): mean 80.8 mmHg (SD 14.6) p-value not significant as compared with controls (mean 81.4, SD 11.7)	SB: low AB: low DB: unclear CF: high RB: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Hypertension complicating pregnancy (excluding preexistent hypertension); ICD10: O13-O16 (n=169)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.18 (0.85 to 1.65) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.17 (0.75 to 1.82) - Nonbrain/nonabdominal: 1.64 (0.89 to 3.02) - Abdominal: 2.69 (1.72 to 4.22) - Abdominal non Wilms: 1.17 (0.48 to 2.83) - Abdominal Wilms only: 3.59 (2.27 to 5.68) - No RT Wilms only: 1.60 (0.70 to 3.64) - P-value for heterogeneity: <0.001	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 1/3, high in 2/3.
Consistency:	-1	Considerable inconsistencies. Two small studies show no increased risk after radiotherapy on the abdomen, one larger study shows an increased risk after radiotherapy exposing the uterus of ovaries.
Directness:	0	Results are direct, population broadly generalizable, outcome heterogeneous.
Precision:	-1	Some imprecision, small total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**

Conclusion:	Statistically significant effect of ovarian-abdominal radiotherapy on the risk of gestational hypertension in CAYA cancer survivors as compared to no radiotherapy. (1 study significant effect, 2 studies non-significant effect ; 2894 pregnancies; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational hypertension in CAYA cancer survivors by dose of radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2010 (update of Green 2002)	499 Wilms tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	Hypertension complicating pregnancy; ICD 642 (n=88)	-	Prevalence of pregnancy-induced hypertension by flank radiation therapy dose: - None: 23 (12.3%) - 0-15 Gy: 9 (18.4%) - 15-25 Gy: 23 (20.7%) - 25-35 Gy: 30 (35.7%) - >35 Gy: 12 (24.0%) - whole abdomen: 0 (0%) - Exact trend test P: <0.001	SB: low AB: high DB: unclear CF: high RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low; Attrition bias high; Detection bias unclear; Confounding high.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population broadly generalizable
Precision:	-2	Important imprecision, only 1 study and low total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Statistically significant increased risk of gestational hypertension with increasing doses of flank radiotherapy in CAYA Wilms tumor survivors. (1 study significant difference across radiation dose, 499 pregnancies, 88 hypertension complicating pregnancy, no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational hypertension in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Pregnancy-induced hypertension: not specified	-	chemotherapy n=2 (4%) vs no chemotherapy n=2 (9%), p-value 0.59	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Important limitations: Selection bias high; Attrition bias high; Detection bias unclear; Confounding high.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population broadly generalizable
Precision:	-2	Important imprecision, only 1 study and low total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant increased risk of chemotherapy on the risk of gestational hypertension in CAYA cancer survivors as compared to no chemotherapy. (1 study no significant effect, 71 pregnancies, 2 events, no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational hypertension in CAYA cancer survivors treated by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Hypertension complicating pregnancy (excluding preexistent hypertension); ICD10: O13-O16 (n=169)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.86 (0.56 to 1.32) - 10-14 yrs: 1.03 (0.60 to 1.79) - P-value for heterogeneity: 0.94	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding high.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population diagnosed only <15 yrs of age
Precision:	-2	Some imprecision, only 1 study with moderate total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of age at diagnosis on the risk of gestational hypertension in CAYA cancer survivors who were diagnosed before 15 yrs of age, compared to diagnosed between 0-4 yrs. (1 study non-significant effect, 2783 pregnancies; 169 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of pre-eclampsia in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Preeclampsia: the onset of hypertension, i.e., systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg from 20 weeks' gestation onwards accompanied by proteinuria (n=69, 4%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 1.44 (1.13-1.87)	SB: low AB: low DB: unclear CF: low RB: low
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Pre-eclampsia not further specified (n=0)	-	Full cohort: n=0 (0%), comparison n=40 (0.4%), p-value na	SB: low AB: low DB: unclear CF: high RB: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Preeclampsia AND eclampsia (130 CCS, 145 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) compared to control group - CCS: 1.01 (0.73-1.42) - cervical/genital cancer survivors: 0.99 (0.70-1.41)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 3/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 1/3.
Consistency:	-1	Inconsistencies: one found an increased risk, two (one large and one very small) studies did not find this association
Directness:	-1	Population and outcomes of Haggar et al are not broadly generalizable as the cohort was relatively old at diagnosis.
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Significant association found in cohort that was 15-39 yrs at diagnosis, relatively old
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant increased risk of pre-eclampsia in CAYA cancer survivors as compared to controls. (2 studies non-significant effect, 1 study significant effect; 3832 pregnancies; 344 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of pre-eclampsia in CAYA cancer survivors by radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Pre-eclampsia not further specified (n=0)	-	After RT to abdomen (n=6): n=0 (0%), general population 40 events (0.4%), p-value na	SB: low AB: low DB: unclear CF: high RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding high
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study with small study group
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant effect of radiotherapy on the risk of pre-eclampsia in CAYA cancer survivors as compared to controls. (1 study non-significant effect; 40 pregnancies; no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of pre-eclampsia in CAYA cancer survivors by chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias

GRADE assessment:	
Study design: Study limitations:	
Consistency: Directness:	
Precision: Publication bias: Effect size: Dose-response: Plausible confounding: Other considerations: **Quality of evidence:**	
Conclusion:	No studies reported on the risk of pre-eclampsia in CAYA cancer survivors treated with chemotherapy.

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of pre-eclampsia in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias

GRADE assessment:	
Study design: Study limitations:	
Consistency: Directness:	
Precision: Publication bias: Effect size: Dose-response: Plausible confounding: Other considerations: **Quality of evidence:**	
Conclusion:	No studies reported on the risk of pre-eclampsia in CAYA cancer survivors by age of diagnosis.

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of maternal anemia in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Maternal anemia not further specified (n=21, 1%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 1.31 (0.71-2.19)	SB: low AB: low DB: unclear CF: low RB: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Maternal anemia not further specified (18 CCS, 12 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) compared to control group - CCS: 1.30 (0.81-2.08) - cervical/genital cancer survivors: 0.65 (0.36-1.17)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	0	No inconsistencies, both studies found no increased risk of maternal anemia.
Directness:	0	Results are direct, population broadly generalizable, outcome homogeneous.
Precision:	-1	Some imprecision, low total number of events and moderate confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant increased risk of maternal anemia in CAYA cancer survivors as compared to controls. (2 studies non-significant effect; 3792 pregnancies; 39 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of maternal anemia in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Maternal anemia not further specified (18 CCS, 12 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) of CCS compared to control group: - RT only: 0.80 (0.12-5.45) - Surgery+RT: 1.98 (0.65-6.07) - Any RT: 0.97 (0.40-2.32)	SB: low AB: low DB: unclear CF: low RB: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Anemia complicating pregnancy, ICD10: O99.0 (n=143)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 0.88 (0.58 to 1.29) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.39 (0.89 to 2.18) - Nonbrain/nonabdominal: 0.57 (0.22 to 1.44) - Abdominal: 2.10 (1.27 to 3.46) - Abdominal non Wilms: 2.25 (1.13 to 4.49) - Abdominal Wilms only: 2.00 (1.13 to 3.57) - No RT Wilms only: 1.05 (0.36 to 3.12) - P-value for heterogeneity: 0.01	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	-1	Some inconsistency. One study found no increased risk after radiation, one study found an increased risk after radiotherapy exposing the abdomen.
Directness:	0	Results are direct, population broadly generalizable, outcome homogeneous.
Precision:	-1	Moderate imprecision, moderate total number of events and moderate confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Event occurs much more often in Reulen 2017
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of abdominal radiotherapy on the risk of maternal anemia in CAYA cancer survivors as compared to no radiotherapy. (1 study non-significant effect, 1 study significant effect; 4681 pregnancies; 173 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of maternal anemia in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Maternal anemia not further specified (18 CCS, 12 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) of CCS compared to control group: - Chemotherapy only: RR 2.45 (1.16-5.17) - Chemo+surgery: 1.23 (0.32-4.64) - Any chemo: 1.39 (0.73-2.63)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only one study and small total number of events
Publication bias:	0	Unlikely
Other considerations:	0	Remarkable that chemotherapy does, while combination with surgery does not pose an increased risk. Possibly due to other diagnosis and heterogeneity of chemotherapy.
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of chemotherapy on the risk of maternal anemia in CAYA cancer survivors as compared to controls. (1 study; 1898 pregnancies; 30 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of maternal anemia in CAYA cancer survivors treated with radiotherapy and chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Maternal anemia not further specified (18 CCS, 12 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) of CCS compared to control group: - Chemo+RT: 0.59 (0.08-4.14) - Chemo+surgery+RT: n/a	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only one study and small total number of events
Publication bias:	0	Unlikely
Other considerations:	0	
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of radiotherapy and chemotherapy on the risk of maternal anemia in CAYA cancer survivors as compared to controls. (1 study; 1898 pregnancies; 30 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of maternal anemia in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Maternal anemia not further specified (18 CCS, 12 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) of CCS compared to control group: - < 5 yrs: 2.03 (0.78-5.25) - 5-9 yrs: 1.32 (0.31-5.65) - 10-14 yrs: 0.31 (0.04-2.18) - 15-19 yrs: 1.53 (0.85-2.73)	SB: low AB: low DB: unclear CF: low RB: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Anemia complicating pregnancy; ICD10: O99.0 (n=143)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.75 (0.46 to 1.24) - 10-14 yrs: 0.67 (0.38 to 1.19) - P-value for heterogeneity: 0.15	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	0	No inconsistencies, both studies found no significant increased risk by age.
Directness:	0	Results are direct, population broadly generalizable, outcome homogeneous.
Precision:	-1	Moderate imprecision, adequate total number of events and moderate confidence intervals
Publication bias:	0	Unlikely
Other considerations:	0	Event occurs much more often in Reulen 2017
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant effect of age at diagnosis on the risk of maternal anemia in CAYA cancer survivors. (2 studies non-significant effect; 4681 pregnancies; 173 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational diabetes in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Gestational diabetes: not specified	-	n=0 (0%)	SB: high AB: high DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Gestational diabetes: diabetes first diagnosed during pregnancy (confirmed by clinical investigations) (n=101, 5%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 1.38 (1.09-2.98)	SB: low AB: low DB: unclear CF: low RB: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Any diabetes (yes/no) (gestational or mellitus) (11 CCS, 13 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) compared to control group: - CCS: 1.02 (0.53-1.95) - cervical/genital cancer survivors: 0.86 (0.49-1.53)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 2/2, high in 1/3.
Consistency:	-1	Inconsistencies, one study found an increased risk of gestational diabetes, one did not find this association to be significant. One small study reported no cases of gestational diabetes and had not control
Directness:	-1	Population not broadly generalizable, as Haggar et al consists of a cohort relatively old at cancer diagnosis.
Precision:	0	No important imprecision, adequate total number of events and moderate confidence intervals
Publication bias:	0	Unlikely
Other considerations:	0	
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant increased risk of gestational diabetes in CAYA cancer survivors as compared to controls. (1 study significant effect, 1 study non-significant effect, 1 descriptive study; 3863 pregnancies; 125 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational diabetes in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Pregnancy-induced hypertension: not specified	-	RT n=0 (0%) vs no RT n=0 (0%), no p-value	SB: high AB: high DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	<u>Age at diagnosis</u> 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) <u>Age at follow-up</u> Not reported.	Gestational diabetes: diabetes first diagnosed during pregnancy (confirmed by clinical investigations) (n=101, 5%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - RT only: 0.80 (0.25-2.56)	SB: low AB: low DB: unclear CF: low RB: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Any diabetes (yes/no) (gestational or mellitus) (11 CCS, 13 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) of CCS compared to control group: - RT only: 1.34 (0.18-9.84) - Surgery+RT: 0.95 (0.13-7.10) - Any RT: 0.90 (0.29-2.81)	SB: low AB: low DB: unclear CF: low RB: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	gestational diabetes; ICD10: O24.4 (n=56)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 0.91 (0.49 to 1.71) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.61 (0.72 to 3.59) - Nonbrain/nonabdominal: 1.61 (0.55 to 4.67) - Abdominal: 3.35 (1.41 to 7.93) - Abdominal non Wilms: 4.27 (1.54 to 11.83) - Abdominal Wilms only: 2.73 (1.00 to 7.62) - No RT Wilms only: n/a - P-value for heterogeneity: 0.23	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
<u>Study design:</u>	+4	Retrospective cohort studies

Study limitations:	0	Minor limitations: Selection bias low in 3/4/, high in 1/4; Attrition bias low in 3/3, high in 1/4; Detection bias unclear in 4/4; Confounding low in 3/3, high in 1/4
Consistency:	-1	Some inconsistency. Three studies found no significant increased risk after radiation, one study found an increased risk after radiotherapy on the abdomen.
Directness:	0	Results are direct, population broadly generalizable, outcome homogeneous.
Precision:	-1	Some imprecision, high total number of events, but the only study that showed a significant effect had broad confidence intervals
Publication bias:		Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of abdominal radiotherapy on the risk of gestational diabetes in CAYA cancer survivors. (2 studies non-significant effect of RT, 1 study significant effect of radiation field; 6646 pregnancies; 181 events, 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational diabetes in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Pregnancy-induced hypertension: not specified	-	RT n=0 (0%) vs no RT n=0 (0%), no p-value	SB: high AB: high DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Gestational diabetes: diabetes first diagnosed during pregnancy (confirmed by clinical investigations) (n=101, 5%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group - Chemo only: 1.25 (0.31-4.99)	SB: low AB: low DB: unclear CF: low RB: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Any diabetes (yes/no) (gestational or mellitus) (11 CCS, 13 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) of CCS compared to control group: - Chemotherapy only: RR 1.25 (0.31-4.99) - Chemo+surgery: 2.54 (0.67-9.65) - Any chemo: 1.26 (0.53-3.04)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 2/2, high in 1/3
Consistency:	0	No inconsistencies, three studies found no increased risk of gestational diabetes after chemotherapy.
Directness:	0	Results are direct, population broadly generalizable, outcome homogeneous.
Precision:	-1	Some imprecision, moderate total number of events and broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant effect of chemotherapy on the risk of gestational diabetes in CAYA cancer survivors as compared to controls (2 studies non-significant effect; 3863 pregnancies; 125 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational diabetes in CAYA cancer survivors treated with radiotherapy and chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Gestational diabetes: diabetes first diagnosed during pregnancy (confirmed by clinical investigations) (n=101, 5%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - Chemoradiation: 2.52 (1.12-5.09)	SB: low AB: low DB: unclear CF: low RB: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Any diabetes (yes/no) (gestational or mellitus) (11 CCS, 13 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) of CCS compared to control group: - Chemo+RT: 0.89 (0.13-6.12) - Chemo+surgery+RT: n/a	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	-1	Some inconsistencies, one study found an increased risk of gestational diabetes after treatment with chemotherapy and radiotherapy, one other study did not find this association to be significant.
Directness:	-1	Population not broadly generalizable, as Haggar et al consists of a cohort relatively old at cancer diagnosis
Precision:	-1	Some imprecision, moderate total number of events and broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Statistically significant effect of chemotherapy in combination with radiotherapy on the risk of gestational diabetes in CAYA cancer survivors as compared to controls. (1 study significant effect, 1 study non-significant effect; 3792 pregnancies; 125 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of gestational diabetes in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Gestational diabetes: diabetes first diagnosed during pregnancy (confirmed by clinical investigations) (n=101, 5%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group - 15-19: 1.12 (0.50-3.96) - 20-29: 1.64 (0.98-2.85)	SB: low AB: low DB: unclear CF: low RB: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Any diabetes (yes/no) (gestational or mellitus) (11 CCS, 13 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) of CCS compared to control group: - < 5 yrs: 0.99 (0.14-7.01) - 5-9 yrs: 3.16 (1.00-10.01) - 10-14 yrs: 1.25 (0.40-4.00) - 15-19 yrs:0.55 (0.18-1.70)	SB: low AB: low DB: unclear CF: low RB: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Gestational diabetes; ICD10: O24.4 (n=56)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.61 (0.28 to 1.34) - 10-14 yrs: 0.81 (0.36 to 1.80) - P-value for heterogeneity: 0.54	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No limitations: Selection bias low in 3/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 3/3.
Consistency:	0	No inconsistencies. Three studies found no significant effect of age.
Directness:	0	Results are direct, population broadly generalizable, outcome homogeneous.
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⨁⨁⨁⨁ **High**
Conclusion:		No statistically significant effect of age on the risk of gestational diabetes in CAYA cancer survivors (3 studies non-significant effect; 6575 pregnancies; 181 events, 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of malposition of the fetus in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Malpresentation included breech presentation, transverse lie, and other malpresentations (n=152, 9.3%)	-	OR (95% CI) of total CAYA cancer survivors group compared to control group: 1.06 (0.88 - 1.29)	SB: low AB: low DB: unclear CF: high RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Minor limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding high
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Some imprecision, only 1 study but with narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant increased risk of malposition of the fetus in CAYA cancer survivors in general compared to controls. (1 study; 1800 pregnancies; 152 events, no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of malposition of the fetus in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Malposition of fetus; ICD10: O32 (n=137)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.08 (0.78 to 1.62) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.12 (0.73 to 1.72) - Nonbrain/nonabdominal: 1.05 (0.52 to 2.10) - Abdominal: 1.07 (0.62 to 1.85) - Abdominal non Wilms: 0.66 (0.24 to 1.81) - Abdominal Wilms only: 1.33 (0.72 to 2.43) - No RT Wilms only: 1.15 (0.46 to 2.91) - P-value for heterogeneity: 0.96	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Moderate imprecision, only 1 study but with high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⨁⨁⨀⨀ **Low**
Conclusion:		No statistically significant effect of radiotherapy on the risk of malposition of the fetus in CAYA cancer survivors compared to survivors treated without radiotherapy. (1 study non-significant effect, 2783 pregnancies; 137 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of malposition of the fetus in CAYA cancer survivors treated by dose of radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2010 (update of Green 2002)	499 Wilm's tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	Malposition of the fetus; ICD 652 (n=39)	-	Prevalence of malposition of the fertus on relationship with flank radiation therapy dose: - None: 8 (4.3%) - 0-15 Gy: 6 (12.2%) - 15-25 Gy: 7 (6.3%) - 25-35 Gy: 11 (13.1%) - >35 Gy: 5 (10.0%) - whole abdomen: 2 (11.1%) - Exact trend test P: <0.04	SB: low AB: high DB: unclear CF: high RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low; Attrition bias high; Detection bias unclear; Confounding high.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only 1 study with low total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Statistically significant effect of radiotherapy dose on the risk of malposition of the fetus in CAYA cancer survivors. (1 study significant trend test, 499 pregnancies; 39 events, no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of malposition of the fetus in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
GRADE assessment:						
Study design: Study limitations:						
Consistency: Directness:						
Precision: Publication bias: Other considerations: Effect size: Dose-response: Plausible confounding: **Quality of evidence:**						
Conclusion:	No studies reported on the risk of malposition of the fetus a in CAYA cancer survivors treated with chemotherapy.					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of malposition of the fetus in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Malpresentation included breech presentation, transverse lie, and other malpresentations (n=152, 9.3%)	-	OR (95% CI) compared to control group: - 0-14 yr at diagnosis: OR 1.08 (0.71-1.63) - 15-24 yr at diagnosis: OR 0.86 (0.61–1.22)	SB: low AB: low DB: unclear CF: high RB: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Malposition of fetus; ICD10: O32 (n=137)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.88 (0.54 to 1.43) - 10-14 yrs: 0.72 (0.39 to 1.33) - P-value for heterogeneity: 0.30	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2.
Consistency:	0	No inconsistencies, two studies found no significant increased risk by age.
Directness:	0	Results are direct, population broadly generalizable, outcome homogeneous.
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⨁⨁⨁⨁ **High**
Conclusion:		No statistically significant effect of age at diagnosis on the risk of malposition of the fetus in CAYA cancer survivors. (2 studies non-significant effect; 4583 pregnancies; 189 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the rate of supervision of high-risk pregnancy in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Supervision of high risk pregnancy; ICD10: Z35 (n=114)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.19 (0.85 to 1.64) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 0.88 (0.55 to 1.40) - Nonbrain/nonabdominal: 0.95 (0.49 to 1.84) - Abdominal: 1.04 (0.58 to 1.87) - Abdominal non Wilms: 0.82 (0.33 to 2.07) - Abdominal Wilms only: 1.16 (0.58 to 2.33) - No RT Wilms only: 1.39 (0.43 to 4.50) - P-value for heterogeneity: 0.94 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.69 (0.38 to 1.25) - 10-14 yrs: 1.30 (0.78 to 2.17) - P-value for heterogeneity: 0.35	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only one study with high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant increased rate of supervision of high-risk pregnancy in CAYA cancer survivors as compared to general population. No statistically significant effect of radiotherapy on any field or age at diagnosis on the rate of supervision of high-risk pregnancy in CAYA cancer survivors. (1 study; 2783 pregnancies; 114 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of retained placenta/manual removal of the placenta in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Retained placenta (n=57, 3%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 0.98 (0.73-1.34) "No significant increases in risk for retained placenta across treatment categories."	SB: low AB: low DB: unclear CF: low RB: low
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Manual removal of the placenta (n=1)	-	Full cohort: n=1 (3%), control: n=251 (3%), p-value na After RT to abdomen (n=6): n=1 (3%), control: n=251 (3%), p-value 0.08	SB: low AB: low DB: unclear CF: high RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in1/2, high in 1/2.
Consistency:	0	No inconsistencies, two studies found no significant increased risk.
Directness:	0	Results are direct, population broadly generalizable, outcome homogeneous.
Precision:	-2	Considerable imprecision, low total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:	0	One study very small
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant increased risk of retained placenta in CAYA cancer survivors compared to controls. (2 studies non-significant effect; 1934 pregnancies; 58 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of placental pathologies in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Placental pathologies: placenta previa, placental abruption, manual removal of the placenta (n=45, 2.76%)	-	OR (95% CI) of total CAYA cancer survivors group compared to control group: 1.27 (0.88-1.82)	SB: low AB: low DB: unclear CF: high RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding high.
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only one study and small total number of events
Publication bias:	0	Unlikely
Other considerations:	0	
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ **Very low**
Conclusion:		No statistically significant increased risk of placental pathologies in CAYA cancer survivors as compared to controls. (1 study; 1800 pregnancies; no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

<u>Working Group 3</u>: Who is at risk of risks around the delivery? What is the risk, what should be done?

Index:

What is the risk of premature birth in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Premature birth: not specified (n=17)	-	n=17 (24%)	SB: high AB: high DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Premature birth: Before 37 weeks of gestation (n=284)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 1.68 (1.21-2.08)	SB: low AB: low DB: unclear CF: low
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Gestational age: linearly assessed (n= NA)	-	Gestational age in full cohort: 38.9 (SD 2.8) weeks, not different in children born to survivors compared with those born to healthy controls (39.2, SD 3.0 weeks)	SB: low AB: low DB: unclear CF: high
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Premature birth: <32 weeks (1.7%) and 32-36 weeks (6.3%)	-	Frequency compared to control group: - <32 weeks: 1.7% vs. 0.9% - 32-36 weeks: 6.3% vs. 4.4% - 37-41 weeks: 85.7% vs. 88.0% - P<0.001	SB: low AB: low DB: unclear CF: high
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Premature birth: < 37 weeks of gestation (130 CCS, 145 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) <37 vs. 37-41 - CCS: 1.54 (1.30-1.83); - cervical/genital cancer survivors: 1.33 (1.13-1.56);	SB: low AB: low DB: unclear CF: low
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Premature birth: Before 37 weeks of gestation (n=441)	maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and us of ART.	OR (95% CI) compared to sibling control group: 1.9 (1.4-2.4)	SB: high AB: low DB: unclear CF: low

Sudour 2010	28 CAYA cancer survivors with 67 pregnancies	Age at diagnosis Median 11.3 yrs (range: 10 mths-17.6 yrs) Age at follow-up Median 27.1 (range 18-45) yrs	Premature birth: <32 weeks (n=1) and 33-37 weeks (n=10)	-	Frequency in cohort: <32 weeks (n=1) 33-37 weeks (n=10)	SB: high AB: low DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 4/7, high in 3/7; Attrition bias low in 6/7, high in 1/7; Detection bias unclear in 7/7; Confounding low in 3/7, high in 4/7.
Consistency:	0	No important inconsistency, 4 studies show increased risk of premature deliveries, 1 study reported no significant difference but had a small cohort size, 2 studies reported mainly descriptive data.
Directness:	0	Results are direct, population broadly generalizable, outcome broadly homogeneous.
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Small magnitude of effect;
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		Increased risk of premature delivery in CAYA cancer survivors as compared to controls. (4 studies significant effect, 1 study non-significant effect, 2 studies mainly descriptive; 7,971 pregnancies; 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of premature birth in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Premature birth: not specified (n=16)	-	RT n=8 (42%) vs no RT n=8 (16%), p-value 0.025	SB: high AB: high DB: unclear CF: high
Van de Loo 2018	110 CCS with 47 pregnancies, 14 after RT	Not specified. RT-group 44 (80%) diagnosed before menarche	Prematurity: < 37 weeks of gestation (n=6, 43%)	Parity and maternal education	OR of abdominopelvic RT-exposed CCS vs population controls, – 9.74 (1.49-63.60), p=0.02	SB: high AB: unclear DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	<u>Age at diagnosis</u> 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) <u>Age at follow-up</u> Not reported.	Premature birth: Before 37 weeks of gestation (n=284)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - RT only: 1.78 (1.53-3.74)	SB: low AB: low DB: unclear CF: low
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Gestational age: Linearly assessed (n= NA)	-	After RT to abdomen (n=6): 34.9 (SD 4.3) weeks, in controls (39.2, SD 3.0 weeks), p=0.001	SB: low AB: low DB: unclear CF: high
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Premature birth: Before 37 weeks of gestation (130 CCS, 145 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) compared to control group: - RT only: 1.06 (0.56-2.00) - Surgery+RT: 1.04 (0.55-1.97) - Any RT: 1.57 (1.19-2.06)	SB: low AB: low DB: unclear CF: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Premature birth not further specified (n=280)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 2.15 (1.74 - 2.74) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 0.89 (0.65,1.22) - Nonbrain/nonabdominal: 1.20 (0.77,1.85)	SB: low AB: low DB: unclear CF: low

	- Abdominal: 1.70 (1.21,2.38) - Abdominal non Wilms: 1.34 (0.77,2.32) - Abdominal Wilms only: 1.89 (1.30,2.74) - No RT Wilms only: 1.37 (0.78,2.41) - P-value for heterogeneity: 0.002

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 4/6 high in 2/6; Attrition bias low in 4/6, high in 1/6, unclear in 1/6; Detection bias unclear in 6/6; Confounding low in 3/6, high in 3/6.
Consistency:	0	No important inconsistencies. Three studies show an increased risk after radiation, two show an increased risk after abdominal radiation, one shows an increased risk after abdominal radiation but also after no radiation.
Directness:	0	Results are direct, population broadly generalizable, outcome heterogeneous.
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊕ **High**
Conclusion:		Statistically significant effect of (abdominal) radiotherapy on the risk of premature birth in CAYA cancer survivors as compared to controls. (6 studies significant effect; 6700 pregnancies; 861 events, 4 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of premature birth in CAYA cancer survivors by dose of radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2010 (update of Green 2002)	499 Wilms tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	Premature birth: Before 36 weeks of gestation (n=81)	-	Prevalence by flank radiation therapy dose: - None: 19 (10.2%) - 0-15 Gy: 3 (6.1%) - 15-25 Gy: 23 (20.7%) - 25-35 Gy: 19 (22.6%) - >35 Gy: 11 (22.0%) - whole abdomen: 6 (33.3%) - Exact trend test P =0.001	SB: low AB: high DB: unclear CF: high
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Premature birth: Before 37 weeks of gestation (n=441)	maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and us of ART.	OR (95% CI) compared to not treated with any radiation: Dose in cGy to uterus all ages: - 0-10: 0.9- (0.6-1.4) - 10-50: 1.2 (0.7-2.0) - 50-250: 1.8 (1.1-3.0) - 250-500: 2.3 (1.0 – 5.1) - >500: 3.5 (1.5 – 8.0) Dose in cGy to uterus before menarche: - 0-10: 0.9 (0.5-1.9) - 10-50: 2.2 (1.0-4.8) - 50-250: 2.1 (1.0-4.6) - >250: 4.9 (1.7-13.9) Dose in cGy to uterus after menarche: - 0-10: 0.9 (0.6-1.5) - 10-20: 1.2-0.7-2.4) - 20-50: 0.9 (0.4-1.7) - 50-100: 1.5 (0.8-3.0) - >100: 1.2 (0.4-3.8) Dose in cGy to ovary: - 0-10: 0.9 (0.6-1.5) - 10-20: 1.2 (0.7-2.4) - 20-50: 0.9 (0.4-1.7) - 50-100: 1.5 (0.8-3.0) - >100: 1.2 (0.4-3.8) Radiation dose in cGy to pituitary - 0-50: 1.6 (1.0-2.7) - 50-250: 1.0 (0.6-1.9)	SB: high AB: low DB: unclear CF: low

		- 250-2000: 1.4 (0.7-2.7) - >2000: 1.0 (0.6-1.6)

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-2	Important limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2;
Consistency:	0	Minor inconsistency, both studies show dose relationship
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, adequate total number of events and adequate confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Although there seems to be a dose-response relationship, the evidence is of low quality
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Increased risk of premature delivery with increasing doses of ovarian-abdominal radiotherapy in CAYA cancer survivors. (2 studies significant effect; 2700 pregnancies; 522 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of premature birth in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Premature birth: not specified (n=17)	-	chemotherapy n=12 (26%) vs no chemotherapy n=4 (8%), p-value 0.55	SB: high AB: high DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Premature birth: Before 37 weeks of gestation (n=284)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - Chemotherapy only: 1.28 (0.99-2.14)	SB: low AB: low DB: unclear CF: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Premature birth: Before 37 weeks of gestation (130 CCS, 145 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity	Adjusted RR (95% CI) compared to control group: - Chemotherapy only: RR 1.99 (1.38-2.86) - Chemo+surgery: 1.63 (0.99-2.68) - Any chemo: 1.98 (1.58-2.48)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 1/3.
Consistency:	-2	Inconsistency, one study shows significant increased risk after chemotherapy, two studies show no increased risk.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, adequate total number of events and narrow confidence intervals.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Authors of Mueller 2009 express reservation regarding validity of the association in paper.
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of chemotherapy on the risk of premature birth in CAYA cancer survivors as compared to controls. (1 study significant effect, 1 study non-significant effect; 3863 pregnancies; 576 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of premature birth in CAYA cancer survivors by dose of chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Premature birth: Before 37 weeks of gestation (n=441)	maternal age, birth order, radiation to uterus, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and use of ART.	OR (95% CI) compared to not treated with any chemotherapy - AAD 0 (nonalkylator): OR 1.1 (0.6-1.9) - AAD 1: OR 1.3 (0.8-2.2) - AAD 2: OR 1.1 (0.6-1.8) - AAD 3: OR 1.6 (0.9-2.7)	SB: high AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, only one study; high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of alkylating agent dose on the risk of premature birth in CAYA cancer survivors. (1 study non-significant effect, 2201 pregnancies; 441 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of premature birth in CAYA cancer survivors treated with chemotherapy and radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Premature birth: Before 37 weeks of gestation (n=284)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - Chemoradiation:1.05 (0.43-2.88)	SB: low AB: low DB: unclear CF: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Premature birth: Before 37 weeks of gestation (130 CCS, 145 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) compared to control group: - Chemo+RT: 2.22 (1.45-3.40) - Chemo+surgery+RT: 2.14 (1.27-3.63)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	-4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	-1	Important inconsistency, 1 study shows no increased risk on terminations and 1 study shows a significant increased risk.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	Moderate imprecision, adequate total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Study not showing an association (Haggar et al) included a cohort relatively old at diagnosis
Quality of evidence:		⊕⊕⊕⊖**Moderate**
Conclusion:		Statistically significant effect of radiotherapy and chemotherapy vs. no radiotherapy and chemotherapy on the risk of premature delivery in CAYA cancer survivors as compared to controls. (1 study significant effect, 1 study non-significant effect; 3792 pregnancies; 559 events, 2 multivariable analyses)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of premature birth in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Premature birth: Before 37 weeks of gestation (n=284)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - 15-19: 1.32 (0.97-1.94) - 20-29: 1.66 (0.99-2.68)	SB: low AB: low DB: unclear CF: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Premature birth: Before 37 weeks of gestation (130 CCS, 145 cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity	Adjusted RR (95% CI) compared to control group: - < 5 yrs: 1.56 (0.88-2.78) - 5-9 yrs: 2.00 (1.28-3.10) - 10-14 yrs: 1.61 (1.16-2.24) - 15-19 yrs: 1.45 (1.15-1.82)	SB: low AB: low DB: unclear CF: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Premature birth not further specified (n=280)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.99 (0.70 - 1.39) - 10-14 yrs: 1.01 (0.68 - 1.49) - P-value for heterogeneity: 0.88	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 3/3; Attrition bias low in 3/3; Detection unclear in 3/3; Confounding low in 3/3
Consistency:	-1	Some inconsistency, 2 studies show no significant effect of age at diagnosis, 1 study shows a higher risk for children aged >5.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, high probability of underpowered studies for specific outcome and effect size remains below the clinical decision threshold
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		One of the studies not showing an association (Haggar et al) included a cohort relatively old at diagnosis
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of age at diagnosis (>5 yrs of age) on the risk of premature delivery in CAYA cancer survivors. (1 study significant effect, 2 studies non-significant effect; 6,575 pregnancies; 839 events, 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of low birth weight in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Birth weight: Linearly assessed	-	2718 (SD 582)	SB: high AB: high DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Low birth weight: Birthweight <2500 g (n=246, 13%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 1.51 (1.23-2.12)	SB: low AB: low DB: unclear CF: low
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Birth weight: Linearly assessed	-	Birthweight: CCS cohort 3266 (SD 705) grams, controls 3271 (SD 714), p-value=ns	SB: low AB: low DB: unclear CF: high
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Low birth weight: <1500 g: (n=32, 1.8%); 1500-2499 g: n=80, 4.4%)	-	Frequency compared to control group: - <1500 g: 1.8% vs. 0.9% - 1500-2499 g: 4.4% vs. 3.2% - P<0.001	SB: low AB: low DB: unclear CF: high
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Low birth weight: <2500 grams (CCS: n=103, 11.6%; cervical cancer: n=122, 12.2%)	state, maternal age, year of delivery, race/ethnicity, and parity, gestational length	Adjusted RR (95% CI) <: <2500 gram vs. 2500-3999 gram - CCS: 1.31 (1.10-1.57) - cervical/genital cancer survivors: 1.29 (1.10-1.53)	SB: low AB: low DB: unclear CF: low
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Low birth weight: Birth weight <2500 grams (n=441)	maternal age, radiation to uterus, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and us of ART.	OR (95% CI) compared to sibling control group: 2.1 (1.5-2.9)	SB: high AB: low DB: unclear CF: low
Sudour 2010	28 CAYA cancer survivors with 67 pregnancies	Age at diagnosis Median 11.3 yrs (range: 10 mths-17.6 yrs) Age at follow-up	Low birth weight: <2,500 g (n=7, 14%)	-	Frequency in cohort: Low birth weight in 7 (14%)	SB: high AB: low DB: unclear CF: high

	Median 27.1 (range 18-45) yrs

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 4/7, high in 3-7; Attrition bias low in 6/7, high in 1/7; Detection bias unclear in 7/7; Confounding low in 3/7, high in 4/7.
Consistency:	0	Minor inconsistency, 4 studies show increased risk of low birth weight, 1 study reported no significant difference but had a small cohort size, 2 studies reported mainly descriptive data.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals, although two studies are too small (<100) to expect sufficient power
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Small magnitude of effect;
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		Increased risk of delivering a child with a low birth weight in CAYA cancer survivors (<2,500 grams) as compared to controls. (4 studies significant effect, 1 study non-significant effect, 2 descriptive studies; 7,971 pregnancies; 1031 events, 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of low birth weight in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Low birth weight: Birthweight <2500 g (n=32, 6.8%)	adjusted for age at pregnancy, number of cigarettes smoked during pregnancy	OR (95% CI) compared with treated with surgery: - abd-pelvic radiation: OR 3.64 (1.33-9.96)	SB: high AB: low DB: unclear CF: low
Van de Loo 2018	110 CCS with 47 pregnancies, 14 after RT	Not specified. RT-group 44 (80%) diagnosed before menarche	Low birth weight: <2500 gram (n=5, 36%)	Parity and maternal education	OR of abdominopelvic RT-exposed CCS vs population controls, – 15.66 (1.43-171.35), p=0.02	SB: high AB: unclear DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	<u>Age at diagnosis</u> 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) <u>Age at follow-up</u> Not reported.	Low birth weight: Birthweight <2500 g (n=246, 13%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - RT only: 1.82 (1.26-2.59)	SB: low AB: low DB: unclear CF: low
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Birthweight: Linearly assessed	-	After RT to abdomen (n=6): 2503 (Sd 1026) grams, controls 3271 (SD 714), p-value=0.02	SB: low AB: low DB: unclear CF: high
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Low birth weight: <2500 grams (CCS: n=103, 11.6%; cervical cancer: n=122, 12.2%)	state, maternal age, year of delivery, race/ethnicity, and parity, gestational length	Adjusted RR (95% CI) in CCS compared to control group: - RT only: ns - Any RT: 1.38 (1.03-1.85)	SB: low AB: low DB: unclear CF: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Low birth weight: not further specified (n=201)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.22 (0.85 - 1.63) RR (95% CI), as compared to survivors treated without radiotherapy	SB: low AB: low DB: unclear CF: low

					- Brain: 1.28 (0.86,1.90) - Nonbrain/nonabdominal: 2.05 (1.25,3.35) - Abdominal: 2.31 (1.50,3.55) - Abdominal non Wilms: 1.40 (0.67,2.90) - Abdominal Wilms only: 2.85 (1.79,4.48) - No RT Wilms only: 1.75 (0.85,3.65) - P-value for heterogeneity: <0.001	
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Birth weight: Linearly assessed	-	RT 2436 (SD 737) vs no RT 2827 (SD 483) p-value 0.010	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 4/7, high in 3/7; Attrition bias low in 5/7, high in 1/7, unclear in 1/7; Detection bias unclear in 7/7; Confounding low in 4/7, high in 3/7.
Consistency:	0	No important inconsistency, 7 studies show increased risk of low(er) birth weight by abdominal RT
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and adequate confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⨁⨁⨁⨁ **High**
Conclusion:		Statistically significant effect of (abdominal) radiotherapy on the risk of delivering a child with a low birth weight in CAYA cancer survivors. (7 studies significant effect; 7290 pregnancies; 709 events; 5 multivariable analyses)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of low birth weight in CAYA cancer survivors by dose of radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Low birth weight: Birthweight <2500 g (n=32, 6.8%)	adjusted for age at pregnancy, number of cigarettes smoked during pregnancy	OR (95% CI) compared with treated with surgery: - low dose (<2500 cGy) abd-Pelvic RT: OR 2.10 (0.58-7.66) - high dose (>2500 cGy) abd-Pelvic RT: OR 3.49 (1.26-9.72)	SB: high AB: low DB: unclear CF: low
Green 2010 (update of Green 2002)	499 Wilms tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	Low birth weight: Birthweight <2500 g (n=67)	-	Prevalence by flank radiation therapy dose: - None: 17 (9.1%) - 0-15 Gy: 4 (8.2%) - 15-25 Gy: 14 (12.6%) - 25-35 Gy: 18 (21.4%) - >35 Gy: 8 (16.0%) - whole abdomen: 6 (33.3%) - Exact trend test P = 0.01	SB: low AB: high DB: unclear CF: high
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Low birth weight: Birth weight <2500 grams (n=441)	maternal age, radiation to uterus, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and us of ART.	OR (95% CI) compared to not treated with any radiation Dose in cGy to uterus: - 0-10: 1.5 (0.7-3.4) - 10-50: 1.2 (0.5-3.2) - 50-250: 1.2 (0.5-3.2) - 250-500: 4.3 (1.4-12.8) - >500: 6.8 (2.1-22.2) Dose in cGy to ovary: - 0-10: 1.6 (0.7-3.6) - 10-20: 0.5 (0.1-2.1) - 20-50: 2.3 (0.7-7.0) - 50-100: 0.9 (0.2-3.1) - >100: 1.7 (0.3-9.6) Radiation dose in cGy to pituitary - 0-50: 1.7 (0.7-3.9) - 50-250: 2.1 (0.8-5.9) - 250-2000: 1.4 (0.4-4.7) - >2000: 1.5 (0.6-3.8)	SB: high AB: low DB: unclear CF: low
Sudour 2010	28 CAYA cancer survivors with 67 pregnancies	Age at diagnosis Median 11.3 yrs (range: 10 mths-17.6 yrs) Age at follow-up	Low birth weight: <2,500 g (n=7, 14%)	-	No relationship between birthweight and radiation dose	SB: high AB: low DB: unclear CF: high

	Median 27.1 (range 18-45) yrs

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/4, high in 3/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 2/4, high in 2/4.
Consistency:	0	Moderate inconsistency. 3 studies reported a significant dose-dependent risk, 1 study reported no significant difference but had a small cohort size
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals, although one study is too small (<100) to expect sufficient power
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		Increased risk of delivering a child with a low birth weight after increasing doses of (abdominal) radiotherapy (>250 cGy) in CAYA cancer survivors. (3 studies significant effect, 1 study mainly descriptive; 3361 pregnancies; 547 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of low birth weight in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Low birth weight: Birthweight <2500 g (n=32, 6.8%)	adjusted for age at pregnancy, number of cigarettes smoked during pregnancy	OR (95% CI) compared with treated with surgery: - CT with AA: OR 0.49 (95% CI 0.10-2.47)	SB: high AB: low DB: unclear CF: low
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Low birth weight: Birthweight <2500 g (n=246, 13%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - Chemo only: 1.25 (0.57-2.98)	SB: low AB: low DB: unclear CF: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Low birth weight: <2500 grams (CCS: n=103, 11.6%; cervical cancer: n=122, 12.2%)	state, maternal age, year of delivery, race/ethnicity, parity and gestational length	Adjusted RR (95% CI) in CCS compared to control group: - Chemotherapy only: RR 1.56 (1.10-2.22) - Chemo+surgery: ns - Any chemo: 1.43 (1.16-1.78)	SB: low AB: low DB: unclear CF: low
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Birth weight: Linearly assessed	-	chemotherapy 2690 (SD 603) vs no chemotherapy 2774 (SD 560) p-value 0.57	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/4, high in 2/4; Attrition bias low in 3/3, high in 1/4; Detection unclear in 4/4; Confounding low in 3/3, high in 1/4
Consistency:	-1	Inconsistency: 1 study shows significant effect of chemotherapy, 3 studies show non-significant effects.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, high probability of underpowered studies for specific outcome and effect size remains below the clinical decision threshold
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Authors of Mueller 2009 express reservation regarding validity of the association in paper.
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Statistically significant effect of chemotherapy on the risk of delivering a child with a low birth weight in CAYA cancer survivors. (1 study significant effect, 3 non-significant effect; 4457 pregnancies; 400 events, 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of low birth weight in CAYA cancer survivors by dose of chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Low birth weight: Birth weight <2500 grams (n=441)	Maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and us of ART.	OR (95% CI) compared to not treated with any chemotherapy: - AAD 0 (nonalkylator): OR 1.5 (0.6-4.1) - AAD 1: OR 1.3 (0.5-3.1) - AAD 2: OR 0.7 (0.2-2.0) - AAD 3: OR 1.0 (0.4-2.9)	SB: high AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Moderate imprecision, adequate total number of events and adequate confidence intervals, but single study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant effect of alkylating agent dose/chemotherapy on the risk of delivering a child with a low birth weight in CAYA cancer survivors. (1 study non-significant effect, 2201 pregnancies, 441 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of low birth weight in CAYA cancer survivors treated with chemotherapy and radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Low birth weight: Birthweight <2500 g (n=32, 6.8%)	adjusted for age at pregnancy, number of cigarettes smoked during pregnancy	OR (95% CI) compared with treated with surgery: - CT with AA and Abd-Pelvic RT: OR 1.13 (95% CI 0.27-4.70)	SB: high AB: low DB: unclear CF: low
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Low birth weight: Birthweight <2500 g (n=246, 13%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - Chemoradiation: 1.52 (1.01-2.43)	SB: low AB: low DB: unclear CF: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Low birth weight: <2500 grams (CCS: n=103, 11.6%; cervical cancer: n=122, 12.2%)	state, maternal age, year of delivery, race/ethnicity, parity and gestational length	Adjusted RR (95% CI) in CCS compared to control group: - Chemo+RT: ns - Chemo+surgery+RT: ns	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 3/3; Detection unclear in 3/3; Confounding low in 3/3
Consistency:	-1	Inconsistency: 1 study shows significant effect of chemotherapy, 2 studies show non-significant effects.
Directness:	-1	Population not broadly generalizable as the study with significant effect (Haggar et al) included a cohort relatively old at diagnosis
Precision:	-1	Moderate imprecision, adequate total number of events and effect size remains below the clinical decision threshold
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response

Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⨁⊖⊖⊖ **Very low**
Conclusion:		Statistically significant effect of chemotherapy and radiotherapy on the risk of delivering a child with a low birth weight in CAYA cancer survivors as compared to controls. (1 study significant effect, 2 non-significant effect; 4386 pregnancies; 400 events, 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of low birth weight in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Low birth weight: Birthweight <2500 g (n=246, 13%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - 15-19: 1.34 (0.97-1.81) - 20-29: 1.75 (1.17-2.64)	SB: low AB: low DB: unclear CF: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Low birth weight: <2500 grams (CCS: n=103, 11.6%; cervical cancer: n=122, 12.2%)	state, maternal age, year of delivery, race/ethnicity, and parity	Adjusted RR (95% CI) compared to control group: - No association with age at diagnosis	SB: low AB: low DB: unclear CF: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Low birth weight: not further specified (n=201)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.83 (0.55 - 1.26) - 10-14 yrs: 0.85 (0.52 - 1.38) - P-value for heterogeneity: 0.43	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 3/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 3/3
Consistency:	-1	Some inconsistency, 2 studies show no significant effect of age at diagnosis, 1 study shows a higher risk for those diagnosed aged >20, which is mainly beyond the scope of this guideline
Directness:	-1	Population not broadly generalizable as the study with significant effect (Haggar et al) included a cohort relatively old at diagnosis
Precision:	-1	Moderate imprecision, adequate total number of events and effect size remains below the clinical decision threshold
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		1 study shows a higher risk for those diagnosed aged >20, which is mainly beyond the scope of this guideline
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Statistically significant effect of age at diagnosis (>20 yrs) on the risk of delivering a child with a low birth weight in CAYA cancer survivors. (1 study significant effect, 2 studies non-significant effect; 6,575 pregnancies; 569 events, 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivery of a child small for gestational age in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Child small for gestational age: <10% birth weight for gestational age and gender (CCS: n=96, 11.1%; cervical cancer: n=149, 15.3%)	state, maternal age, year of delivery, race/ethnicity, and parity	Adjusted RR (95% CI) compared to control group: - CCS vs controls: RR: 0.87 (0.67-1.12); - cervical/genital cancer survivors: RR 1.09 (0.90-1.33)	SB: low AB: low DB: unclear CF: low
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Child small for gestational age: birth weight in bottom 10th percentile of infants of the same sex born during the same gestational week (n=191, 9.5%)	maternal age, birth order, radiation to uterus, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and use of ART.	OR (95% CI) compared to control group: 1.0 (0.8-1.4)	SB: high AB: low DB: unclear CF: low
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Child small for gestational age: <10% birth weight for gestational age (n=4, 5%)	-	n=4 (5%)	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/3, high in 2/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 1/3
Consistency:	0	No important inconsistency, 2 studies show no increased risk of delivery of a child small for gestational age, one is a descriptive study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, adequate total number of events and effect size remains below the clinical decision threshold
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding

Other considerations:	
Quality of evidence:	⊕⊕⊖⊖ **Low**
Conclusion:	No statistically significant increased risk of delivering a child small for gestational age among CAYA cancer survivors in general as compared to controls. (2 studies non-significant effect, 1 descriptive study; 4,170 pregnancies; 344 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivery of a child small for gestational age in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Child small for gestational age: premature low birth weight infant (a low birth weight infant born before 37 weeks of gestation) (n=23, 4.9%)	adjusted for age at pregnancy, number of cigarettes smoked during pregnancy	OR (95% CI) compared with treated with surgery: - abd-Pelvic radiation: OR 3.29 (95% CI 0.97-11.1)	SB: high AB: low DB: unclear CF: low
Van de Loo 2018	110 CCS with 47 pregnancies, 14 after RT	Not specified. RT-group 44 (80%) diagnosed before menarche	Small for gestational age: <p10 (n=1)	Parity and maternal education	OR of abdominopelvic RT-exposed CCS vs population controls, – 1.67 (0.13-21.50), p=0.69	SB: high AB: unclear DB: unclear CF: high
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Child small for gestational age: Linearly assessed birth weight adjusted for gestational age	adjusted for gestational age	After RT to abdomen (n=6): 2503 (SD 1026) grams, controls 3271 (SD 714), p-value=ns when data is adjusted for gestational age	SB: low AB: low DB: unclear CF: high
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Child small for gestational age: <10% birth weight for gestational age (n=4, 5%)	-	RT n=3 (15%) vs no RT n=1 (2%), p-value 0.062	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/4, high 3/4; Attrition bias low in 2/4, high in 1/4, unclear in 1/4; Detection bias unclear in 4/4; Confounding low in 1/4, high in 3/4.
Consistency:	0	No important inconsistency, 4 studies show no increased risk on SGA
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, low total number of events and broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		

Quality of evidence:	⊕⊕⊖⊖ **Low**
Conclusion:	No statistically significant effect of (abdominal) radiotherapy on the risk of delivering a child small for gestational age among CAYA cancer survivors. (4 studies non-significant effect; 719 pregnancies; 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivery of a child small for gestational age in CAYA cancer survivors by dose of radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Child small for gestational age: premature low birth weight infant (a low birth weight infant born before 37 weeks of gestation) (n=23, 4.9%)	adjusted for age at pregnancy, number of cigarettes smoked during pregnancy	OR (95% CI) compared with treated with surgery: - low dose (<2500 cGy) abd-Pelvic RT: OR 2.69 (95% CI 0.52-13.9) - high dose (>2500 cGy) abd-Pelvic RT: OR 3.65 (95% CI 1.10-12.1)	SB: high AB: low DB: unclear CF: low
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Child small for gestational age: birth weight in bottom 10th percentile of infants of the same sex born during the same gestational week (n=191, 9.5%)	maternal age, birth order, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and us of ART.	OR (95% CI) compared to not treated with any radiation Dose in cGy to uterus all ages: - 0-10: 1.1 (0.6-2.1) - 10-50: 1.3 (0.6-2.8) - 50-250: 1.0 (0.4-2.2) - 250-500: 4.0 (1.6-9.8) - >500: 4.0 (1.6-9.8) Dose in cGy to ovary: - 0-10: 1.2 (0.6-2.2) - 10-20: 0.8 (0.3-2.5) - 20-50: 1.4 (0.6-3.3) - 50-100: 0.7 (0.2-2.2) - >100: 1.2 (0.2-6.7) Radiation dose in cGy to pituitary - 0-50: 1.7 (0.8-3.4) - 50-250: 1.7 (0.7-4.7) - 250-2000: 0.3 (0.1-1.4) - >2000: 1.1 (0.6-2.1)	SB: high AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	0	No important inconsistency, 2 studies show an increased risk on SGA after higher doses of radiotherapy on the uterus
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Substantial imprecision, low total number of events and broad confidence intervals
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant effect of (abdominal) radiotherapy dose (>2500 cGy) on the risk of delivering a child small for gestational age among CAYA cancer survivors. (2 studies significant effect; 2795 pregnancies; 214 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivery of a child small for gestational age in CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Child small for gestational age: <10% birth weight for gestational age (n=4, 5%)	-	chemotherapy n=3 (6%) vs no chemotherapy n=1 (4%), p-value 1.00	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-2	Some limitations: Selection bias high; Attrition bias high; Detection bias unclear; Confounding high
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, one study with low total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant effect of chemotherapy on the risk of delivering a child small for gestational age among CAYA cancer survivors. (1 study non-significant effect; 71 pregnancies; 4 events, no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivery of a child small for gestational age in CAYA cancer survivors by dose of chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Signorello 2006	2201 pregnancies from CAYA cancer survivors	mean maternal age 24.4 (SD 4.7)	Child small for gestational age: birth weight in bottom 10th percentile of infants of the same sex born during the same gestational week (n=191, 9.5%)	maternal age, birth order, radiation to uterus, sex of child, maternal drinking of alcohol during pregnancy, maternal smoking of cigarettes during pregnancy and us of ART.	OR (95% CI) compared to not treated with any chemotherapy - AAD 0 (nonalkylator): OR 1.1 (0.5-2.2) - AAD 1: OR 0.9 (0.5-1.9) - AAD 2: OR 0.8 (0.4-1.9) - AAD 3: OR 1.1 (0.5-2.4)	SB: high AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision, one study with moderate total number of events, but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of alkylating agents (dose) on the risk of delivering a child small for gestational age among CAYA cancer survivors. (1 study non-significant effect; 2201 pregnancies; 191 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivery of a child small for gestational age in CAYA cancer survivors treated with chemotherapy and radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Child small for gestational age: premature low birth weight infant (a low birth weight infant born before 37 weeks of gestation) (n=23, 4.9%)	adjusted for age at pregnancy, number of cigarettes smoked during pregnancy	OR (95% CI) compared with treated with surgery: - CT with AA and Abd-Pelvic RT: OR 1.78 (95% CI 0.39-8.08)	SB: high AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias high; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, one study and with low total number of events and broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⨁⊖⊖⊖ **Very low**
Conclusion:		No statistically significant effect of alkylating agents and abdominal radiotherapy on the risk of delivering a child small for gestational age among CAYA cancer survivors as compared to patients treated without chemotherapy and/or radiotherapy. (1 study non-significant effect; 594 pregnancies; 23 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivery of a child small for gestational age in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
GRADE assessment:						
Study design: Study limitations:						
Consistency: Directness:						
Precision: Publication bias: Other considerations: Effect size: Dose-response: Plausible confounding: **Quality of evidence:**						
Conclusion:	No studies reported on the risk on siring a child small for gestational age by age ag diagnosis.					

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of intrauterine/fetal growth restriction in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Not specified (n=119, 6%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group from general population: 1.21 (0.97–2.06)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	-1	Population not broadly generalizable, as Haggar et al included a cohort relatively old at cancer diagnosis
Precision:	-2	Important imprecision, moderate confidence intervals, one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant increased risk of intrauterine growth restriction in CAYA cancer survivors as compared to controls. (1 study; 1894 pregnancies; 119 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of early or threatened labor in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2010 (update of Green 2002)	499 Wilms tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	early or threatened labor (ICD 644) (N=99)	-	Prevalence by flank radiation therapy dose: - None: 28 (15%) - 0-15 Gy: 6 (12.2%) - 15-25 Gy: 28 (25.2%) - 25-35 Gy: 22 (26.2%) - >35 Gy: 15 (30%) - whole abdomen: 8 (44.4%) - Exact trend test P: <0.002	SB: low AB: high DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Threatened preterm labor: 20-36 weeks (N=54, 3%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 1.28 (0.88-1.88)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Heterogeneous, one study shows no increased risk on early or threatened labor, one study shows differences in prevalence by flank radiation therapy dose.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, small total number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Very different incidence, Haggar et al consists of a cohort relatively old at diagnosis
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Two studies reported on risk of early or threatened labor in CAYA cancer survivors and one showed a higher prevalence in patients treated with higher flank radiation therapy dose. (2 studies; 2393 pregnancies; 153 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of obstructed labor in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2010 (update of Green 2002)	499 Wilms tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	obstructed labor (ICD 660) (n=35)	-	Prevalence by flank radiation therapy dose: - None: 12 (6.4%) - 0-15 Gy: 1 (2.0%) - 15-25 Gy: 7 (6.3%) - 25-35 Gy: 13 (15.5%) - >35 Gy: 2 (4.0%) - whole abdomen: 0 (0.0%) - Exact trend test P: <0.23	SB: low AB: high DB: unclear CF: high
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	obstructed labor due to malposition of fetus (ICD 10 O64-O66) (n=119)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.04 (0.72 to 1.54) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.30 (0.83 to 2.03) - Nonbrain/nonabdominal: 0.86 (0.41 to 1.83) - Abdominal: 0.85 (0.43 to 1.69) - Abdominal non Wilms: 1.38 (0.43 to 1.69) - Abdominal Wilms only 0.54 (0.19 to 1.48) - No RT Wilms only: 0.76 (0.23 to 2.51) - P-value for heterogeneity: 0.46 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 1.08 (0.65 to 1.79) - 10-14 yrs: 1.78 (1.05 to 3.04) - P-value for heterogeneity: 0.05	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Minor inconsistencies. Both studies show no difference in prevalence by radiation therapy, but one study shows an increased risk in patients diagnosed at 10-14 yr.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, moderate confidence intervals
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Two studies reported on risk of obstructed labor in CAYA cancer survivors and show no increased risk by radiotherapy, one showed an increased risk in patients 10-14 yrs at diagnosis. (2 studies; 3,282 pregnancies; 154 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of abnormality of forces of labor in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2010 (update of Green 2002)	499 Wilms tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	obstructed labor (ICD 661) (n=32)	-	Prevalence by flank radiation therapy dose: - None: 14 (7.5%) - 0-15 Gy: 4 (8.2%) - 15-25 Gy: 7 (6.3%) - 25-35 Gy: 5 (6.0%) - >35 Gy: 2 (4.0%) - whole abdomen: 0 (0.0%) - Exact trend test P: <0.40	SB: low AB: high DB: unclear CF: high
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	obstructed labor due to malposition of fetus (ICD 10 O62, For example, primary inadequate contractions; secondary uterine inertia; precipitate labor; hypertonic, incoordinate, and prolonged uterine contractions) (n=76)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.14 (0.74 to 1.58) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 0.86 (0.48 to 1.55) - Nonbrain/nonabdominal: 1.04 (0.45 to 2.41) - Abdominal: 0.98 (0.44 to 2.17) - Abdominal non Wilms: 1.37 (0.47 to 4.00) - Abdominal Wilms only 0.74 (0.26 to 2.10) - No RT Wilms only: 0.81 (0.20 to 3.23) - P-value for heterogeneity: 0.96 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 1.29 (0.67 to 2.50) - 10-14 yrs: 1.77 (0.82 to 3.85) P-value for heterogeneity: 0.15	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No inconsistencies. Both studies show no difference in prevalence by radiation therapy, one study shows no difference in age at diagnosis.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, moderate confidence intervals
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Two studies reported on risk of abnormality of forces of labor in CAYA cancer survivors and show no increased risk by radiotherapy or age at diagnosis. (2 studies; 3,282 pregnancies; 108 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of umbilical cord complications in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2010 (update of Green 2002)	499 Wilms tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	Umbilical cord complications (ICD 663) (n=113)	-	Prevalence by flank radiation therapy dose: - None: 36 (19.3%) - 0-15 Gy: 16 (32.7%) - 15-25 Gy: 30 (27.0%) - 25-35 Gy: 16 (19.1%) - >35 Gy: 10 (20.0%) - whole abdomen: 5 (27.8%) - Exact trend test P: <0.89	SB: low AB: high DB: unclear CF: high
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Umbilical cord complications (ICD10-O69)(n=83)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.28 (0.86 to 1.88) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 0.99 (0.59 to 1.67) - Nonbrain/nonabdominal: 1.56 (0.79 to 3.10) - Abdominal: 0.86 (0.40 to 1.86) - Abdominal non Wilms: 0.56 (0.14 to 2.30) - Abdominal Wilms only 1.01 (0.43 to 2.39) - No RT Wilms only: 1.46 (0.51 to 4.15) - P-value for heterogeneity: 0.51 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.90 (0.49 to 1.62) - 10-14 yrs 1.21 (0.62 to 2.34) P-value for heterogeneity: 0.66	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	No inconsistencies. Both studies show no difference in prevalence by radiation therapy, one study shows no difference in age at diagnosis.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, moderate confidence intervals
Publication bias:	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Two studies reported on risk of umbilical cord complications in CAYA cancer survivors and show no increased risk by radiotherapy or age at diagnosis. (2 studies; 3,282 pregnancies; 196 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of premature rupture of the membranes (PROM) in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Green 2010 (update of Green 2002)	499 Wilms tumor survivors with 499 pregnancies	Age at diagnosis 55.7 ± 40.3 months at diagnosis Age at follow-up 31.2 ± 5.2 years at follow-up	Premature rupture of the membranes: ICD 658.1) (n=22)	-	Prevalence by flank radiation therapy dose: - None: 11 (5.9%) - 0-15 Gy: 1 (2.0%) - 15-25 Gy: 5 (4.5%) - 25-35 Gy: 1 (1.2%) - >35 Gy: 2 (4.0%) - whole abdomen: 2 (11.1%) - Exact trend test P: <0.25	SB: low AB: high DB: unclear CF: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Pre-labor rupture of membranes: PROM, rupture >12h before onset of labor irrespective of gestation at time of rupture (N=99, 5%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 0.99 (0.83-1.31)	SB: low AB: low DB: unclear CF: low
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	premature rupture of membranes (i.e., rupture of the amniotic sac; O42) (n=160)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 0.83 (0.63 to 1.09) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.49 (1.07 to 2.08) - Nonbrain/nonabdominal: 1.27 (0.77 to 2.09) - Abdominal: 1.01 (0.61 to 1.68) - Abdominal non Wilms: 1.18 (0.56 to 2.45) - Abdominal Wilms only 0.93 (0.51 to 1.70) - No RT Wilms only: 1.47 (0.69 to 3.15) - P-value for heterogeneity: 0.09 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 1.29 (0.91 to 1.83) - 10-14 yrs 0.92 (0.58 to 1.46) - P-value for heterogeneity: 0.99	SB: low AB: low DB: unclear CF: low

GRADE assessment:

Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/3; Attrition bias low in 2/3, high in 1/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 1/3.
Consistency:	0	All studies show no increased risk on PROM, not by flank radiation, radiotherapy or by age at diagnosis.
Directness:	0	Results are direct, population and outcomes broadly generalizable.
Precision:	-1	Some imprecision, broad confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Three studies reported on risk of premature rupture of the membranes (PROM) in CAYA cancer survivors and show no increased risk by radiotherapy or age at diagnosis. (3 studies; 5,176 pregnancies; 281 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of a fetal problems in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Fetal problems (such as poor fetal growth); ICD10: O36 (n=188)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.08 (0.82 to 1.41) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.24 (0.86 to 1.79) - Nonbrain/nonabdominal: 1.13 (0.65 to 1.97) - Abdominal: 1.26 (0.78 to 2.03) - Abdominal non Wilms: 0.80 (0.32 to 2.04) - Abdominal Wilms only 1.47 (0.88 to 2.47) - No RT Wilms only: 1.68 (0.75 to 3.79) - P-value for heterogeneity: 0.66 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 1.07 (0.72 to 1.60) - 10-14 yrs: 0.78 (0.47 to 1.30) - P-value for heterogeneity: 0.46	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Moderate imprecision, broad confidence intervals, one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		One study reported on the risk of fetal problems in CAYA cancer survivors and suggests no increased risk of fetal problems. (1 study; 2783 pregnancies; 188 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivery complicated by fetal stress in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	For example, labor and delivery complicated by fetal heart rate anomaly, meconium in amniotic fluid, or other evidence of fetal stress; ICD10: O68 (n=619)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.10 (0.96 to 1.24) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.11 (0.94 to 1.31) - Nonbrain/nonabdominal: 0.97 (0.74 to 1.27) - Abdominal: 0.84 (0.65 to 1.09) - Abdominal non Wilms: 1.01 (0.71 to 1.43) - Abdominal Wilms only 0.72 (0.51 to 1.03) - No RT Wilms only: 0.90 (0.59 to 1.37) - P-value for heterogeneity: 0.18 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.89 (0.73 to 1.09) - 10-14 yrs: 1.02 (0.80 to 1.28) - P-value for heterogeneity: 0.96	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Moderate imprecision, broad confidence intervals, one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		One study reported on the risk of delivery complicated by fetal stress in CAYA cancer survivors and suggests no increased risk as compared to controls. (1 study; 2783 pregnancies; 619 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of a long labor in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Long labor; ICD10: O63 (n=335)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.21 (0.98 to 1.44) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.01 (0.78 to 1.31) - Nonbrain/nonabdominal: 1.08 (0.74 to 1.57) - Abdominal: 0.93 (0.64 to 1.33) - Abdominal non Wilms: 1.35 (0.87 to 2.09) - Abdominal Wilms only 0.66 (0.39 to 1.11) - No RT Wilms only: 0.88 (0.44 to 1.77) - P-value for heterogeneity: 0.93 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.94 (0.71 to 1.25) - 10-14 yrs: 0.90 (0.64 to 1.27) - P-value for heterogeneity: 0.55	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Moderate imprecision, broad confidence intervals, one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		One study reported on the risk of a long labor in CAYA cancer survivors and suggests no increased risk as compared to controls. (1 study; 2783 pregnancies; 335 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of antepartum hemorrhage in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Antepartum hemorrhage: occurrence of placental abruption, placenta previa, or other excessive bleeding during labor and delivery (n=17, 1%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 0.92 (0.59–1.78)	SB: low AB: low DB: unclear CF: low
Van der Kooi 2018	186 first singleton live births in women diagnosed with cancer between 0-14 years and 588 in women diagnosed between 15-24 yrs	Not specified	Antepartum hemorrhage ICD 10 O441,O45, O46	Matched on age, diagnosis date and deprivation quintile	0-14 yr RR 0.55 (0.24 – 1.24) 15-24 yr RR 1.31 (0.81 – 2.13)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2
Consistency:	0	No inconsistencies, both studies show no increased risk
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, moderate confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Two studies reported on the risk of antepartum hemorrhage in CAYA cancer survivors and suggest no increased risk as compared to controls. (2 studies; 2668 pregnancies; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of failure to progress in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Antepartum hemorrhage: occurrence of placental abruption, placenta previa, or other excessive bleeding during labor and delivery (n=32, 2%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 1.51 (0.97-2.37)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	-1	Population not broadly generalizable as the included study consisted of a cohort relatively old at cancer diagnosis
Precision:	-2	Moderate imprecision, broad confidence intervals, one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		One study reported on the risk of failure to progress in CAYA cancer survivors and suggests no increased risk as compared to controls. (1 study; 1894 pregnancies; 32 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of induction of labor in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Induction of labor: performed either by intravaginal or oral administration of misoprostol, intravenous administration of oxytocin, or mechanical rupture of amniotic membranes; (n=344, 19.1%)	-	OR (95% CI) compared to control group: - total: OR 1.17 (1.02–1.35) - age at diagnosis 0-14 yrs: OR 1.38 (1.02–1.86) - age at diagnosis 15-24 yrs: OR 1.19 (0.94–1.50)	SB: low AB: low DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding high
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Moderate imprecision, broad confidence intervals, one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		One study reported on the risk of induction of labor in CAYA cancer survivors and suggests an increased risk as compared to controls, specifically when diagnosed aged 0-14 yrs. (1 study; 1800 pregnancies; 344 events, no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of vaginal birth in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Vaginal birth	-	OR (95% CI) compared to control group: - total: OR 0.86 (0.77–0.97) - age at diagnosis 0-14 yrs: OR 0.70 (0.54–0.90) - age at diagnosis 15-24 yrs: OR 0.91 (0.75–1.11)	SB: low AB: low DB: unclear CF: high
Van der Kooi 2018	186 first singleton live births in women diagnosed with cancer between 0-14 years and 588 in women diagnosed between 15-24 yrs	Not specified	Spontaneous vaginal birth (n=401)	Matched on age, diagnosis date and deprivation quintile	RR (95% CI) compared to matched controls: 0-14 yr RR 0.63 (0.47 – 0.83) 15-24 yr RR 0.72 (0.61 – 0.84)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	0	Consistent results, lower incidence of vaginal birth in CAYA cancer survivors
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⨁⨁⨁⨁ **High**
Conclusion:		Statistically significant lower incidence of vaginal birth in CAYA cancer survivors (2 studies; 2574 pregnancies; no multivariable analysis, 1 matched control group)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of assisted vaginal delivery in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Assisted vaginal delivery (n=12, 30%)	-	Frequency compared to control group: Survivors: n=12 (30%), controls: n=2746 (31%), p-value=ns	SB: low AB: low DB: unclear CF: high
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Instrumental vaginal delivery (including delivery by forceps or vacuum-assisted delivery)(n=241, 4.3%)	-	OR (95% CI) compared to control group: - total group: OR 1.07 (95% CI 0.91-1.25)	SB: low AB: low DB: unclear CF: high
Van der Kooi 2018	186 first singleton live births in women diagnosed with cancer between 0-14 years and 588 in women diagnosed between 15-24 yrs	Not specified	Assisted vaginal delivery or breech (n=106)	Matched on age, diagnosis date and deprivation quintile	RR (95% CI) compared to matched controls: – 0-14 yr RR 1.25 (0.87 – 1.79) – 15-24 yr RR 1.11 (0.89 – 1.39)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 3/3
Consistency:	0	None of the studies show an increased or decreased risk on assisted vaginal delivery
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant higher incidence of assisted vaginal delivery in CAYA cancer survivors (2 studies; 1840 pregnancies; 253 events, no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of assisted vaginal delivery in CAYA cancer survivors after radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Assisted vaginal delivery (n=12, 30%)	-	After RT to abdomen (n=6): Survivors: n=1 (17%), controls: n=2746 (31%), p-value=ns	SB: low AB: low DB: unclear CF: high
GRADE assessment:						
Study design:	+4	Retrospective cohort studies				
Study limitations:	-1	Some limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding high				
Consistency:	0	N/A, only one study				
Directness:	-2	Extremely small remaining sub-cohort.				
Precision:	0	No important imprecision, narrow confidence intervals				
Publication bias:	0	Unlikely				
Effect size:	0	No large magnitude of effect				
Dose-response:	0	No evidence of dose response				
Plausible confounding:	0	No plausible confounding				
Other considerations:						
Quality of evidence:		⊕⊖⊖⊖ **Very low**				
Conclusion:		No statistically significant higher incidence of assisted vaginal delivery in CAYA cancer survivors after radiotherapy (1 study, 6 pregnancies, 1 event, no multivariable analysis)				

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of assisted vaginal delivery in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Instrumental vaginal delivery (including delivery by forceps or vacuum-assisted delivery)(n=241, 4.3%)	-	OR (95% CI) compared to control group: – 0-14 yr at diagnosis: OR 1.20 (95% CI 0.84-1.70) – 15-24 yr at diagnosis: OR 1.14 (95% CI 0.87-1.49)	SB: low AB: low DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1
Consistency:	-1	One study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant higher incidence of assisted vaginal delivery in CAYA cancer survivors in any age category (2 studies; 2574 pregnancies; 347 events, one age matched control group)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of any cesarean section delivery in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Any cesarean delivery (n=342, 18%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - General: 2.62 (2.22-3.04)	SB: low AB: low DB: unclear CF: low
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Combination of elective and urgent cesarean delivery, (n=424, 23.6%)	-	OR (95% CI) compared to control group: - total group: OR 1.15 (95% CI 1.01-1.31)	SB: low AB: low DB: unclear CF: high
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	>41 weeks (n not specified)	Any c-section (CCS n=163, cervical n=154)	state, maternal age, year of delivery, race/ethnicity, and parity, gestational length	Adjusted RR (95% CI) compared to control group: - CCS: 1.15 (0.99 – 1.33); - cervical/genital cancer survivors: 0.97 (0.83-1.13)	SB: low AB: low DB: unclear CF: low
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Cesarean delivery, not specified (n=23)	-	Overall n=23 (32%)	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/4, high in 1/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 2/4, high in 2/4.
Consistency:	-1	Two studies show an increased incidence, one study does not see a changed incidence
Directness:	0	Population of Haggar et al not broadly generalizable as the included study consisted of a cohort relatively old at cancer diagnosis
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		

Quality of evidence:	⊕⊕⊖⊖ **Low**
Conclusion:	Statistically significant higher incidence of any cesarean section in CAYA cancer survivors (4 studies; 5663 pregnancies; 943 events; 2 multivariable analysis).

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of any cesarean section delivery in CAYA cancer survivors by radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Any cesarean delivery (n=342, 18%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - RT only: 1.35 (1.11-2.80) - Chemoradiation: 1.45 (0.96-2.09)	SB: low AB: low DB: unclear CF: low
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Cesarean delivery, not specified (n=23)	-	RT n=7 (37%) vs no RT n=16 (33%), p-value 0.74	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2.
Consistency:	-1	Larger studies shows increased risk after RT only, other study does not show an effect.
Directness:	-1	Population of Haggar et al not broadly generalizable as the included study consisted of a cohort relatively old at cancer diagnosis
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant higher incidence of any cesarean section in CAYA cancer survivors after radiotherapy (1 study significant effect, 1 study non-significant effect, 1965 pregnancies, 365 events, one multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of any cesarean section delivery in CAYA cancer survivors by chemotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Any cesarean delivery (n=342, 18%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: Treatment type - Chemo only: 1.78 (1.27-2.49) - Chemoradiation: 1.45 (0.96-2.09)	SB: low AB: low DB: unclear CF: low
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Cesarean delivery, not specified (n=23)	-	Overall n=23 (32%) - chemotherapy n=15 (33%) vs no chemotherapy n=8 (36%), p-value 0.76	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 1/2, high in 1/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2.
Consistency:	-1	Larger studies shows increased risk after RT only, other study does not show an effect.
Directness:	-1	Population of Haggar et al not broadly generalizable as the included study consisted of a cohort relatively old at cancer diagnosis
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant higher incidence of any cesarean section in CAYA cancer survivors after chemotherapy (1 study significant effect, 1 study non-significant effect, 1965 pregnancies, 365 events, one multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of any cesarean section delivery in CAYA cancer survivors by age?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Any cesarean delivery (n=342, 18%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: By age at diagnosis (yrs) - 15-19: 0.66 (0.47-1.88) - 20-29: 1.22 (0.97-3.32) - 30-39: 3.16 (1.01-10.0)	SB: low AB: low DB: unclear CF: low
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Combination of elective and urgent cesarean delivery, (n=424, 23.6%)	-	OR (95% CI) compared to control group: - 0-14 yr at diagnosis: OR 1.48 (95% CI 1.11-1.96) - 15-24 yr at diagnosis: OR 1.04 (95% CI 0.83-1.30)	SB: low AB: low DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2.
Consistency:	-1	There are some inconsistencies. One study shows the increased risk especially in the subgroup diagnosed 30-39 yrs of age, while another study shows the increased risk only in the group 0-14 yrs at diagnosis.
Directness:	-1	Population of Haggar et al not broadly generalizable as the included study consisted of a cohort relatively old at cancer diagnosis
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Statistically significant higher incidence of any cesarean section in CAYA cancer survivors in the group 0-14 yrs at diagnosis but not in the group 15-25 yrs at diagnosis (1 study significant effect, 1 study non-significant effect, 3694 pregnancies, 766 events, one multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of an elective/primary cesarean delivery in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Elective cesarean delivery, and combination (n=153, 9.4%)	-	OR (95% CI) compared to control group: 1.36 (95% CI 1.11-1.67)	SB: low AB: low DB: unclear CF: high
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	>41 weeks (n not specified)	primary c-section (CCS n=145, cervical n=110)	state, maternal age, year of delivery, race/ethnicity, and parity, gestational length	Adjusted RR (95% CI) compared to control group: - CCS vs. controls: 1.14 (0.97-1.33); - cervical/genital cancer survivors vs. controls: 1.11 (0.92-1.32);	SB: low AB: low DB: unclear CF: low
Reulen 2017	2783 pregnancies from 1712 female CCS	Mean maternal age was 28.7 (SD = 5.4) yrs	Elective cesarean section (n=390)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.39 (1.16 to 1.70)	SB: low AB: low DB: unclear CF: low
Van der Kooi 2018	186 first singleton live births in women diagnosed with cancer between 0-14 years and 588 in women diagnosed between 15-24 yrs	Not specified	Elective cesarean section (n=49)	Matched on age, diagnosis date and deprivation quintile	RR (95% CI) compared to matched controls: - 0-14 yr RR 3.15 (2.04 – 4.88) - 15-24 yr RR 1.79 (1.34– 2.39)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 4/4; Attrition bias low in 4/4; Detection bias unclear in 4/4; Confounding low in 3/4, high in 1/4.
Consistency:	0	Some inconsistencies. Three studies show an increased risk on an elective c-section, one shows not a significant difference.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⨁⨁⨁⨁ **High**
Conclusion:		Statistically significant increased risk of an elective/primary caesarean section in CAYA cancer survivors in general, as compared to controls. (3 studies significant effect, 1 study non-significant effect; 7255 pregnancies; 702 events, 2 multivariable analysis, one matched)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of an elective/primary cesarean delivery in CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	2783 pregnancies from 1712 female CCS	Mean maternal age was 28.7 (SD = 5.4) yrs	Elective cesarean section (n=390)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.39 (1.16 to 1.70) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.15 (0.90 to 1.49) - Nonbrain/nonabdominal: 0.90 (0.59 to 1.37) - Abdominal: 1.46 (1.07 to 1.99) - Abdominal non Wilms: 1.36 (0.87 to 2.13) - Abdominal Wilms only: 1.46 (1.01 to 2.11) - No RT Wilms only: 1.10 (0.57 to 2.12) - P-value for heterogeneity: 0.07	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1.
Consistency:	0	The study shows an increased risk after abdominal radiotherapy, especially in Wilms patients.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	No important imprecision, high total number of events and narrow confidence intervals, but only one study.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		Statistically significant effect of radiotherapy on the risk of an elective/primary caesarean section in CAYA cancer survivors, as compared to controls, specifically after abdominal radiotherapy in Wilms survivors. (1 study significant effect; 2,783 pregnancies, 390 events, multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of an elective/primary cesarean delivery in CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	2783 pregnancies from 1712 female CCS	Mean maternal age was 28.7 (SD = 5.4) yrs	Elective cesarean section (n=390)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.79 (0.60 to 1.05) - 10-14 yrs: 0.85 (0.61 to 1.19) - P-value for heterogeneity: 0.004	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1.
Consistency:	0	The study shows no increased risk by age at diagnosis.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	No important imprecision, high total number of events and narrow confidence intervals, but only one study.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant effect of age at diagnosis on the risk of an elective/primary caesarean section in CAYA cancer survivors, as compared to controls, specifically after abdominal radiotherapy in Wilms survivors. (1 study significant effect; 2,783 pregnancies, 390 events, multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of a secondary/urgent cesarean delivery in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Secondary caesarean section (n=5, 12.5%)	-	Frequency compared to control group: Survivors: n=5 (12.5%), controls: n=1296 (14%), p-value=ns	SB: low AB: low DB: unclear CF: high
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Elective and urgent cesarean delivery, and combination (n=243, 14.9%)	-	OR (95% CI) compared to control group: 1.04 (95% CI 0.89-1.23)	SB: low AB: low DB: unclear CF: high
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Emergency cesarean section (n=387)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.08 (0.91 to 1.27)	SB: low AB: low DB: unclear CF: low
Van der Kooi 2018	186 first singleton live births in women diagnosed with cancer between 0-14 years and 588 in women diagnosed between 15-24 yrs	Not specified	Emergency cesarean section (n=133)	Matched on age, diagnosis date and deprivation quintile	RR (95% CI) compared to matched controls: - 0-14 yr RR 1.40 (1.00 – 1.96) - 15-24 yr RR 1.16 (0.95– 1.41)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 4/4; Attrition bias low in 4/4; Detection bias unclear in 4/4; Confounding high in 2/4, low in 2/4.
Consistency:	0	No important inconsistencies. All studies show no significant increased risks
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant increased risk of a secondary/urgent caesarean section in CAYA cancer survivors in general, as compared to controls. (3 studies non-significant effect; 5397 pregnancies; 768 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of a secondary/urgent cesarean delivery in CAYA cancer survivors by radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Secondary caesarean section (n=5, 12.5%)	-	After RT to abdomen (n=6): Survivors: n=0 (0%), controls: n=1296 (14%), p-value=na	SB: low AB: low DB: unclear CF: high
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Emergency cesarean section (n=387)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.08 (0.91 to 1.27) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.21 (0.95 to 1.53) - Nonbrain/nonabdominal: 0.97 (0.67 to 1.40) - Abdominal: 1.35 (1.00 to 1.83) - Abdominal non Wilms: 1.36 (0.87 to 2.11) - Abdominal Wilms only: 1.32 (0.92 to 1.89) - No RT Wilms only: 1.06 (0.59 to 1.90) - P-value for heterogeneity: 0.14	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 1/2 , high in 1/2.
Consistency:	0	No important inconsistencies. All studies show no significant increased risks
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊕ **High**
Conclusion:		No statistically significant effect of radiotherapy on a secondary/urgent caesarean section in CAYA cancer survivors, as compared to controls. (2 studies non-significant effect; 2823 pregnancies; 392 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of a secondary/urgent cesarean delivery in CAYA cancer survivors by age?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Emergency cesarean section (n=387)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.92 (0.70 to 1.21) - 10-14 yrs: 1.15 (0.84 to 1.56) - P-value for heterogeneity: 0.52	SB: low AB: low DB: unclear CF: low
Van der Kooi 2018	186 first singleton live births in women diagnosed with cancer between 0-14 years and 588 in women diagnosed between 15-24 yrs	Not specified	Emergency cesarean section (n=133)	Matched on age, diagnosis date and deprivation quintile	RR (95% CI) compared to matched controls: - 0-14 yr RR 1.40 (1.00 – 1.96) - 15-24 yr RR 1.16 (0.95– 1.41)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 2/2.
Consistency:	0	No important inconsistencies. All studies show no significant increased risks
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊕⊕ **High**
Conclusion:		No statistically significant effect of age on a secondary/urgent caesarean section in CAYA cancer survivors, as compared to controls. (2 studies non-significant effect; 3557 pregnancies; 520 events, 1 multivariable analysis, one matched study)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of a uterine scar from previous surgery in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Uterine scar from previous surgery; ICD10: O34.2 (n=188)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.23 (0.98 to 1.56) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.15 (0.84 to 1.57) - Nonbrain/nonabdominal: 0.66 (0.36 to 1.18) - Abdominal: 1.31 (0.88 to 1.93) - Abdominal non Wilms: 1.41 (0.83 to 2.40) - Abdominal Wilms only 1.26 (0.79 to 2.02) - No RT Wilms only: 1.47 0.82 (0.32 to 2.14) - P-value for heterogeneity: 0.14 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 0.89 (0.62 to 1.27) - 10-14 yrs: 0.92 (0.62 to 1.37) - P-value for heterogeneity: 0.63	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Moderate imprecision, broad confidence intervals, one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		One study reported on risk of a uterine scar from previous surgery in CAYA cancer survivors and showed no increased risk as compared to controls. (1 study; 2783 pregnancies; 188 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of a perineal laceration/rupture in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	Uterine scar from previous surgery; ICD10: O34.2 (n=188)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 0.99 (0.89 to 1.10) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 0.91 (0.80 to 1.05) - Nonbrain/nonabdominal: 0.94 (0.76 to 1.15) - Abdominal: 0.88 (0.72 to 1.07) - Abdominal non Wilms: 0.83 (0.61 to 1.13) - Abdominal Wilms only 0.90 (0.70 to 1.14) - No RT Wilms only: 0.98 (0.71 to 1.35) - P-value for heterogeneity: 0.49 RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 1.01 (0.86 to 1.18) - 10-14 yrs: 0.96 (0.80 to 1.16) - P-value for heterogeneity: 0.73	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Moderate imprecision, broad confidence intervals, one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		One study reported on risk of a risk of a perineal laceration in CAYA cancer survivors and showed no increased risk as compared to controls. (1 study; 2783 pregnancies; 188 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of delivering a child with a low Apgar score in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Low 1-min Apgar score: <7 (n=189, 10%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: - General ARR: 2.83 (2.28-3.56) By age at diagnosis (yrs) - 15-19: 1.34 (0.81-2.43) - 20-29: 2.24 (1.56-3.65) Treatment type - Chemo only: 0.98 (0.34-5.64) - RT only: 2.14 (1.13-3.96) - Surgery only: 1.08 (0.83-1.72) - Chemoradiation: 1.78 (1.11-3.04) - Other/unknown: 1.11 (0.74-1.61)	SB: low AB: low DB: unclear CF: low
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Low 5-min Apgar score: <8 (n=0, 0%)	-	Frequency compared to control group: Survivors: n=0 (0%), controls: n=1296 (14%), p-value=na After RT to abdomen (n=6): Survivors: n=0 (0%), controls: n=1296 (14%), p-value=na	SB: low AB: low DB: unclear CF: high
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	>41 weeks (n not specified)	Low 5-min Apgar score: <7 (CCS n=13 (2.4%), cervical n= 15, 3.3%)	state, maternal age, year of delivery, race/ethnicity, and parity, gestational length	Adjusted RR (95% CI) compared to control group: - CCS: 1.30 (0.72 – 2.35) - cervical/genital cancer survivors: 2.01 (1.15 – 3.50)	SB: low AB: low DB: unclear CF: low
Sekiguchi 2018	61 female CCS of 71 pregnancies including 5 twin pregnancies	Not specified	Low 5-min Apgar score: <7 (n=5, 7%)	-	- Total n=5 (7%) - chemotherapy n=3 (6%) vs no chemotherapy n=2 (8%), p-value 1.00 - RT n=2 (10%) vs no RT n=3 (6%), p-value 0.61	SB: high AB: high DB: unclear CF: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/4, high in 1/4; Attrition bias low in 3/4, high in 1/4; Detection bias unclear in 4/4; Confounding low in 2/4, high in 2/4.
Consistency:	0	Some inconsistencies, one study shows an increased risk, specifically in the group diagnosed aged 20-29 yrs and one shows an increased risk in the cervical/genital cancer survivors. One study shows an increased risk after radiation, two small studies did not find an increased risk after radiation.

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, high probability of underpowered studies for specific outcome
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Four studies reported on risk of delivery of a child with a low Apgar score in CAYA cancer survivors and showed an increased risk especially for survivors diagnosed in their twenties or treated with radiotherapy. (4 studies; 3,903 pregnancies; 209 events; 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of postpartum hemorrhage in CAYA cancer survivors?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up Not reported.	Postpartum hemorrhage: ≥500 ml (N=95, 5%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 0.99 (0.83-1.31)	SB: low AB: low DB: unclear CF: low
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Post-partum haemorrhage: >1 l blood loss within 24 h after the delivery (n=3, 8%)	-	Frequency compared to control group: Survivors: n=3 (8%), controls: n=449 (5%), p-value=ns	SB: low AB: low DB: unclear CF: high
Melin 2015	1800 CAYA cancer survivors with 1800 pregnancies	At least 9 months to 34 years from diagnosis to delivery	Postpartum hemorrhage = >1000 mL of blood within the first 24 hours after childbirth (n=34, 4.3%)	-	OR (95% CI) compared to control group: 1.27 (95% CI 0.82-1.96)	SB: low AB: low DB: unclear CF: high
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	postpartum hemorrhage (O72) (n=281)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.08 (0.93 to 1.28)	SB: low AB: low DB: unclear CF: low
Van der Kooi 2018	186 first singleton live births in women diagnosed with cancer between 0-14 years and 588 in women diagnosed between 15-24 yrs	Not specified	Postpartum hemorrhage: >500 mL after vaginal or >1000 mL after c-section (n=173)	Matched on age, diagnosis date and deprivation quintile	RR (95% CI) compared to matched controls: - 0-14 yr RR 1.62 (1.23 – 2.13) - 15-24 yr RR 1.28 (1.08 – 1.53)	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Minor limitations: Selection bias low in 5/5; Attrition bias low in 5/5; Detection bias unclear in 5/5; Confounding low in 3/5, high in 2/5.
Consistency:	-2	Important inconsistency, one study shows an increased risk while 4 other studies show no increased risk.
Directness:	0	Results are direct, population and outcomes broadly generalizable

Precision:	0	No important imprecision, high total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		Increased risk of postpartum hemorrhage in CAYA cancer survivors in general, as compared to controls. (1 study significant effect, 4 studies non-significant effect; 6,220 pregnancies; 586 events, 2 multivariable analysis, one matched control group)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of postpartum hemorrhage in CAYA cancer survivors by radiotherapy?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Post-partum haemorrhage: >1 l blood loss within 24 h after the delivery (n=3, 8%)	-	After RT to abdomen (n=6): Survivors: n=2 (33%), controls: n=449 (5%), p-value 0.007	SB: low AB: low DB: unclear CF: high
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	postpartum hemorrhage (O72) (n=281)	Maternal age and parity	RR (95% CI), as compared to general population - Survivors not treated with any radiotherapy: RR 1.08 (0.93 to 1.28) RR (95% CI), as compared to survivors treated without radiotherapy - Brain: 1.14 (0.85 to 1.53) - Nonbrain/nonabdominal: 0.98 (0.62 to 1.55) - Abdominal: 1.33 (0.93 to 1.89) - Abdominal non Wilms: 1.25 (0.75 to 2.07) - Abdominal Wilms only 1.37 (0.89 to 2.10) - No RT Wilms only: 1.37 (0.74 to 2.53) - P-value for heterogeneity: 0.42	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias unclear in 2/2; Confounding low in 1/2, high in 1/2
Consistency:	-1	Some inconsistency. One small study shows an increased risk after radiotherapy on the abdomen (3 events in sub-cohort of 6), one larger study does not find a significantly increased risk.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision, medium total number of events and narrow confidence intervals, but only one study shows a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Statistically significant effect of (abdominal) radiotherapy on the risk of premature birth in CAYA cancer survivors. (1 study significant effect, 1 study non-significant effect; 2823 pregnancies; 284 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of postpartum hemorrhage in CAYA cancer survivors by age?

Study	No. of participants	Follow up (median/mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Reulen 2017	1712 CCS with 2783 pregnancies	Mean maternal age was 28.7 (SD = 5.4) yrs	postpartum hemorrhage (O72) (n=281)	Maternal age and parity	RR (95% CI), as compared to 0-4 yrs: - 5-9 yrs: 1.13 (0.81 to 1.58) - 10-14 yrs: 1.08 (0.71 to 1.63) - P-value for heterogeneity: 0.65	SB: low AB: low DB: unclear CF: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population broadly generalizable,
Precision:	-2	Moderate imprecision, only one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊕⊖⊖ **Low**
Conclusion:		No statistically significant effect of age at diagnosis on the risk of postpartum hemorrhage in CAYA cancer survivors. (1 study non-significant effect; 2783 pregnancies; 281 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

<u>Working Group 4</u>: Who is at risk of problems in neonates born to female CAYA cancer survivors. What is the risk, what should be done?

Index:

What is the risk of congenital anomalies/abnormalities in neonates born to CAYA cancer survivors?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Byrne 1998	626 CAYA cancer survivors with 1282 pregnancies/ offspring	Time until pregnancy at least 9 months after diagnosis	Genetic disease: crossed eyes (strabismus); stomach blockage (pyloric stenosis); hole in roof of mouth (cleft palate); hare lip (cleft lip); rupture in groin (inguinal hernia); clubfoot; absent, fused, or extra fingers or toes; hole in the heart; hip displacement; diverted urinary stream (hypospadias); mongolism (Down syndrome); open spine (spina bifida); water on the brain (hydrocephalus); exposed brain (anencephaly); undescended testicle (cryptorchidism); prematurity; hyalinemembrane disease; chondroplasia, acrocephalosyndactyly, aniridia, Apert syndrome, cancer, dystrophia myotonica, Gardner syndrome, Marfan syndrome, multiple polyposis, neurofibromatosis, osteogenesis imperfecta, polycystic disease of the kidney, Recklinghausen disease, retinoblastoma, and Steinert syndrome (n=51, 4.0%)	-	Frequency of genetic disease in comparison with controls: - 51/1282 (4.0%) of offspring of survivors, vs 75/25.0 (3.0%) in offspring of controls, p-value = 0.3	SB: low AB: low DB: unclear CF: high RB: high
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis: 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up: Not reported.	Congenital abnormalities: identified prior to discharge from hospital (n=12, 1%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group: 0.78 (0.41-1.37)	SB: low AB: low DB: unclear CF: low RB: low
Hawkins 1995	382 offspring of male and female CCS, 225 female CCS	Mean 7.3 and median 5.8 yrs (ages offspring)	Deaths occurred until follow-up time (n=7)		RR (95% CI) based on observed and expected frequency - Death by congenital abnormalities: Observed: 1, Expected 0.74, RR 1.35 (0.03-7.54)	SB: low AB: low DB: unclear CF: high RB: high

					- Malignant neoplasms: Observed 0, Expected 0.15, RR 0.00 - Other causes of death: Observed 6, Expected 2.61, RR 2.30 (0.84-5.02) - Total: Observed 7, Expected 3.51, RR 2.00 (0.80-4.11)	
Kenney 1996	140 offspring of male and female ALL survivors, 56 female ALL survivors	Age 22.6 (+/- 3.2) year, range 18-33	birth defects: could result in physical or mental impairment or require surgical or medical intervention and are registered by the Centers for Disease Control's Metropolitan Atlanta Congenital Defects Program (MACDP) (n=15)	-	Frequency and RR (95% CI) in comparison with controls: - 3.6% of offspring of male and female CCS vs 3.5% in siblings, RR = 1.02 (95% CI 0.34-3.05)	SB: low AB: low DB: unclear CF: high RB: high
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Congenital malformations not specified (n=0)	-	Full cohort: n=0 (0%), comparison n=145 (2%), p-value na	SB: low AB: low DB: unclear CF: high RB: low
Mueller 2009	1898 pregnancies from 892 CCS and 1006 cervical/genital cancer survivors	8.5 ± SD 5.8 yrs from diagnosis to delivery; Genital carcinoma survivors: 4.0 ± SD 3.4 yrs	Presence of any malformation (n=10 (1.3%) in CCS, n=14 (1.6%) in cervical cancer survivors)	state, maternal age, year of delivery, race/ethnicity, and parity,	Adjusted RR (95% CI) compared to control group - CCS: 0.92 (0.48-1.75) - cervical/genital cancer survivors: 1.16 (0.66-2.04)	SB: low AB: low DB: unclear CF: low RB: low
Nygaard 1991	23 ALL survivors with 41 offspring	4.3-26.5 years (time interval from end of therapy to end of study)	Specific for this sole case: exophthalmos, low-sitting ears, marked neck fold, abnormalities of the toes and profound generalized hypotonic musculature, left-sided pelvoureteric stenosis with hydronephrosis and agenesis of the right kidney. Normal chromosome analysis (n=1)	-	One child had multiple congenital defects and died 13 months old;	SB: low AB: low DB: unclear CF: high RB: high
Reinmuth 2008	44 CAYA cancer survivors achieved 69 pregnancies, 50 in female	Mean age at diagnosis: 10.9 Mean age at follow-up: 24.3	Not specified (n=1)	-	1 of 41 total live children with pes equinovarus	SB: low AB: high DB: unclear CF: high RB: high

	CAYA cancer survivors, 41 live births					
Winther 2009	1715 offspring from 970 CAYA cancer survivors (male and female), 896 from female CAYA cancer survivors	Diagnosis before 20, follow-up after 15 yrs of age	Malformation codes ICD 8/10: 740-759 and Q09-Q99, registered at birth (n=44, 2.6%)	maternal age, birth year and sex of offspring	Prevalence proportion ratios (95% CI) in comparison with offspring of siblings - Offspring of female survivors: PPR 1.2 (0.8-1.9) - Malformations in multiple organ systems: n=1; PPR 0.5 (0.1-4.6)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 9/9; Attrition bias low in 8/9, high in 1/9; Detection bias unclear in 9/9; Confounding low in 3/9, high in 6/9; sufficient high quality evidence
Consistency:	0	No inconsistency, none of the studies showed a significant increased risk. Two studies reported mainly descriptive data.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important, moderate total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Heterogeneity of definition. Sufficient high quality of evidence with consistent results.
Quality of evidence:		⊕⊕⊕⊕ **High**
Conclusion:		No increased risk of congenital anomalies among neonates of CAYA cancer survivors vs siblings/controls. (7 studies non-significant effect, 2 descriptive studies; 6,614 pregnancies; 155 congenital anomalies, 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of congenital anomalies in neonates born to CAYA cancer survivors treated with radiotherapy?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Child with a major congenital anomaly diagnosed at birth or during the 1st year (n=22, 4.7%)	age at pregnancy, maternal endocrine condition and paternal occupational exposure to organic solvents	OR (95% CI) compared with treated with surgery: - abd-pelvic RT: 0.45 (95% CI 0.12-1.70)	SB: high AB: low DB: unclear CF: low RB: high
Kenney 1996	140 offspring of male and female ALL survivors, 56 female ALL survivors	Age 22.6 (+/- 3.2) year, range 18-33	birth defects: could result in physical or mental impairment or require surgical or medical intervention and are registered by the Centers for Disease Control's Metropolitan Atlanta Congenital Defects Program (MACDP) (n=15)	-	Frequency and OR (95% CI) in comparison with controls: - 80% of the parents of 5 offspring with birth defects were exposed to radiation versus 92.6% of the parents of 135 offspring without birth defects, OR 0.3 (0.03-17.32)	SB: low AB: low DB: unclear CF: high RB: high
Lie Fong 2010	40 CAYA cancer survivors with 40 pregnancies	21.6 years (range 7.6-36.1)	Congenital malformations not specified (n=0)	-	After RT (n=6): n=0 (0%), comparison n=145 (2%), p-value n/a	SB: low AB: low DB: unclear CF: high RB: low
Nygaard 1991	23 ALL survivors with 41 offspring	4.3-26.5 years (time interval from end of therapy to end of study)	Specific for this sole case: exophthalmos, low-sitting ears, marked neck fold, abnormalities of the toes and profound generalized hypotonic musculature, left-sided pelveoureteric stenosis with hydronephrosis and agenesis of the right kidney. Normal chromosome analysis (n=1)	-	One child had multiple congenital defects and died 13 months old; mother not treated with RT, MTX or cyclophosphamide; not more than expected from the incidence of birth defects in the general population	SB: low AB: low DB: unclear CF: high RB: high
Signorello 2012 (CCSS)	1627 female CAYA cancer survivors with 2774 offspring	Not specified	Congenital anomalies: cytogenetic abnormalities (eg trisomy 21), single-gen defects (eg. Achondroplasia), and congenital malformations (eg. Cleft lip) (n=93)	calendar year of birth and maternal age	Frequency in irradiated mothers versus non-radiated mothers - Congenital malformations: 2.9% vs 2.6% - Single-gene defects: 0.3% vs 0.6% - Cytogenetic abnormalities: 0% vs 0.4%	SB: high AB: low DB: unclear CF: high RB: high

Winther 2009	1715 offspring from 970 CAYA cancer survivors (male and female), 896 from female CAYA cancer survivors	Diagnosis before 20, follow-up after 15 yrs of age	Malformation codes ICD 8/10: 740-759 and Q09-Q99, registered at birth (n=44, 2.6%)	maternal age, birth year and sex of offspring	Prevalence proportion ratios (95% CI) in comparison with offspring of siblings: - Non-irradiated mother (n=611): PPR 1.3 (0.8-2.1) - Irradiated mother (n=275): PPR 1.1 (0.5-2.2)	SB: low AB: low DB: unclear CF: low RB: low
Winther 2012	752 female CAYA cancer survivors, 85 female CAYA cancer survivors with offspring with any genetic condition and in the sub-cohort 189 CAYA cancer survivors with offspring without genetic condition	Age at diagnosis Before 20 yrs of age Age at follow-up Above 15 yrs	Genetic disease defined as still births, neonatal deaths , chromosomal abnormalities and congenital malformations throughout life (n=97)	birth order, maternal age and chemotherapy/radiotherapy	RR (95% CI) compared with nonirradiated group: Irradiated: RR 1.02 (0.59-1.44)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	Some limitations: Selection bias low in 5/7, high in 2/7; Attrition bias low in 7/7, Detection bias unclear in 7/7; Confounding low in 3/7, high in 4/7; sufficient high quality evidence
Consistency:	0	No inconsistency, none of the studies showed a significant increased risk. One study reported mainly descriptive data.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, moderate total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Heterogeneity of definition. Sufficient high quality of evidence with consistent results.
Quality of evidence:		⊕⊕⊕⊕ **High**
Conclusion:		No statistically significant effect of radiotherapy on the risk of congenital anomalies among neonates of CAYA cancer survivors. (6 studies non-significant effect, 1 descriptive study; 6,645 pregnancies; 272 events, 4 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of congenital anomalies in neonates born to CAYA cancer survivors by dose of radiotherapy?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Child with a major congenital anomaly diagnosed at birth or during the 1st year (n=22, 4.7%)	age at pregnancy, maternal endocrine condition and paternal occupational exposure to organic solvents	OR (95% CI) compared with treated with surgery: - low dose (<2500 cGy) abd-pelvic RT: 0.47 (95% CI 0.09-2.20) - high dose (>2500 cGy) abd-pelvic RT: OR 0.35 (95% CI 0.07-1.70)	SB: high AB: low DB: unclear CF: low RB: high
Green 2010 (Wilms)	499 Wilms tumor survivors with 499 pregnancies	55.7 ± 40.3 months at diagnosis and 31.2 ± 5.2 years at follow-up	Congenital anomalies defined by the Metropolitan Atlanta Congenital Defects Program, which excludes some of the anomalies using ICD-9-CM codes 740 to 759 (n=44)	-	Number of congenital malformations in offspring by radiation therapy dose - None: 10 with 1, 4 with 2 and 2 with 3 congenital malformations - 0-15 Gy: 3 with 1 malformation - 15-25 Gy: 9 with 1, 1 with 2 and 1 with 4 congenital malformations - 25-35 Gy: 6 with 1 malformation - >35 Gy: 5 with 1, 2 with 2 malformations - whole abdomen: 1 with 1 malformation - Exact linear-by-linear associations test P =0.94	SB: low AB: high DB: unclear CF: high RB: high
Signorello 2012 (CCSS)	1627 female CAYA cancer survivors with 2774 offspring	Not specified	Congenital anomalies: cytogenetic abnormalities (eg trisomy 21), single-gen defects (eg. Achondroplasia), and congenital malformations (eg. Cleft lip) (n=93)	calendar year of birth and maternal age	OR (95%-CI) in comparison with not treated with radiation: - 0.001-0.99 Gy: 0.87 (0.55-1.38) - 1.00-2.50 Gy: 0.80 (0.33-1.92) - 2.50 + Gy: 0.59 (0.20-1.75)	SB: high AB: low DB: unclear CF: high RB: high
Winther 2009	1715 offspring from 970 CAYA cancer survivors (male and female), 896 from female CAYA cancer survivors	Diagnosis before 20, follow-up after 15 yrs of age	Malformation codes ICD 8/10: 740-759 and Q09-Q99, registered at birth (n=44, 2.6%)	maternal age, birth year and sex of offspring	Prevalence proportion ratios (95%-CI) in comparison with offspring of siblings: Gonadal radiation dose of parent (m/f): - Low: 1.1 (0.5-2.8) - Low-medium: 1.9 (0.8-4.5) - Medium-high: 1.2 (0.3-4.8) - High: 0.6 (0.1-4.5)	SB: low AB: low DB: unclear CF: low RB: low
Winther 2012	752 female CAYA cancer survivors, 85 female CAYA cancer survivors with	Age at diagnosis Before 20 yrs of age Age at follow-up	Genetic disease defined as still births, neonatal deaths , chromosomal abnormalities	birth order, maternal age and	RR (95% CI) compared with nonirradiated on the ovaries: RT on ovaries:	SB: low AB: low DB: unclear

	offspring with any genetic condition and in the subcohort 189 CAYA cancer survivors with offspring without genetic condition	Above 15 yrs	and congenital malformations throughout life (n=97)	chemotherapy/ radiotherapy	- 0-<0.50: RR 1.12 (0.52-2.38) - ≥ 0.50: RR 1.04 (0.17-6.25) RR (95% CI) compared with nonirradiated on the uterus: RT on uterus: - 0-<0.50: RR 1.34 (0.77-2.32) - ≥ 0.50: RR 2.30 (0.95-5.56)	CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/5, high in 2/5; Attrition bias low in 3/5, high in 2/5; Detection bias unclear in 5/5; Confounding low in 3/5, high in 2/5.
Consistency:	0	No important inconsistency, all studies show non-significant effect of dose of radiation
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	Moderate imprecision, moderate total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Heterogeneity of definition
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant effect of ovarian-abdominal radiotherapy dose on the risk of congenital anomalies among neonates of CAYA cancer survivors. (5 studies non-significant effect ; 6,645 pregnancies; 300 events, 4 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of congenital anomalies in neonates born to CAYA cancer survivors treated with chemotherapy?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Child with a major congenital anomaly diagnosed at birth or during the 1st year (n=22, 4.7%)	age at pregnancy, maternal endocrine condition and paternal occupational exposure to organic solvents	OR (95% CI) compared with treated with surgery: - CT with AA: 0.23 (95% CI 0.05-1.12)	SB: high AB: low DB: unclear CF: low RB: high
Green 1997	54 pediatric cancer survivors with 92 live births	Not specified, at least 5-year survivors	a ventricular septal defect, the tetralogy of Fallot, and Sturge-Weber syndrome	-	3 (3.3) out of 92 births, "no statistically significant differences in the frequency of congenital anomalies among the offspring of women who were or were not treated with any of these agents."	SB: high AB: high DB: unclear CF: high RB: high
Kenney 1996	140 offspring of male and female ALL survivors, 56 female ALL survivors	Age 22.6 (+/- 3.2) year, range 18-33	birth defects: could result in physical or mental impairment or require surgical or medical intervention and are registered by the Centers for Disease Control's Metropolitan Atlanta Congenital Defects Program (MACDP) (n=15)	-	Frequency and OR (95% CI) in comparison with controls: - 60% of the parents of 5 offspring with birth defects were exposed to cyclophosphamide versus 24.4% of the 135 offspring without birth defects, OR 4.6 (0.5-56.96) - 40% of the parents of 5 offspring with birth defects were exposed to anthracyclines versus 23.7% of 135 offspring without birth defects, OR 2.1 (0.17-13.82)	SB: low AB: low DB: unclear CF: high RB: high
Nygaard 1991	23 ALL survivors with 41 offspring	4.3-26.5 years (time interval from end of therapy to end of study)	Specific for this sole case: exophthalmos, low-sitting ears, marked neck fold, abnormalities of the toes and profound generalized hypotonic musculature, left-sided pelveoureteric stenosis with hydronephrosis and agenesis of the	-	One child had multiple congenital defects and died 13 months old; mother not treated with RT, MTX or cyclophosphamide; not more than expected from the incidence of birth defects in the general population	SB: low AB: low DB: unclear CF: high RB: high

			right kidney. Normal chromosome analysis (n=1)			
Signorello 2012 (CCSS)	1627 female CAYA cancer survivors with 2774 offspring	Not specified	Congenital anomalies: cytogenetic abnormalities (eg trisomy 21), single-gen defects (eg. Achondroplasia), and congenital malformations (eg. Cleft lip) (n=93)	calendar year of birth and maternal age	OR (95%-CI) in comparison with not treated with chemotherapy: - nonalkylators only: OR 0.73 (0.37-1.44) - AAD 1: 0.63 (0.29-1.37) - AAD 2: 1.00 (0.49-2.03) - AAD 3: 1.13 (0.57-2.25)	SB: high AB: low DB: unclear CF: high RB: high
Winther 2012	752 female CAYA cancer survivors, 85 female CAYA cancer survivors with offspring with any genetic condition and in the sub-cohort 189 CAYA cancer survivors with offspring without genetic condition	Age at diagnosis Before 20 yrs of age Age at follow-up Above 15 yrs	Genetic disease defined as still births, neonatal deaths , chromosomal abnormalities and congenital malformations throughout life (n=97)	birth order, maternal age and chemotherapy/ radiotherapy	RR (95% CI) in comparison with not treated with chemotherapy: - Alkylating drug: 0.82 (0.53-1.28)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 3/6, high in 3/6; Attrition bias low in 5/6, high in 1/6; Detection bias unclear in 6/6; Confounding low in 2/6, high in 4/6.
Consistency:	0	No important inconsistency, none of the studies showed a significant increased risk. One study reported mainly descriptive data.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	Moderate imprecision, moderate total number of events and narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Heterogeneity in definition
Quality of evidence:		⊕⊕⊕⊖ **Moderate**
Conclusion:		No statistically significant effect of alkylating agents on the risk of congenital anomalies among neonates of CAYA cancer survivors. (6 studies non-significant effect; 4393 offspring, 231 events; 3 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of congenital anomalies in neonates born to CAYA cancer survivors by dose of chemotherapy?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Signorello 2012 (CCSS)	1627 female CAYA cancer survivors with 2774 offspring	Not specified	Congenital anomalies: cytogenetic abnormalities (eg trisomy 21), single-gen defects (eg. Achondroplasia), and congenital malformations (eg. Cleft lip) (n=93)	calendar year of birth and maternal age	OR (95%-CI) in comparison with not treated with chemotherapy: - nonalkylators only: OR 0.73 (0.37-1.44) - AAD 1: 0.63 (0.29-1.37) - AAD 2: 1.00 (0.49-2.03) - AAD 3: 1.13 (0.57-2.25)	SB: high AB: low DB: unclear CF: high RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-2	Limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Important imprecision as a result of a sole study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Only one study
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant effect of alkylating agent dose on the risk of congenital anomalies among neonates of CAYA cancer survivors. (1 study non-significant effect; 2774 offspring, 93 events; 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of congenital anomalies in neonates born to CAYA cancer survivors treated with chemotherapy and radiotherapy?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Chiarelli 2000	340 CAYA cancer survivors with 594 pregnancies	Not specified	Child with a major congenital anomaly diagnosed at birth or during the 1st year (n=22, 4.7%)	age at pregnancy, maternal endocrine condition and paternal occupational exposure to organic solvents	OR (95% CI) compared with treated with surgery: - CT with AA and abd-pelvic RT: 0.27 (95% CI 0.03-2.16)	SB: high AB: low DB: unclear CF: low RB: high
Hawkins 1991	568 live births in female CCS	Not specified	Serious congenital anomaly: potentially lethal or handicapping malformations (n=13)	-	3.6% in the exposed vs 2.1% in the group not exposed to RT on gonads or alkylating agents (p-value ns)	SB: low AB: low DB: unclear CF: high RB: high
Winther 2012	752 female CAYA cancer survivors, 85 female CAYA cancer survivors with offspring with any genetic condition and in the sub-cohort 189 CAYA cancer survivors with offspring without genetic condition	Age at diagnosis Before 20 yrs of age Age at follow-up Above 15 yrs	Genetic disease defined as still births, neonatal deaths , chromosomal abnormalities and congenital malformations throughout life (n=97)	birth order, maternal age and chemotherapy/ radiotherapy	RR (95% CI) in comparison with not treated with chemotherapy or radiation: Alkylating drug: 0.75 (0.26-2.13)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	0	No important limitations: Selection bias low in 2/3, high in 1/3; Attrition bias low in 3/3; Detection bias unclear in 3/3; Confounding low in 2/3, high in 1/3.
Consistency:	0	No inconsistency, none of the studies showed a significant increased risk.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Moderate imprecision, small total number of events but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Heterogeneity in definition
Quality of evidence:		⊕⊕⊕⊖ **Moderate**

Conclusion:	No statistically significant effect of alkylating agents in combination with abdominal-pelvic radiation on the risk of congenital anomalies among neonates of CAYA cancer survivors. (3 studies non-significant effect; 1436 offspring, 132 events, 2 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of congenital anomalies in neonates born to CAYA cancer survivors by age at diagnosis?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Kenney 1996	140 offspring of male and female ALL survivors, 56 female ALL survivors	Age 22.6 (+/- 3.2) year, range 18-33	birth defects: could result in physical or mental impairment or require surgical or medical intervention and are registered by the Centers for Disease Control's Metropolitan Atlanta Congenital Defects Program (MACDP) (n=15)	-	Characteristics of survivors with offspring with birth defects vs offspring without birth defect: - mean age at diagnosis: 13.7 vs 12.9 (p=ns) - mean age at conception: 21.2 vs 22.2 (p=ns) - mean time interval from diagnosis to conception: 7.5 vs 9.4 (p=ns)	SB: low AB: low DB: unclear CF: high RB: high

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding high in 1/1
Consistency:	0	N/A, one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision as a result of a sole study and low number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		No statistically significant effect of age at diagnosis on the risk of congenital anomalies among neonates of CAYA cancer survivors. (1 study non-significant effect; 140 pregnancies; 15 events, no multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of resuscitation in neonates born to CAYA cancer survivors?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis: 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up: Not reported.	defined as the need for endotracheal intubation or external cardiac massage (n=164, 9%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group from the general population: - General: 1.66 (1.27-2.19) By age at diagnosis (yrs) - 15-19: 1.13 (0.68-1.72) - 20-29: 1.35 (0.72-2.81) - 30-39: 1.68 (1.18-2.35) Treatment type - Chemo only: 1.84 (1.19-4.54) - RT only: 1.63 (0.94-2.72) - Surgery only: 1.17 (0.96-1.62) - Chemoradiation:1.04 (0.55-2.29) - Other/unknown: 2.82 (0.37-12.8)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding low in 1/1
Consistency:	0	N/A, one study
Directness:	-1	Population not broadly generalizable as Haggar et al included a cohort relatively old at cancer diagnosis.
Precision:	-2	Important imprecision as a result of a sole study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		
Quality of evidence:		⊕⊖⊖⊖ **Very low**
Conclusion:		Increased risk of resuscitation among neonates of CAYA cancer survivors treated with chemotherapy vs. controls from the general population. (1 study significant effect; 1894 pregnancies; 164 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.

What is the risk of admission to a special care unit in neonates born to CAYA cancer survivors?

Study	No. of participants	Follow up (median/ mean, range) yr	Definition endpoint (events in total cohort)	Multivariable analysis	Effect size	Risk of bias
Haggar 2014	1894 AYA cancer survivors	Age at diagnosis: 15-19 yrs: 739 (39%) 20-29 yrs: 980 (52%) 30-39 yrs: 170 (9%) Age at follow-up: Not reported.	Admission to a special care unit (neonate) (n=97, 5%)	aboriginal status, previous cesarean section, maternal smoking during pregnancy, use of fertility treatment, residential remoteness, hospital insurance status	Adjusted RR (95% CI) compared to control group from the general population: 1.44 (1.13-1.78)	SB: low AB: low DB: unclear CF: low RB: low

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	0	Limitations: Selection bias low; Attrition bias low; Detection bias unclear; Confounding low
Consistency:	0	N/A, one study
Directness:	-1	Population not broadly generalizable as Haggar et al included a cohort relatively old at cancer diagnosis.
Precision:	-2	Important imprecision as a result of a sole study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No evidence of dose response
Plausible confounding:	0	No plausible confounding
Other considerations:		Only one study
Quality of evidence:		⨁⊖⊖⊖ **Very low**
Conclusion:		Increased risk of admission to a special care unit among neonates of CAYA cancer survivors vs controls from the general population. (1 study significant effect; 1894 pregnancies; 97 events, 1 multivariable analysis)

Abbreviations: AB, attrition bias; CAYA, childhood, adolescent and young adult; CCS, childhood cancer survivors; CF, confounding; RT, radiotherapy; DB, detection bias; SB, selection bias; RB, reporting bias; RR, relative risk; PR, proportion ratio; OR, odds ratio; yr, year.