Evidence tables from the systematic literature search for premature ovarian insufficiency surveillance in female CAYA cancer survivors.

Who needs surveillance?				
Chiarelli et al. Early menopause and Infertility in Females after Treatment for Childhood Cancer diagnosed in 1964-1988 in Ontario, Canada. Am J Epidemiol 1999;150(3):245-54.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective cohort study 1964-1988 Follow-up >5 yrs after diagnosis: 5-10 yrs: 25.2% 11-15 yrs: 24.9% 16-20 yrs: 26.3% 21-30 yrs: 23.6%	719 from total cohort of 1,581 female childhood cancers survivors. Median age: 28 yrs (range 18-49). Excluded: sterilising surgery	Alkylating agents: 150 (21%). Antimetabolites: not reported. Platinum compounds: not reported. Radiotherapy involving ovaries: 154 (21%) Alkylating agents + radiotherapy involving ovaries: 71 (10%). RT: < 20 Gy, 20-35 Gy, > 35 Gy abdominal pelvic. CT: AA (number of Alkylating agents, number of months). AA<: 1-13 low, 14-21 medium, >22 high risk.	<u>Outcome definition:</u> Menopausal status based on Telephone questionnaire: “Have you stopped having periods?”, “Have you ever used hormonal supplement pills?” 63 women (8.8%) menopausal after treatment (29 (46%) surgical menopause). <u>Risk of menopause in multivariate analyses:</u> Alkylating agents and abdominal-pelvic RT vs. non-sterilizing surgery: RR 2.58 (95% CI 1.14-5.80) Alkylating agents vs. non-sterilizing surgery: RR 0.77 (95% CI 0.30-1.97) Other treatments vs. non-sterilizing surgery: RR 0.75 (95% CI 0.34-1.65) Abdominal-pelvic RT vs. non-sterilizing surgery: <2000 cGy: RR 1.02 (95% CI 0.29- 3.59) 2000-3499 cGy: RR 1.36 (95% CI 0.57-3.25) ≥3500 cGy: RR 3.27 (95% CI 1.57-6.81) Alkylating agent score vs. non-sterilizing surgery: 1-13: RR 1.13 (95% CI 0.41-3.09)	Subset not representative for cohort. Based on telephone questionnaire No controls Unclear if patients treated with BMT or TBI were included

			14-21: RR 1.90 (95% CI 0.52-6.92) ≥21: RR 3.08 (95% CI 1.15-8.21)	

Abbreviations: Yrs, years; CT, chemotherapy; AA, alkylating agents; RT, radiotherapy; BMT, bone marrow transplantation; TBI, total body irradiation.

Who needs surveillance?				
Byrne et al. Early menopause in long-term survivors of cancer during adolescence. Am J Obstet Gynecol 1992;166:788-793				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study 1945-1974 <u>Follow-up:</u> >19 yr after cancer diagnosis	1048 female CCS ≥21 years of age at study entry; 954 were menstruating before study entry and 94 became menopausal before they were eligible for the cohort <u>Diagnoses:</u> Female genital cancer (n=90), Hodgkin's disease (n=206), non-Hodgkin's lymphoma (n=31), soft tissue sarcoma (n=115), leukaemia (n=15), brain or CNS tumour (n=133), bone cancer (n=65), other (n=393) <u>Age at diagnosis:</u> Mean 13.6 yr <u>Age at follow-up:</u> Mean 32.3 yr <u>Controls:</u> 1596 menstruating siblings at age 21 yr; Mean age at follow-up 33.0 yr	<u>Chemotherapy only:</u> 68 (6.5%) <u>Alkylating agents and radiotherapy above diaphragm:</u> 38 (3.6%) <u>Alkylating agents and radiotherapy below diaphragm:</u> 79 (7.5%) <u>Radiotherapy only:</u> 261 (24.9%) <u>Surgery only:</u> 493 (47.0%) <u>Sterilizing surgery and chemotherapy and radiotherapy:</u> 25 (2.4%) <u>Other treatments:</u> 84 (8.0%)	<u>Outcome definitions:</u> - Amenorrhea: woman's report of whether she was still having menstrual periods <u>Amenorrhea:</u> - 123/954 (12.9%) menopausal after study entry - 831/954 (87.1%) still menstruating <u>Age-specific relative risks for amenorrhea survivors vs. controls:</u> - All survivors aged 21-25: RR 4.32, 95% CI 2.28-8.17 - All survivors aged 26-30: RR 1.61, p>0.05 - All survivors aged 31-40: RR 0.78, p>0.05 - All survivors aged 41+: RR 0.98, p>0.05 - Alkylating agents alone aged 21-25: RR 9.17, 95% CI 2.67-31.49 - Radiotherapy below diaphragm and alkylating agents aged 21-25: RR 27.39, 95% CI 12.42-60.35 - Radiotherapy below diaphragm and alkylating agents aged 26-30: RR 4.64, p<0.01 - Radiotherapy alone aged 21-25: RR 3.66, 95% CI 1.34-9.99 - Radiotherapy alone aged 26-30: RR 2.41, p<0.05 - Radiotherapy alone aged 31-40: RR 0.90, p>0.05 - Radiotherapy alone aged 41+: RR 1.22, p>0.05	91% of both groups agreed to be interviewed. At follow-up, 10% of the survivors and 1% of the controls had died. 90% of eligible survivors completed follow-up assessment. Control group not representative for general population

			- Aged 0-12 at diagnosis aged 21-30 at follow-up: RR 0.62, p>0.05 - Aged 13-19 at diagnosis aged 21-30 at follow-up: RR 2.32, 95% CI 1.63-3.291	

Abbreviations: yr, years; CCS, childhood cancer survivors; CNS, central nervous system.

Who needs surveillance?				
Gracia et al. Impact of cancer therapies on ovarian reserve. Fertil Steril 2012;97:134-140.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center cohort study Treatment era not mentioned <u>Follow-up:</u> >1 yr after cancer treatment	71 postmenarchal female cancer survivors 15-39 years of age <u>Diagnoses:</u> Hodgkin lymphoma (n=15), non-Hodgkin lymphoma (n=9), leukaemia (n=23), sarcoma (n=10), Wilms' tumour (n=4), breast cancer (n=3), other (n=7) <u>Age at diagnosis:</u> Median 11 (0.3-29) yr <u>Age at follow-up:</u> Mean 25.7 (24.2-27.2) yr <u>Controls:</u> 67 postmenarchal controls; Mean age 27.3 (26.1-28.4) yr	<u>Alkylating agents:</u> 63 (88.7%) <u>Pelvic radiation (including TBI):</u> 13 (18.3%) <u>BMT:</u> 16 (22.5%) of which 10 (14.1%) TBI	<u>Outcome definitions:</u> - Amenorrhea: woman's report of whether she was still having menstrual periods <u>Menstrual characteristics:</u> - Age at menarche: 12.5 yr survivors vs, 12.4 yr controls (p=0.67) - Regular cycles: 49 (69.0%) survivors vs. 65 (91.5%) controls <u>Geometric mean (95% CI) reproductive hormone measures survivors vs. controls adjusted for age, race and BMI:</u> - FSH (mIU/mL): 11.12 (9.47-13.6) vs. 7.25 (6.0-8.8), p=0.001 - E_2 (pg/mL): 24.2 (20.9-28.1) vs. 29.4 (24.7-34.9), p=0.084 - AMH (ng/mL): 0.8 (0.6-1.1) vs. 2.9 (2.1-3.9), p<0.001 - AFC: 14.6 (10.8-18.3) vs. 27.2 (23.1-31.4), p<0.001 <u>Geometric mean (95% CI) reproductive hormone measures survivors treated with alkylating agent score ≥3 or pelvic radiation or TBI vs. other treatment vs. controls adjusted for race and BMI:</u> - FSH (mIU/mL): 10.6 (8.7-12.9) vs. 7.9 (6.6-9.5) vs. 6.9 (6.1-7.9), p<0.001 - E_2 (pg/mL): 10.6 (18.1-29.1) vs. 24.5 (19.9-30.3) vs. 31.8 (27.3-37.1), p<0.05	Unclear what proportion of eligible patients were included in the study

			- AMH (ng/mL): 0.5 (0.3-0.9) vs. 1.9 (1.2-3.2) vs. 3.1 (2.2-4.4) <u>Geometric mean (95% CI) reproductive hormone measures survivors treated with pelvic radiation vs. controls adjusted for age, race and BMI:</u> - FSH (mIU/mL): 28.4 vs. 9.4, p<0.001 - AMH (ng/mL): 0.15 vs. 1.24, p<0.001 - AFC: 2.9 vs. 17.5, p=0.001 <u>Effect alkylating agent score in survivors treated without pelvic radiation corrected for age, race and BMI:</u> - Each unit increase in alkylator score, geometric mean FSH values increased by 0.91 mIU/mL (p=0.016) and geometric mean AMH levels decreased by 0.55 ng/mL (p=0.003) - Differences in E_2 and AFC were not significant	

Abbreviations: yr, years; TBI, total body irradiation; BMT, bone marrow transplantation; FSH, follicle-stimulating hormone; E2, oestradiol; AMH, anti-Müllerian hormone; AFC, antral follicle count; BMI, body mass index.

Who needs surveillance?				
Sklar et al 2006. Premature Menopause in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98(13):890-6.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective, multicentre survey: self-report 1970 – 1989 Years of FU: not stated. Follow up study: 2000-01 →FU from diagnosis: 14-30 yrs	2,819 female CCS from total cohort of 6,079 females alive, >18y of age at Nov 2000. Median age at diagnosis 7 yrs (range 0-20 yrs), median age at study 29 yrs (range 18-50 yrs). Diagnoses N (%): Leukaemia 1,025(36); HL 404 (14); tumours of bone 324(11); kidney 297(11); brain 137(5); sarcomas 271(10); NBl 154(5). Exclusion criteria (n=1,801): diagnosis associated with ovarian dysfunction, primary amenorrhoea, menses ceased <5y from diagnosis, AOF (6%), questionnaire completed by other than participant.	Surgery only: 287 (10%) CT only: 287 (10%) RT only: 2 (<1%) CT+RT: 487 (17%) Surgery+CT: 573 (20%) Surgery+RT: 238 (8%) Surgery+CT+RT: 942 (33%) SCT: 32 (1%) No information reported on specific chemotherapy agents. Radiation dosimetry for each ovary separately was calculated from institution records (quantified by a single dosimetrist) RT doses grouped as No RT, 1-99,100-999, or ≥1000 cGy Chemotherapy: 7 broad classes of CT drugs from treatment records. Total exposure to (AA) was calculated for an individual by the overall AA score of 0,1,2 or 3 according to the dose distribution tertiles	<u>Outcome definition:</u> Self-reported: if subjects had not experienced a spontaneous menses for >6 months and other causes, e.g. pregnancy, use of agents such as injectable progesterone and GnRH-a have been excluded. <u>Premature menopause (<40yrs):</u> - 15% (RR 1.05, 95% CI 1.04-1.07, p<0.001) compared to siblings.. - Surgical premature menopause ns different in CCS and siblings (RR 0.8, 95% CI 0.52-1.23) - Non-surgical PM: 8% in CCS, 0.8% in siblings (RR 13.21, 95% CI 3.26-53.51, p<0.001) <u>Risk-factors non-surgical premature menopause in multivariate analyses:</u> - Attained age: RR 1.15, 95% CI 1.09-1.21, p< 0.001 - RT dose to ovary: RT 1-99 cGy: RR 4.30, 95% CI 1.20-15.47, p=0.04) RT 100-999 cGy: RR 5.70, 95% CI 1.12-28.99, p=0.04	<u>Authors Conclusion</u> Risk for non-surgical PM 8% in CCS compared to 0.8% in siblings. Risk factors for non-surgical PM: attained age, HL, exposure to increasing doses of AA and/ or RT to ovaries (any dose). The highest risk of non-surgical PM was associated with treatment including abdominopelvic RT and AA <u>Comments</u> Excellent large study with some limitations: - Self-reported - Large number of participants were excluded (1801 from 4620) - Among non-menopausal women 20% of survivors and 24% siblings were taking OC (however after exclusion of these subjects results were almost identical to entire cohort)

	Controls: N=1,065 siblings Sibling subset of CCS cohort with spontaneous menstruation Median age: not reported.	(none, lower, middle or upper)	RT ≥1000 cGy: RR 109.59, 95% CI 28.15-426.70, p<0.001 - AA score: AA score 1-2: RR 2.3, 95% CI1.08-4.90, p=0.03 AA score 3 RR 5.78, 95% CI 2.9-11.55, p<0.001 - HL (minimum ovarian RT): No ovarian RT: RR 9.18, 95% CI 1.52-55.24, p=0.02 1-99 cGy: RR 12.26, 95% CI 3.41-44.14, p<0.001 100-999 cGy: RR 11.41, 95% CI 2.75-47.26, p<0.001 ≥1000 cGy: RR 6.74, 95% CI 0.63-71.74, p=0.11 (Age at diagnosis not associated, data not shown) <u>Cumulative incidence of non-surgical premature menopause by age 40 years (see figure below):</u> - AA only: ± 15% - Abdominopelvic RT only: ± 5% - AA + abdominopelvic RT: ± 30% Among CCS without RT to ovaries, HL 9.18-fold higher risk of premature menopause than other types of cancer (95% CI 1.52-55.24, p=0.02).	

Abbreviations: FU, follow-up; yrs, years; CCS, childhood cancer survivors; n, number; HL, hodgkin lymphoma; Nbl, neuroblastoma; AOF, acute ovarian failure; CT, chemotherapy; RT, radiotherapy; SCT, stem cell transplantation; PM, premature menopause; AA, Alkylating agents; GnRH-a, gonadotrophin-releasing hormone analogue.

Who needs surveillance?				
Chemaitilly et al. Acute ovarian failure in the childhood cancer survivor study. J Clin Endocrinol Metab. 2006;91(5):1723-8.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective, multicentre, survey: self-report 1970-1986 Follow-up: 0-5 years after diagnosis (median unknown)	3,390 CCS with and without AOF <21 yrs at diagnosis Exclusion criteria: cranial radiotherapy >30 Gy, tumour in area of hypothalamus or pituitary, bilateral oophorectomy, incomplete radiation records	Alkylating agents: 1,684/3,390 (49.7%) Antimetabolites: Included, but percentage not reported. Platinum compounds: Included, but percentage not reported. Abdominal/pelvic radiotherapy: 832/3,390 (24.5%) Alkylating agents (AA)+ abdominal/pelvic radiotherapy (RT): 393/3,390 (11.6%) Cumulative doses of RT to ovaries were calculated and grouped as follows: <100, 100-999, 1000-1999, and 2000cGy+	Outcome definition: Self-reported: primary amenorrhoea or secondary amenorrhoea <5 years after cancer diagnosis. Prevalence of AOF: 215/ 3,390 (6.3%) Univariate analysis age at diagnosis: ≥12 yrs: OR 1.8 (1.4-2.4) Multivariate analyses: Age at diagnosis 0-12 yr: - procarbazine: OR 3.2 (1.3-7.3) - cyclophosphamide: OR 1.2 (0.7-2.1) - ovarian irradiation (cGy) 1-99: OR 3.7 (1.6-10.2) 100-999: OR 9.0 (3.4-26.5) 1000-1999: OR 55.3 (22.3-157.8) ≥2000: OR 950.1 (352.9-3043.2) Age at diagnosis 13-20 yr: - proacarbazine: OR 2.6 (1.4-4.7) - cyclophosphamide: OR 4.9 (2.8-9.2) - ovarian irradiation (cGy) 1-99: OR 2.9 (1.2-8.3) 100-999: OR 17.2 (6.8-49.5) 1000-1999: OR 90.9 (29.1-323.5) ≥2000: OR 171.2 (55.8-609.8)	Limitation: AOF defined as no spontaneous menses within 5 yr after cancer diagnosis and never spontaneous menses (all self-reported). Median follow-up >2.5 yr (only stated: follow-up 0-5 years)

Abbreviations: Yrs, years; CCS, childhood cancer survivors; AOF, acute ovarian failure; AA, alkylating agents; RT, radiotherapy.

Who needs surveillance?				
Jadoul et al 2011. Clinical and biologic evaluation of ovarian function in women treated by bone marrow transplantation for various indications during childhood or adolescence. Fertil Steril 2011;96(1):126-133.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Cross-sectional, single-centre study Treatment era not reported Years of FU from BMT: Mean (range) 15.5yrs (3.3-33.7) FU from diagnosis not reported	35 (of 59 eligible) females >16 yrs who underwent BMT at age , <19 yrs, in complete remission for ≥3 yrs 23 (66%) diagnosed with a malignancy, 12 (34%) diagnosed with a benign disease. 66% pre-menarcheal at BMT Mean age at BMT (range): 9.8 +/-5.2y (1.2-19.0) Mean age at study: 25.3+/-7.2y (16.6-46.4) Mean years of follow up from BMT: 15.5+/-5.5y (3.3-33.7)	<u>Alkylating agents:</u> 35 (100%): busulfan + cyclophosphamide, busulfan + melfalan, cyclophosphamide only, melfalan only <u>Antimetabolites:</u> 0 (0.0%) <u>Platinum compounds:</u> 0 (0.0%) Radiotherapy involving ovaries: 18 (51.4%) TBI (4-12Gy) <u>BMT:</u> 19 (54%) allogeneic; 16 (46%) autologous All patients with malignancy had appropriate previous CT for their disease.	<u>Outcome definition:</u> Absence of pubertal development or progression and secondary amenorrhea, confirmed by menopausal FSH levels. <u>Whole Cohort</u> 16/35 (45.7%) persistent ovarian function, but 85% low AMH levels (<1.2 ug/L). <u>Persistent ovarian function:</u> BMT for malignancy 8/23 (35%) v BMT benign disease 8/12 (67%) (p =0.07). After 10y post- BMT 5/21 (24%) v 7/12 respectively, significant (p 0.047). <u>Clinically proven ovarian failure and hormone measurement:</u> Prevalence POI post-BMT: 21 (60.0%) (immediate 19, subsequently 2) 35 (100%) low oestradiol and high FSH 35 (100%) low AMH 0.16-1.03 microg/L (median 0.5). AMH 0.25-2.83 microg/L (median 0.90) No significant difference in AMH levels between patients treated for a malignant disease and those transplanted for a benign pathology. <u>Persistence of ovarian function by treatment (not analysed for malignant disease separately)</u> TBI + alkylating agents:4/18 (22%)	<u>Authors' Conclusion:</u> - After BMT ovarian function is impaired in the majority of women even without clinical signs of ovarian failure (as judged by AMH) - This impairment is mainly related to older age at BMT (>10y) and TBI <u>Comments</u> - Multivariate analyses: only p-values shown. - Fractionation of TBI not stated. Single fraction TBI generally has greater adverse effect on ovarian function. - Previous cranial or other radiation not stated. - Small numbers but all had hormonal assessment - No separate analyses for group with BMT for malignant disease We only reported risk factors in multivariate analyses

			Alkylating agents only: 12/17 (71%) (p<0.005); this remained significant at 10 yrs post-BMT (p=0.01) Multivariate regression analysis: independent negative effect of TBI on ovarian failure (p=0.014) AMH levels and pregnancy N/S difference (other variables within the model: not reported). <u>Age and menarcheal status</u> Multivariate regression analysis: independent protective effect of young age at BMT (p=0.004). 100% girls >10y at BMT with TBI had irreversible premature ovarian failure vs. 40% girls <10y at BMT spontaneous puberty (other variables in the model not reported). <u>Age at evaluation and time since BMT:</u> Not significant (p-value not reported).	

Abbreviations: Yrs, years; FU, follow up; TBI, total body irradiation; BMT, bone marrow transplantation; FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone; CT, chemotherapy; v, versus; POI, premature ovarian insufficiency; N/S, not significant.

Who needs surveillance?				
Wallace et al. The radiosensitivity of the human oocyte. Hum Reprod 2003;18(1):117-121.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective study Cohort 1: Treatment era not reported, Scotland Cohort 2: treatment 1966-1975, UK Years of follow-up not reported.	Two cohorts (n=27): Cohort 1 (n=8) Median age: 17.1 yr (15.4-21.5), leukaemia, Scotland Cohort 2 (n=19): intra-abdominal tumour	Cohort 1: CT +TBI, 14.4 Gy in 8 fractions over 2 days, leukaemia (1st or second remission), median 11.5 yrs (4.9-15.1), no shields to the ovaries. Cohort 2: whole abdominal RT (30 Gy, 16-26 fractions), surgery and CT. median age at treatment 4 yrs (1.3-13.1), 8 pts no CT, remaining 11 vincristine/adriamycin/actinomycin D.	Cohort 1: POI 6/8 Cohort 2: POI 18/19 Based on Faddy-Gosden mathematical model : LD50 (Dose of radiation required to destroy 50% of the oocytes) = 1.99 Gy.	Not based on exact radiation dose received by each ovary, homogeneous, small sample.

Abbreviations: UK, United Kingdom; yr(s), year(s); CT, chemotherapy; TBI, total body irradiation; RT, radiotherapy; POI, premature ovarian insufficiency.

Who needs surveillance?				
Wallace et al. Predicting age of ovarian failure after radiation to the field that includes the ovaries. Int J Radiation Oncology Biol Phys 2005;62(3):738-744.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Retrospective study Cohorts previously described in Wallace et al, 2003 Cohort 1: Treatment era not reported, Scotland Cohort 2: treatment 1966-1975, UK Years of follow-up not reported.	Two cohorts (n=27): Cohort 1 (n=8) Median age at treatment 11.5 yrs (4.9-15.1), median age at assessment: 17.1 (15.4-21.5), leukaemia, Scotland Cohort 2 (n=19): intra-abdominal tumour, median age at treatment 4 yrs (1.3-13.1), median age at follow-up not stated.	Cohort 1: CT +TBI, 14.4 Gy in 8 fractions over 2 days, leukaemia (1st or second remission), no shields to the ovaries. Cohort 2: whole abdominal RT (30 Gy, 16-26 fractions), surgery and CT, 8 pts no CT, remaining 11 vincristine/adriamycin/actinomycin D.	Cohort 1: POI 6/8 (reported previously) Cohort 2: POI 18/19 (reported previously) Based on Faddy-Gosden mathematical model (estimation): Effective sterilizing dose (POI occurs immediately after treatment in 97.5% of patients): At birth: 20.3 Gy; at 10 yrs: 18.4 Gy; at 20 yrs: 16.5 Gy; at 30 yrs: 14.3 Gy Dy/day x = -y[0.0595 + 3.716 / (11.780 + y)] X=age, y(x)=population at age x, y(0)=population at birth Surviving % oocyte population = log(10) g(z)=2-0.15z. Z= dose (Gy) Using average oocyte population at x(chron) -> calculating age at menopause. 95% CI= (age at menopause) ± (1.96xSD) (see table for age at POI below)	Small sample n=27, mathematical model. -estimation -cohort 1: TBI, cohort 2: abdominal irradiation (comparable?)

Abbreviations: UK, United Kingdom; yr(s), year(s); CT, chemotherapy; TBI, total body irradiation; RT, radiotherapy; POI, premature ovarian insufficiency.