

Nuorena syövän sairastaneiden naisten raskaudet ja synnytykset

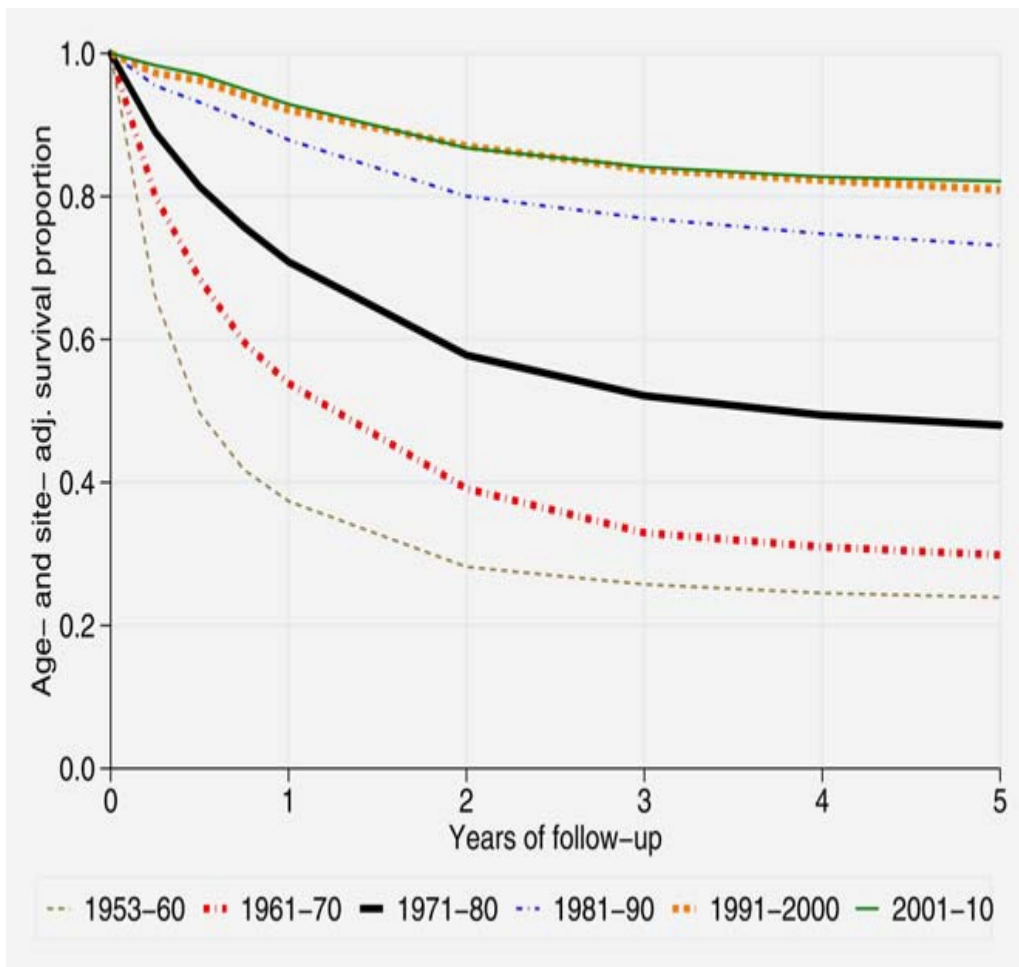
Laura Madanat-Harjuoja, LT
SGY:n koulutuspäivät
Turku 27.11.2014

Sidonnaisuudet

Ei sidonnaisuuksia.

Childhood cancer survival in Finland

Finnish Cancer registry 1953-2010



Survivorship Statistics

- Approximately 150 children are diagnosed with cancer annually
- Annual age standardized incidence rate in 1988-1997 in Finland was 173.2 per million (vs. 139.5 in Europe)

*

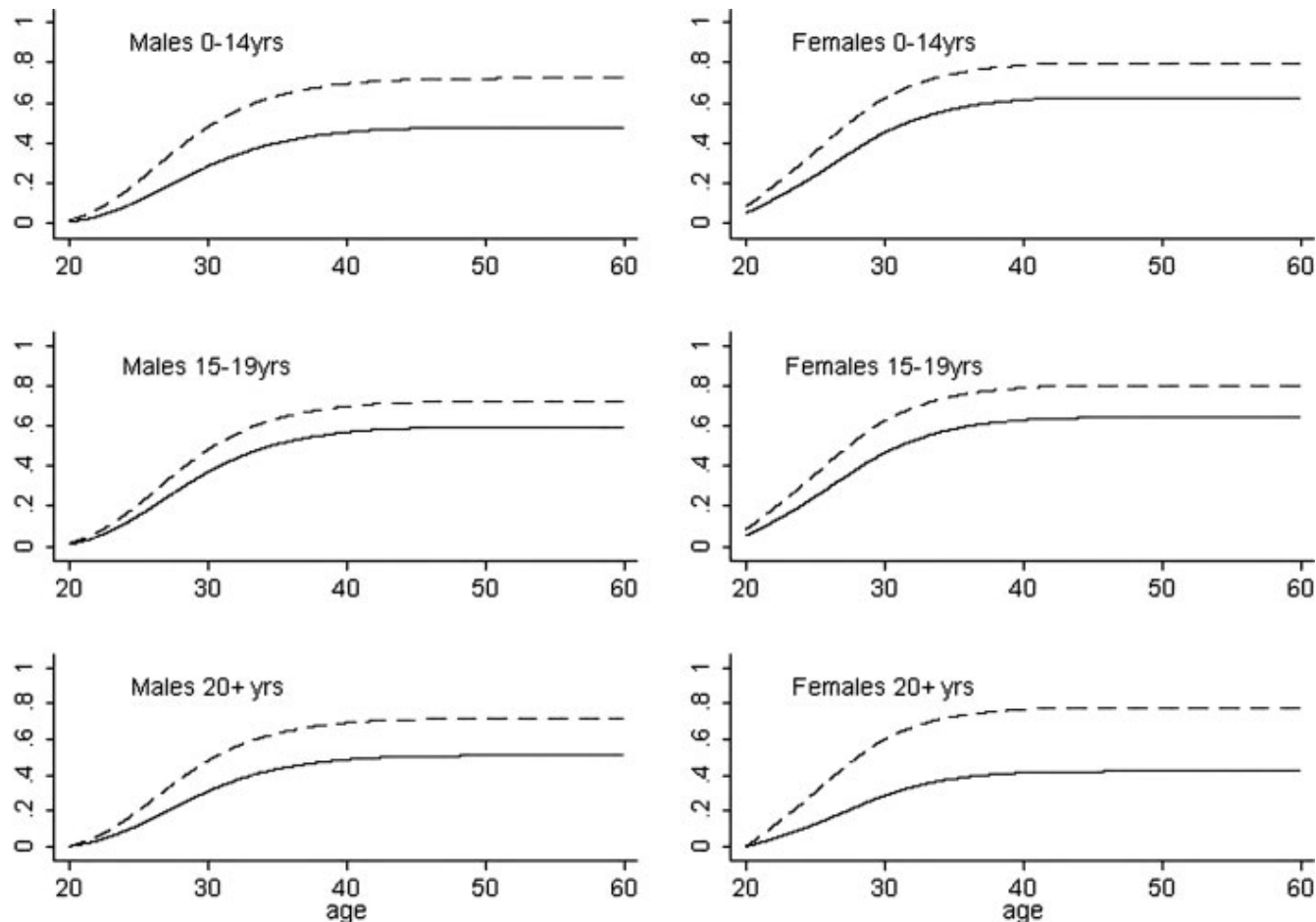
Surviving childhood cancer: how many reach adulthood?

- 1 : 640 < 40-yrs of age is a childhood cancer survivor
 - at the moment in Finland the figure is ca. 4000 childhood cancer survivors and 7000 (diag under 25yrs)
- the majority are leukemia and Hodgkin's lymphoma survivors
- less than one third reach adulthood without any late effects of treatment

Scope of published cancer survivorship research

2	Alcohol/Diet	2	Mortality
2	Cardiovascular	4	Neurologic/Neurosensory
1	Chronic Health Conditions	1	Osteonecrosis
1	Comp/Alternative Rx	12	Physical Function/QOL
1	Dental	10	Psychology
8	Education/Employ/Insurance	1	Pulmonary
5	Endocrine	1	Recurrence
12	General Survivorship	17	Reviews of CCSS Data
4	Genetics/Family History	13	Second Neoplasms
10	Gonadal Function/Pregnancy	1	Sleep/Fatigue
4	Growth Hormone	7	Smoking
1	Health Status	2	Stroke
9	Healthcare/Screening	1	Sun Exposure
1	Infection	11	Survivorship Methods
1	Cancer History Knowledge	6	Weight/Body Mass Index

Model based cumulative probabilities of first post-diagnosis parenthood



-----siblings _____patients

Madanat et al, Int J Cancer, 2009

Chemotherapy and damage to fertility

High Risk	Medium Risk	Low Risk
Cyclophosphamide	Cisplan	Vincristine
Ifosfamide	Carboplatinum	Methotrexate
Mustine	Adriamycin	Actinomycin D
Busulphan		Bleomycin
Melphalan		6 mercaptopurine
Procarbazine		Vinblastine
Chorambucil		

Consequences of Chemotherapy to Female Fertility

Acute Ovarian Failure

- occurs during treatment
- no chance of pregnancy
- permanent menopause
- often recovers in younger women depending on exposure

Premature Ovarian Insufficiency

- ovarian cycling may or may not cease during therapy
- recovers after therapy
 - may have normal pregnancy
- total number of years remaining of normal ovarian cycling are reduced = early menopause

Radiotherapy

Direct damage to
ovaries

Damage to hypothalamic-
pituitary axis

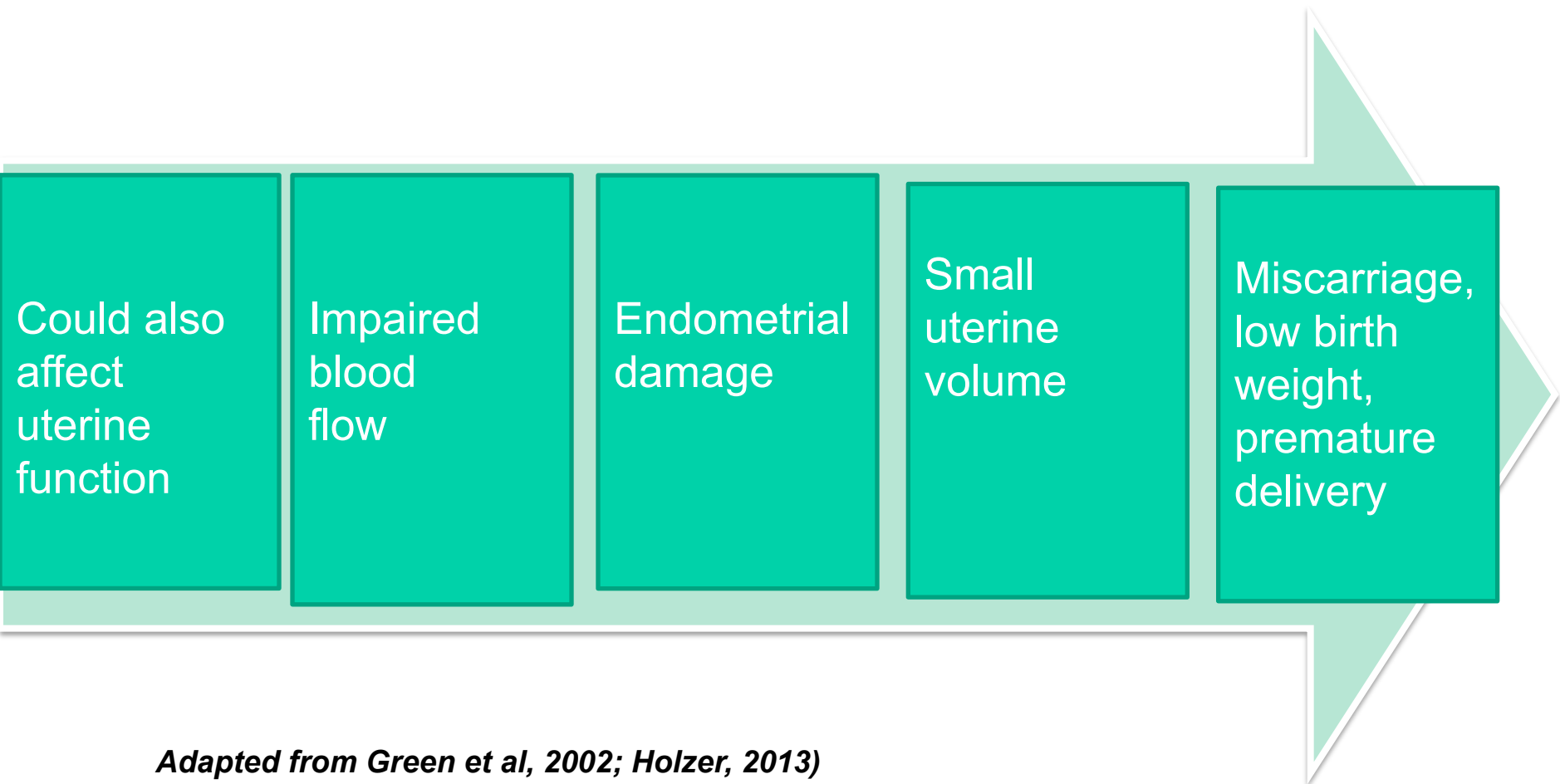
Dose
dependent;
total dose and
fractionation
schedule

Age dependent;
size of primordial
follicle pool

Radiation field
dependent

(Adapted from Ogilvy-Stuart & Shalet, 1993; Holzer, 2013)

Radiotherapy



Radiotherapy and damage to fertility

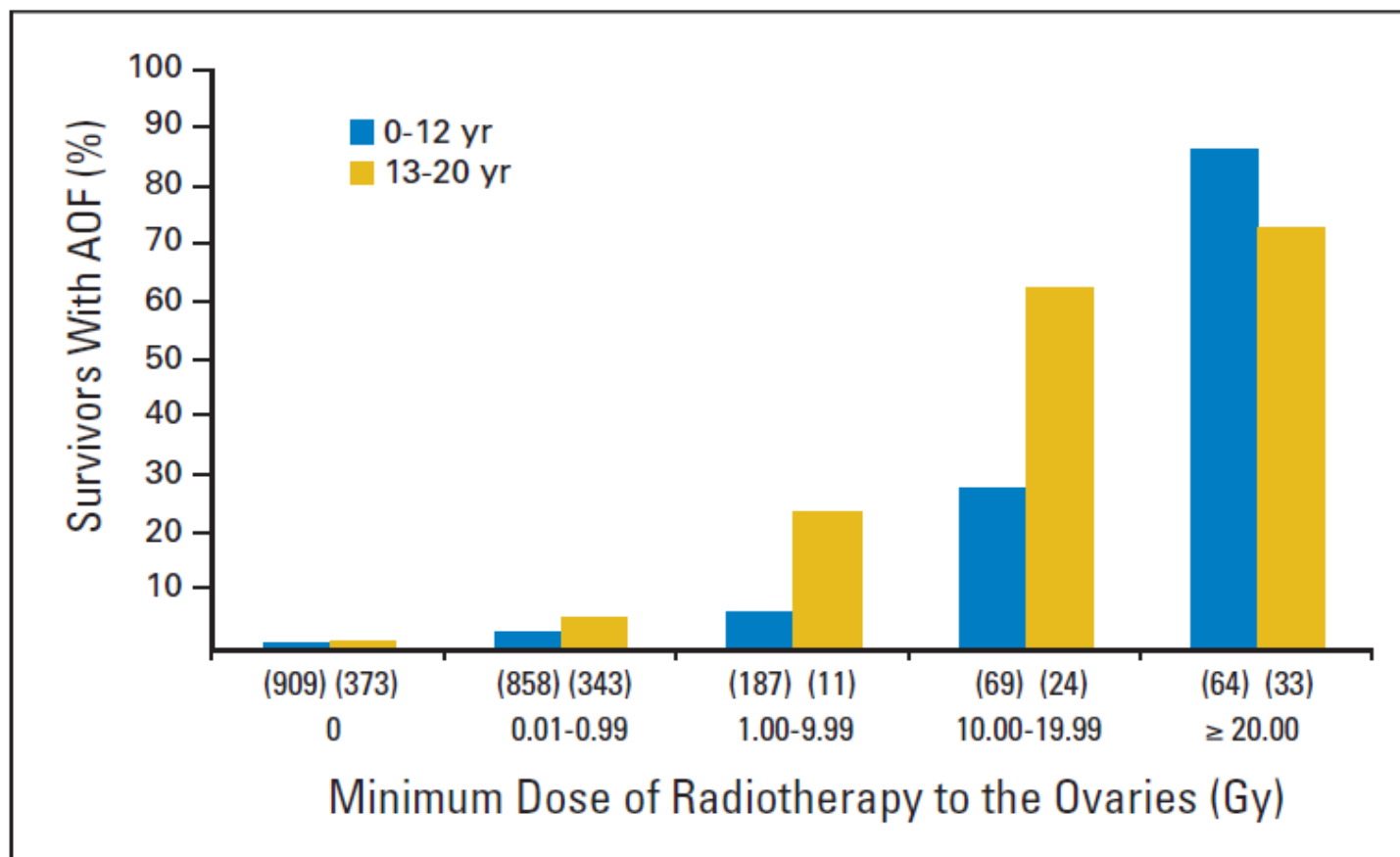


Fig 1. Percentage of subjects with acute ovarian failure (AOF) by age at diagnosis of cancer of 0 to 12 years, 13 to 20 years, and radiation dose to the ovary.

Alkylating agents, abdominal pelvic RT and both

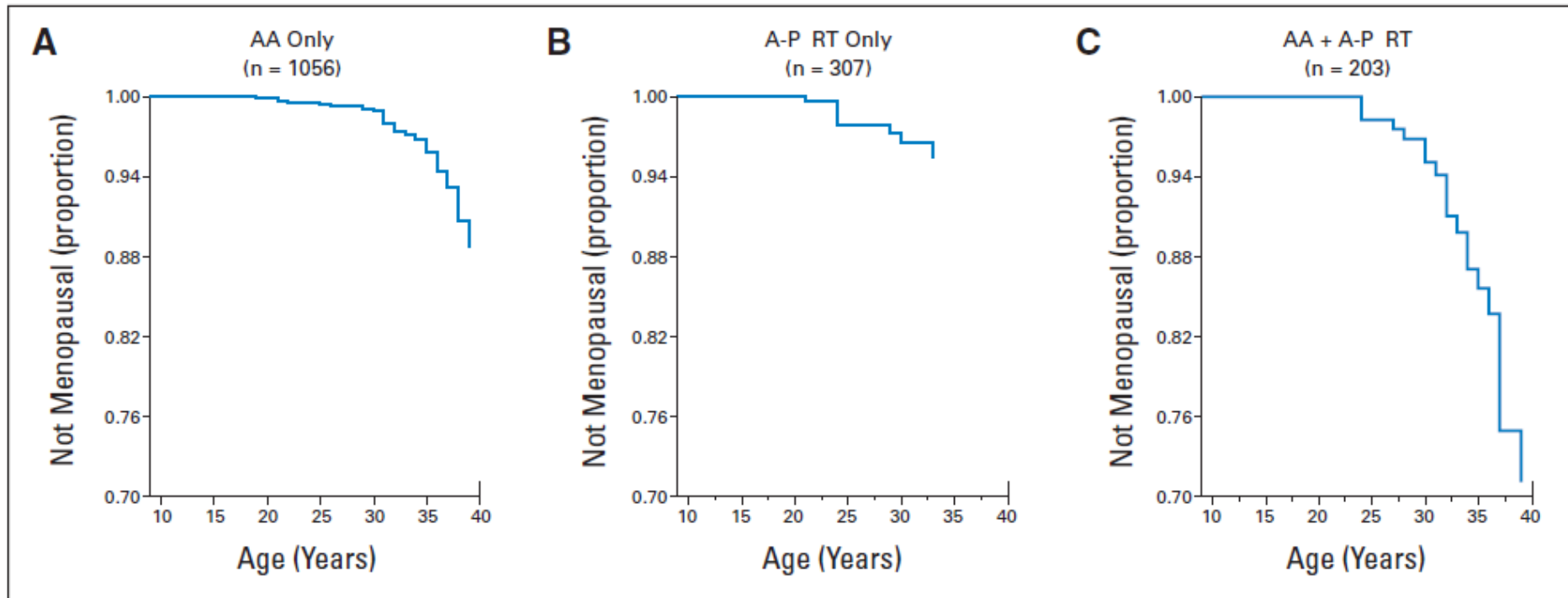
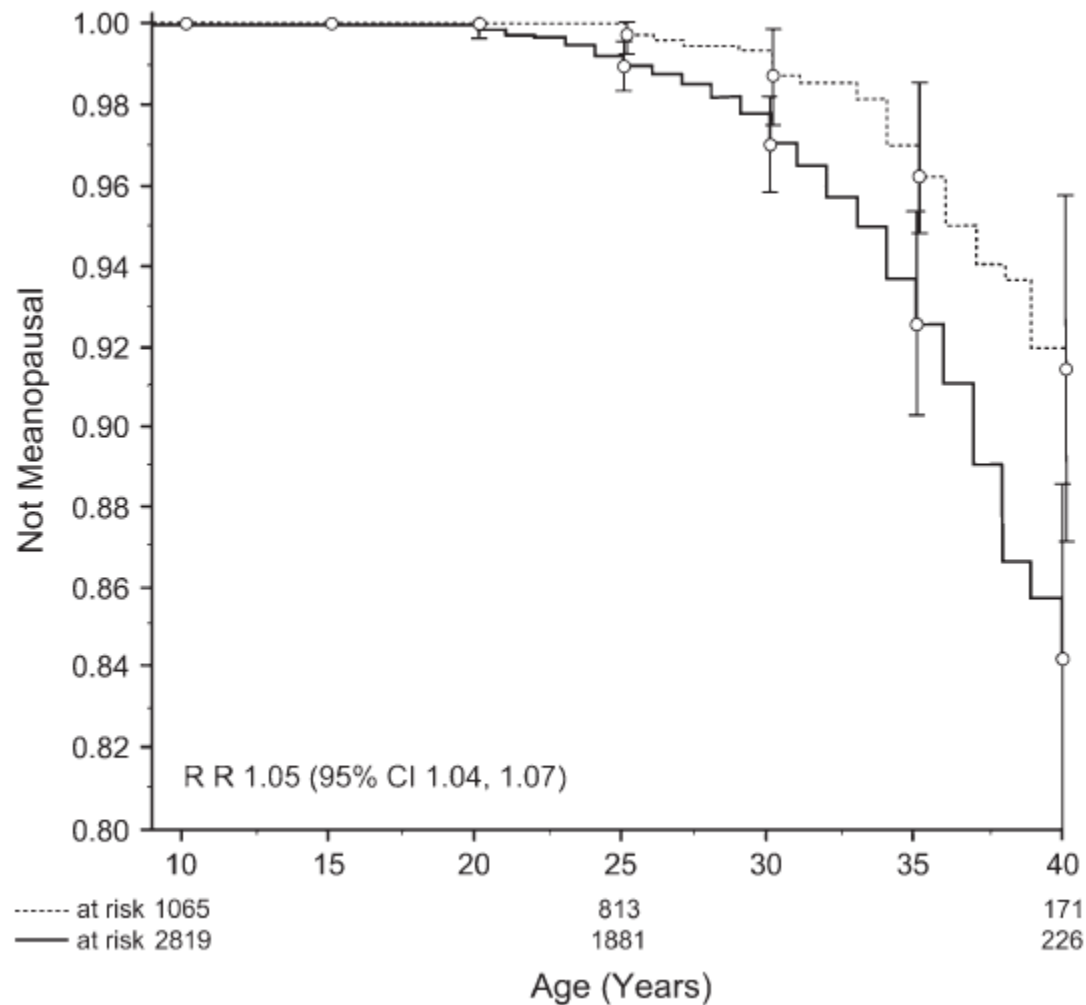


Fig 3. Cumulative incidence curves of nonsurgical premature menopause in survivors according to treatment exposures. (A) Survivors treated with alkylating agents (AA) but not with abdominal-pelvic radiation therapy (A-P RT). (B) Survivors treated with A-P RT but not AA. (C) Survivors treated with AA and A-P RT.

Premature menopause in survivors and siblings



You are cured. Now, hurry up and HAVE A BABY

Dating

Meeting
someone

Risk of relapse

Sexuality



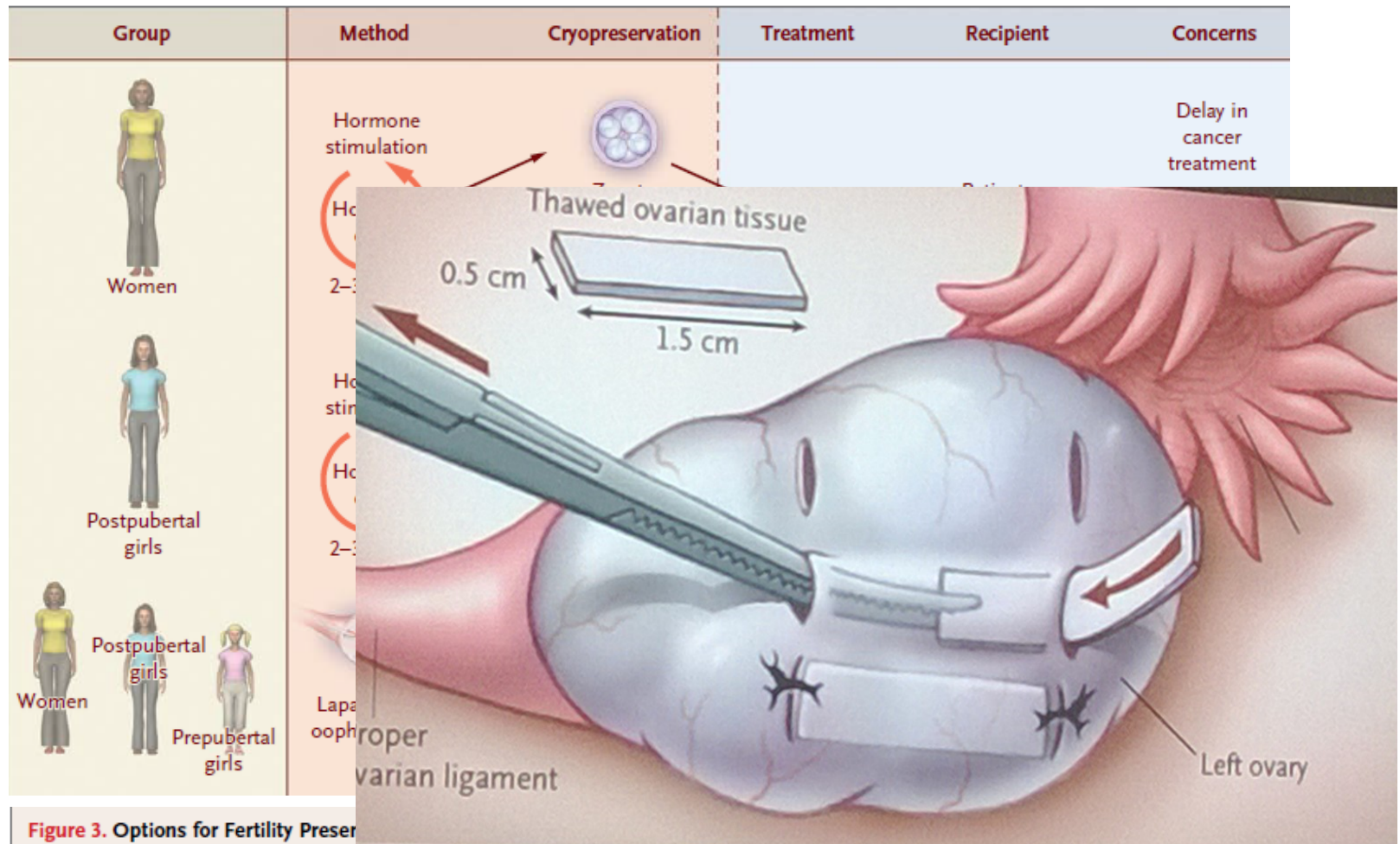
Body
image

Vocational
security

Financial security

Self confidence

Fertility preservation in females



Fertility preservation for patients with cancer:

American Society for Clinical Oncology Clinical Practice Guideline Update *J Clin Oncol 2013*

Key recommendations:

- **PRESENT** both embryo and oocyte preservation
- **DISCUSS** ovarian transposition (oophoropexy) when pelvic radiation is indicated
- **INFORM** patients of conservative surgical options
- **INFORM** that insufficient evidence to support ovarian suppression with GnRH analogs
- **INFORM** that other methods (eg, ovarian tissue cryopreservation are experimental

Edinburg criteria for fertility preservation in children and adolescents

- Age <35 years
- No previous chemotherapy (or low risk)
- High risk (>50%) of ovarian failure:
 - high dose of alkylating agents
 - radiotherapy to the pelvis
- Good (>50%) chance of survival

Adverse pregnancy outcomes

- Spontaneous abortions
- Induced abortions
- Stillbirths
- Perinatal mortality
- Preterm delivery and low birth weight

Abortions, stillbirths and perinatal mortality

Table 1. Pregnancies, Pregnancy Outcomes, and Estimated PRs Among Childhood Cancer Survivors, Sisters, and a Population Comparison Group, With Sisters As Referent

Study Group	Size of Cohort	Pregnancies	Fetuses*	Livebirths				All Abortions†				Stillbirths			
				No.	%	PR‡	95% CI	No.	%	PR‡	95% CI	No.	%	PR§	95% CI
Survivors	1,688	1,479	1,497	1,022	69.1	0.97	0.94 to 1.01	470	31.8	1.06	0.97 to 1.15	5	0.3	1.1	0.4 to 2.9
Sisters	2,737	5,092	5,139	3,574	70.2	1	Referent	1,548	30.4	1	Referent	17	0.3	1	Referent
Population comparisons	16,700	27,989	28,286	19,535	69.8	0.98	0.96 to 1.00	8,657	30.9	1.03	0.99 to 1.08	94	0.3	1.1	0.6 to 1.8

Abbreviation: PR, proportion ratio.

*Multiple births were included in the analyses. For example, twins born alive were counted as one livebirth, whereas a twin who was stillborn would be counted as stillborn and the other as liveborn.

†Including spontaneous abortions, induced abortions, ectopic pregnancies, hydatidiform moles, and other, primarily nonhydatidiform mole and missed abortions.

‡Adjusted for age of mother at pregnancy (linear spline) and calendar time (linear).

§Unadjusted estimate.

Winther et al, J Clin Oncol, 2008

Spontaneous and induced Abortions

Spontaneous Abortions in Childhood Cancer Survivors

Table 2. Various Types of Abortions and Estimated PRs Among Childhood Cancer Survivors, Sisters, and a Population Comparison Group, With Sisters As Referent

Study Group	Spontaneous Abortion (643; DO03)*				Induced Abortion (640-642; DO04-06)*				Ectopic Pregnancy (631; DO00)*				Hydatidiform Mole (631.90, 634.29, 634.60, 634.69, 645.0; DO01)*				Other Types (634.61, 645.1, 645.2; DO02)*†			
	No.	%	PR‡	95% CI	No.	%	PR‡	95% CI	No.	%	PR§	95% CI	No.	%	PR§	95% CI	No.	%	PR§	95% CI
Survivors	109	7.4	1.23	1.00 to 1.52	292	19.7	1.08	0.96 to 1.22	17	1.1	0.9	0.5 to 1.5	3	0.2	1.0	0.2 to 5.0	49	3.3	0.8	0.6 to 1.1
Sisters	304	6.0	1	Referent	961	18.9	1	Referent	66	1.3	1	Referent	10	0.2	1	Referent	207	4.1	1	Referent
Population comparisons	1,718	6.1	0.98	0.87 to 1.11	5,505	19.7	1.07	1.01 to 1.14	433	1.5	1.2	0.9 to 1.6	34	0.1	0.6	0.3 to 1.3	967	3.5	0.8	0.7 to 1.0

Abbreviation: PR, proportion ratio.

*Discharge diagnoses were coded according to a modified version of the *International Classification of Diseases*, eighth revision (ICD-8),¹⁵ until 1993, and thereafter to ICD-10.¹⁶

†Primarily nonhydatidiform mole and missed abortion.

‡Adjusted for age of mother at pregnancy (linear spline) and calendar time (linear).

§Unadjusted estimate.

Stillbirths and neonatal deaths

	All pregnancies lasting at least 20 weeks*	Stillbirth or neonatal death	Relative risk (95% CI) of stillbirth or neonatal death		Relative risk (95% CI) of stillbirth
			Crude	Adjusted†	Adjusted†
Women					
Not treated with radiation	1075	21 (2%)	Reference	Reference	Reference
Radiation dose to uterus and ovaries (Gy)					
0.01–0.99	1404	24 (2%)	0.8 (0.4–1.4)	0.7‡ (0.4–1.4)	0.7§ (0.3–1.5)
1.00–2.49	155	5 (3%)	2.1 (0.8–5.7)	1.9‡ (0.7–5.4)	2.4§ (0.8–7.3)
2.50–9.99	126	5 (4%)	1.6 (0.4–6.0)	1.6‡ (0.4–6.5)	1.9§ (0.5–7.6)
≥10.00	28	5 (18%)	9.2 (3.3–25.4)	9.1‡ (3.4–24.6)	7.3§ (2.3–23.0)

Signorello et al, Lancet, 2010

Stillbirths and neonatal deaths

	Treatment before menarche		Treatment after menarche	
	Risk of stillbirth or neonatal death	Relative risk*† (95% CI)	Risk of stillbirth or neonatal death	Relative risk*‡ (95% CI)
No radiation	5/494 (1%)	Reference	13/447 (3%)	Reference
0.01–0.99 Gy	11/636 (2%)	1.3 (0.5–3.9)	7/599 (1%)	0.3 (0.1–1.0)
1.00–2.49 Gy	3/69 (4%)	4.7 (1.2–19.0)	2/70 (3%)	1.2 (0.2–6.4)
≥2.50 Gy	11/82 (13%)	12.3 (4.2–36.0)	1/85 (1%)	0.2 (0.0–1.4)

Preterm delivery and low birth weight

Birth outcome	Offspring of survivors; N = 1,309 (%)	Offspring of siblings; N = 5,916 (%)	Crude OR	95% CI ¹	Adjusted OR ²	95% CI
Preterm birth (<37wks)	102 (7.8%)	298 (5.0%)	1.59	1.26–2.01	1.46	1.14–1.85
Preterm birth (<34wks)	31 (2.4%)	71 (1.2%)	2.0	1.30–3.06	1.75	1.12–2.72
Low birth weight	80 (6.1%)	221 (3.7%)	1.68	1.29–2.18	1.11 ³	0.76–1.64
Small-for-gestational-age	37 (2.8%)	162 (2.7%)	1.03	0.72–1.48	0.89	0.61–1.29

Madanat-Harjuoja et al, Int J Cancer, 2010

Risk of preterm birth by radiation dose

	Preterm birth, N (%)†	Full-term birth, N (%)†	OR (95% CI)	P‡
Not treated with any radiation	121 (19.6)	496 (80.4)	1.0 (referent)	
Radiation dose to uterus, cGy (treatment at all ages)				
0–10	81 (17.3)	386 (82.7)	0.9 (0.6 to 1.4)	.72
10–50	53 (19.9)	214 (80.1)	1.2 (0.7 to 2.0)	.53
50–250§	74 (26.1)	209 (73.9)	1.8 (1.1 to 3.0)	.03
250–500	21 (39.6)	32 (60.4)	2.3 (1.0 to 5.1)	.04
>500	23 (50.0)	23 (50.0)	3.5 (1.5 to 8.0)	.003

Signorello et al., JNCI, 2006

Pubertal status and risk of preterm delivery

	Preterm birth, N (%)†	Full-term birth, N (%)†	OR (95% CI)	P‡
Radiation dose to uterus, cGy (treatment premenarche)				
0–10	29 (16.9)	143 (83.1)	0.9 (0.5 to 1.9)	.85
10–50	23 (27.4)	61 (72.6)	2.2 (1.0 to 4.8)	.05
50–250	21 (26.3)	59 (73.8)	2.1 (1.0 to 4.6)	.05
>250	15 (48.4)	16 (51.6)	4.9 (1.7 to 13.9)	.003
Radiation dose to uterus, cGy (treatment postmenarche)				
0–10	39 (21.2)	145 (78.8)	1.2 (0.6 to 2.4)	.69
10–50	20 (15.4)	110 (84.6)	0.8 (0.3 to 1.7)	.52
50–250	39 (27.5)	103 (72.5)	1.8 (0.8 to 4.3)	.18
>250	24 (40.7)	35 (59.3)	1.9 (0.7 to 4.9)	.21

Other adverse obstetric outcomes

Table 3. Crude and Adjusted Odds Ratios for Pregnancy and Birth Outcomes in Women With a History of Cancer Compared With Women Without a History of Cancer

	Cancer Survivors (Exposed Group) N=917 [n (%)]	Women Without a History of Cancer (Unexposed Group) N=5,496 [n (%)]	P	Crude OR (95% CI)	Adjusted OR (95% CI)*
Preeclampsia	51 (5.6)	378 (6.9)	.140	0.80 (0.59–1.08)	1.07 (0.78–1.48)
Antepartum hemorrhage	22 (2.4)	83 (1.5)	.050	1.60 (1.00–2.58)	1.54 (0.92–2.57)
Preterm premature rupture of membranes	58 (6.3)	116 (2.1)	<.001	3.13 (2.27–4.33) [†]	1.39 (0.98–1.98)
Induction of labor	271 (29.6)	1,527 (27.8)	.271	1.09 (0.94–1.27)	1.00 (0.85–1.18)
Malpresentation	58 (6.3)	293 (5.3)	.221	1.20 (0.90–1.60)	1.10 (0.80–1.50)
Operative delivery (abdominal or vaginal)	454 (49.6)	1,857 (33.8)	<.001	1.93 (1.67–2.22) [†]	1.33 (1.14–1.54) [†]
Instrumental vaginal delivery (forceps/vacuum)	204 (22.2)	911 (16.6)	<.001	1.44 (1.21–1.71) [†]	1.24 (1.03–1.49) [†]
Cesarean delivery	250 (27.3)	946 (17.2)	<.001	1.80 (1.53–2.12) [†]	1.19 (1.00–1.41)
Postpartum hemorrhage	43 (4.7)	220 (4.0)	.332	1.18 (0.84–1.65)	1.56 (1.09–2.23) [†]

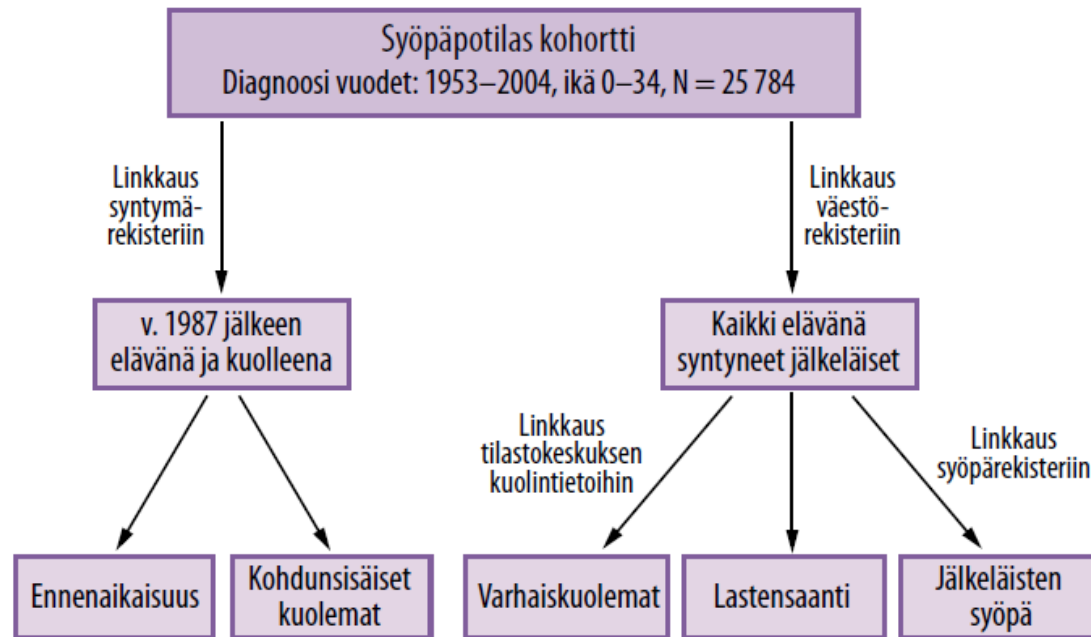
Cardiac surveillance during pregnancy

Cardiomyopathy surveillance *is reasonable* prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and /or chest irradiation

No recommendation could be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal cardiac function immediately prior to or during the first trimester of pregnancy

"Health care providers should maintain a high index of suspicion for cardiomyopathy in survivors treated with anthracyclines and/or radiation who present with shortness of breath, fatigue or ankle swelling as they are commonly reported during pregnancy"

The Finnish Cancer Survivor Study



KUVA.

Results

TAULUKKO. Syöpäpotilaiden lastensaannin sekä syntyvien lasten ennenaikaisuuden ja pienipainaisuuden riskisuhteet (vertailuryhmänä potilaiden sisarukset).

	Potilaat (%)	Sisarukset (%)	Naiset		Miehet	
			RR	95 %:n LV	RR	95 %:n LV
Lastensaanti	15,0	58,0	0,46	0,44–0,48	0,57	0,54–0,60
Ennenaikaisuus						
(alle 37 viikkoa)	7,8	5,0	1,46	1,14–1,85		
(alle 34 viikkoa)	2,4	1,2	1,75	1,12–2,72		
Vastasyntyneen pienipainaisuus (alle 2 500 g)	6,1	3,7	1,11	0,76–1,64		

Ydinasiat

- need for accurate, patient specific risk to fertility and ovarian function
- development of evidence –based algorithms to enable truly informed clinical oncofertility decisions
- fertility should be discussed at diagnosis

Ydinasiat

- women who have received abdomino-pelvic irradiation are at risk of preterm delivery
- women who have received chest RT or anthracyclines should be screened with cardiac US at baseline
- a large proportion of survivors have metabolic/ cardiovascular risk factors which may complicate pregnancy
- adequate treatment of early menopause to reduce risk of associated morbidities

NOPHO

Nordic Society of Paediatric Haematology and Oncology

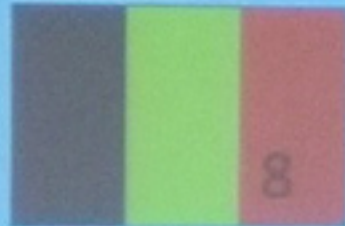
Annual Meeting

WELCOME

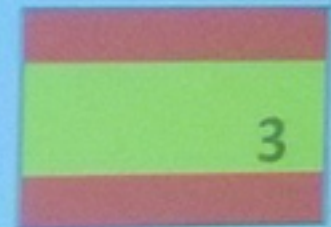
2015

MAY 22ND - MAY 26TH
OULU, FINLAND

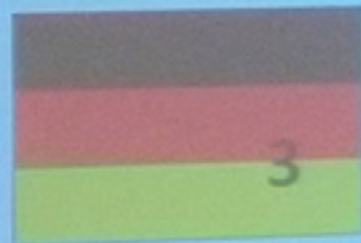
Children born from transplantation of frozen/thawed ovarian tissue



All Normal Babies
weight and duration
Orthotopic >> heterotopic



All except for one is a result of a
slow-freezing protocol



An estimated excess of 150
transplantations have been performed

