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Primary Ovarian Insufficiency in Childhood Cancer Survivors: A Report from the St. Jude Lifetime (SJLIFE) Cohort

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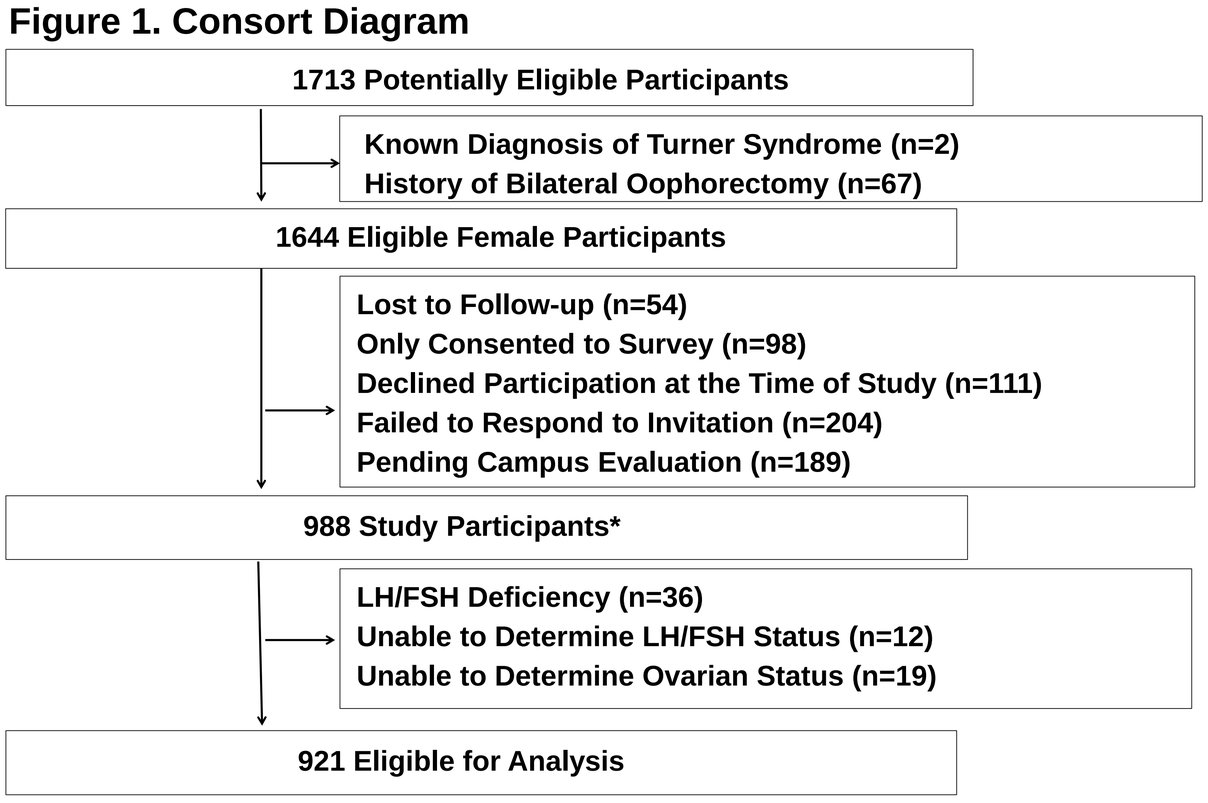
Introduction

- Primary ovarian insufficiency (POI) and infertility are common concerns of female childhood cancer survivors (CCS) and are known to adversely impact their quality of life.
- Patients with POI may present with delayed or arrested puberty or persistent amenorrhea within the first 5 years of completing therapy (acute ovarian failure [AOF]) or cessation of menses more than 5 yrs after completing therapy but before age 40 yrs (premature menopause [PM]).
- The objective of this study was to describe the prevalence of and risk factors for POI in a cohort of adult CCS.

Patients and Methods

- Cross-sectional study of clinically assessed participants in SJLIFE, an established cohort of adult CCS who have survived their initial cancer for ≥ 10 years (Figure 1).
- The diagnosis of POI, AOF and PM was based on the medical history in regards to puberty, menarche, menses, pregnancies, childbirth, use of hormonal therapies and timing of menopause supplemented by clinical data and laboratory results from the SJLIFE evaluation.
- In amenorrheic women <40 years old who were not on hormonal therapies such as oral contraceptives, estradiol <17 pg/mL associated with FSH >30 IU/L were considered indicative of POI.
- Multivariable logistic regression was used to study associations between demographic and treatment-related risk factors and POI.
- The mean radiation dose based on the estimated average location was used to calculate the ovarian radiotherapy dose.
- Exposure to alkylating agents (AA) was quantified using the validated cyclophosphamide equivalent dose (CED).

Figure 1. Consort Diagram



*Study participants were more likely to have received treatment with cranial radiation (p=0.03) or AA (p<0.0001) than non-participants. No differences were noted in terms of age at cancer diagnosis, demographic or lifestyle factors between study participants and non-participants.

Table 1. Risk factors of POI: Multivariable Analysis

	Primary Ovarian Insufficiency (AOF or PM)				
Characteristic	n	%	OR	CI	p
Age at study (years)					
18 – 25	42	6.75	1.00		
>25	58	19.40	6.55	2.8-15.37	<0.0001
BMI (kg/m^2)					
18.5-24.9	42	12.43	1.00		
<18.5	12	27.91	1.97	0.4-9.74	0.4
25-29	29	12.95	1.12	0.49-2.56	0.79
≥30	17	5.38	0.27	0.1-0.7	0.01
Ovarian radiation dose (cGy)†					
None	10	1.39	1.00		
>0 to 999	21	24.42	11.77	4.18-33.1	<0.0001
≥1000	52	65.82	254.23	93.78-686.15	<0.0001
CED (mg/m^2)					
0	19	5.01	1.00		
> 0 to < 8000	32	12.75	2.04	0.78-5.37	0.15
≥ 8000 to < 12000	16	9.76	2.59	0.82-8.16	0.1
≥ 12000	33	25.98	4.71	1.67-13.29	0.004

Table 2. Risk factors of AOF: Multivariable Analysis

	Acute Ovarian Failure (AOF)				
Characteristic	n	%	OR	CI	p
Age at study (years)					
18 – 25	28	4.50	1.00		
>25	30	10.03	3.84	1.59-9.29	0.003
BMI (kg/m^2)					
18.5-24.9	27	7.99	1.00		
<18.5	7	16.28	0.86	0.2-3.64	0.83
25-29	15	6.7	0.84	0.33-2.14	0.71
≥ 30	9	2.85	0.29	0.09-0.92	0.04
Ovarian radiation dose (cGy)*†					
None	2	0.28	1.00		
>0 to 999	8	9.3	36.87	7.69-176.7	<0.0001
≥1000	38	48.10	333.20	77.7-1429.5	<0.0001
CED (mg/m^2)					
0	14	3.69	1.00		
> 0 to < 8000	18	7.17	1.38	0.49-3.87	0.54
≥ 8000 to < 12000	11	6.71	2.04	0.56-7.44	0.28
≥ 12000	15	11.81	1.32	0.43-4.12	0.63

Table 3. Risk factors of PM: Multivariable Analysis

	Premature Menopause (PM)				
Characteristic	N	%	OR	CI	p
Age at study (years)					
18– 25	14	2.25	1.00		
>25	28	9.36	3.03	1.27-7.21	0.01
Ovarian radiation dose (cGy)					
None	8	1.11	1.00		
>0 to 999	18	15.12	8.90	2.93-32.24	0.0001
≥1000	9	17.72	14.55	5.53-38.33	<0.0001
CED (mg/m^2)					
0	5	1.32	1.00		
> 0 to < 8000	14	5.58	2.59	0.73-9.22	0.14
≥ 8000 to < 12000	5	3.05	2.11	0.48-9.21	0.32
≥ 12000	18	14.7	6.05	1.77-20.66	0.004

†= Radiation dose information missing on n=7 patients.
*= Univariable analysis was used because of OR>999.9 and very wide confidence interval.

Results

- 921 patients (median age 31.7 years, range 19.0-60.6) were evaluated at a median of 24.0 years (range 10.2-48.1) after the primary diagnosis.
- 153 (13.3%) were exposed to pelvic radiation and 546 (59.3%) to AA.
- 100 (10.9%) had POI; 58 had AOF and 42 PM.
- Associations between risk of POI, age > 25 years at the time of the study, ovarian exposure to any radiotherapy and CED ≥ 12000 mg/m2 were found to be significant (Table 1).
- Similar associations were noted when AOF and PM were assessed as separate outcomes (Tables 2 and 3).

Conclusions

- POI is a frequent complication of childhood cancer and its treatments with a prevalence of nearly 11%.
- POI was associated with any dose of radiation to the ovaries and CED ≥ 12000 mg/m^2. Increased risk of POI in older survivors (> 25 years old) highlights its possible occurrence as a late-effect.
- Host factors affecting ovarian reserve may influence vulnerability to cancer treatments; genetic markers in particular deserve further study.

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