Journal of Clinical Endocrinology and Metabolism
Volume 91 • Number 5 • May 2006

Endocrine Care

Acute Ovarian Failure in the Childhood Cancer Survivor Study

Wassim Chemaitilly [1] [2]
Ann C. Mertens [3]
Pauline Mitby [3]
John Whitton [4]
Marilyn Stovall [5]
Yutaka Yasui [6]
Leslie L. Robison [7]
Charles A. Sklar [1]

[1] *Department of Pediatrics (W.C., C.A.S.), Memorial Sloan-Kettering Cancer, New York, New York 10021;*
[2] *Division of Pediatric Endocrinology (W.C.), New York Presbyterian Hospital, Weill Cornell Medical College, New York, New York 10021;*
[3] *Department of Pediatrics (A.C.M., P.M.), University of Minnesota School of Medicine, Minneapolis, Minnesota 55455;*
[4] *Cancer Prevention Research Program (J.W.), Fred Hutchinson Cancer Research Center, Seattle, Washington 98104;*
[5] *Department of Radiation Physics (M.S.), University of Texas, M.D. Anderson Cancer Center, Houston, Texas 77030;*
[6] *Department of Public Health Sciences (Y.Y.), University of Alberta, Edmonton, Alberta, Canada T6G2G3;*
[7] *and Department of Epidemiology and Cancer Control (L.L.R.), St. Jude Children's Research Hospital, Memphis, Tennessee 38105*

Received January 5, 2006.
Accepted February 13, 2006.

Address all correspondence and requests for reprints to: Charles A. Sklar, Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021. E-mail: sklarc@mskcc.org.

This work was supported by U24-CA55727 and R01CA79024 (awarded to C.A.S.) from the National Institutes of Health.

Disclosures: The authors have nothing to declare.

F

Abbreviations:

AOF

AOF
: Acute ovarian failure

CCSS
: Childhood Cancer Survivor Study

CI
: confidence interval

OR
: odds ratio

Context: Defined as the loss of ovarian function within 5 yr of diagnosis, acute ovarian failure (AOF) is known to develop in a subset of survivors of pediatric and adolescent cancers. Its precise incidence is unknown, and data concerning its risk factors are limited.

Objective: Our objective was to determine the incidence of and patient/treatment factors associated with AOF in a large cohort of pediatric cancer survivors.

Design and Setting: We conducted a retrospective cohort, multi-center study.

Patients: Female participants from the Childhood Cancer Survivor Study who were greater than 18 yr of age were considered for inclusion. We excluded survivors who received cranial irradiation at doses of more than 3000 cGy, those with hypothalamic/pituitary tumors, and survivors who underwent bilateral oophorectomy. Survivors who reported never menstruating or who had ceased having menses within 5 yr after their cancer diagnosis were considered to have AOF.

Main Outcome: We assessed incidence and risk factors for AOF.

Results: Of a total of 3390 eligible survivors, 215 cases (6.3%) developed AOF. Survivors with AOF were older at diagnosis and more likely to have been diagnosed with Hodgkin's lymphoma or to have received abdominal or pelvic radiotherapy than survivors without AOF. Among survivors with AOF, 116 (54%) had received at least 1000-cGy ovarian irradiation. In a multivariable logistic regression model, increasing doses of ovarian irradiation, exposure to procarbazine, and exposure to cyclophosphamido at ages 13–20 yr were independent risk factors for AOF.

Conclusions: AOF develops in a small subset of survivors, especially those treated with at least 1000-cGy ovarian radiation. These results will facilitate patient counseling and selection of candidates for newer fertility preservation techniques. (*J Clin Endocrinol Metab* 91: 1723–1728, 2006)

SURVIVAL RATES FOR children and adolescents with cancer have increased markedly over the past 30 yr as a result of advances in supportive care and changes in cancer therapies. The use of multimodality therapy (*e.g.* combining surgery, multiagent chemotherapy, and radiotherapy) is now routine in the treatment of children with cancer. The 5-yr survival rates currently exceed 70% in children and adolescents, are near 80% in those treated for acute lymphoblastic leukemia, and are above 90% in those treated for Hodgkin's lymphoma [1] . Beyond survival, attention is increasingly drawn to the consequences of cancer and its treatments and to the different health issues surrounding cancer survivorship. In particular, abdominal, pelvic, and spinal radiotherapy and certain chemotherapeutic drugs, especially alkylating agents, have been shown to increase the risk of ovarian failure in female cancer survivors [2] [3] [4] [5] [6] [7] .

Depending on the extent of damage to the ovaries, two forms of premature ovarian failure can be distinguished [8] . The subset of survivors that loses ovarian function during cancer therapy or shortly after its completion is classified as having acute ovarian failure (AOF). For survivors who retain ovarian function after the completion of cancer treatment, a subset will go on to experience menopause before age 40 yr and is classified as having premature menopause [4] [8] . Subjects at high risk of developing AOF may benefit from the newer techniques of fertility preservation (*e.g.* ovarian tissue cryopreservation) and need to be counseled accordingly [9] . However, the data on the incidence of and risk factors for AOF are somewhat limited. Furthermore, previous studies are often based on small cohorts of patients, and generally the data regarding therapeutic exposures are incomplete [2] [10] .

In the present work, we have assessed the incidence of AOF as well as the patient and treatment factors associated with AOF in a large cohort of subjects enrolled in the Childhood Cancer Survivor Study (CCSS) [11] . A unique strength of this cohort, beyond its size, is the availability of detailed treatment information,

including cumulative doses of key chemotherapeutic agents and estimates of radiation dose to the ovaries [12] .

First Published Online February 21, 2006

Subjects and Methods

CCSS

The details of the conduct and characteristics of the CCSS, also known to study participants as the Long-Term Follow-Up Study, have been published previously [11] . In brief, the CCSS is a retrospective cohort of 5-yr survivors of childhood cancer diagnosed before the age of 21 yr between the years 1970 and 1986 and treated at one of the 26 contributing centers located in the United States or Canada (see *Acknowledgments*). The primary aim of the study is to determine late adverse outcomes that follow treatment for childhood and adolescent cancer. The CCSS has been approved by the Institutional Review Board at the University of Minnesota (the study coordinating center) and each of the participating centers.

Participation in the Long-Term Follow-Up Study consisted of completion of a 24-page baseline questionnaire (all CCSS questionnaires are available at http://www.cancer.umn.edu/ccss). A proxy completed the baseline questionnaire if the participant was less than 18 yr at entry or was deceased after achieving 5-yr survivorship but before study entry. In addition, detailed medical information was abstracted from the medical record of each participant. Data collected included all treatments for the primary diagnosis, including the initial treatment for any relapse, and preparatory regimens for bone marrow transplant. Information about cancer treatment included qualitative information on 42 chemotherapeutic agents, quantitative information on 22 selected chemotherapeutic agents, surgeries performed from the time of diagnosis, and quantitative radiation data on field size, site, and dose.

AOF study

The inclusion criteria consisted of female CCSS participants who were greater than 18 yr of age at the time of completion of the questionnaire (see below) and for whom menstrual history was available. Exclusion criteria were diagnoses associated with ovarian dysfunction (*e.g.* Turner syndrome), cranial irradiation above 3000 cGy (known to cause hypogonadotropic hypogonadism) [3] , tumor located in the hypothalamicpituitary region, history of bilateral oophorectomy, and incomplete radiation records.

Of the 14,372 participants in the CCSS, 6,079 females were greater than 18 yr and known to be alive as of November 2000. Of those 6079 survivors 4608 (76%) completed a follow-up questionnaire (complete questionnaire is available at www.cancer.umn.edu/ccss) during 2000 and 2001. This questionnaire included a specific section on menstrual status, which requested information on age at menarche, current menstrual status, age at last menstrual period, and etiology of menopause (*i.e.* surgical *vs.* nonsurgical) for those who were currently menopausal. From among these 4608 subjects, 1218 patients were excluded. Thus, 3390 survivors were deemed eligible for this study. Survivors who reported never menstruating or who reported that they had ceased having spontaneous menses within 5 yr after their cancer diagnosis were considered to have AOF.

Radiation dosimetry

Radiation dose to the ovaries and pituitary was quantified by a radiation dosimetrist who evaluated radiation therapy records collected by the 26 centers. Complete records included photographs of patients in treatment position or diagrams of treatment fields, beam energy, field size, blocking information, and daily treatment doses. When diagrams were not available, a written description of the treatment from the radiation therapy record or medical record was used to estimate the extent of the treatment and the dose administered. For treatments very near the sites of interest, the records were reviewed to determine oophoropexy status, special gonadal shielding, beam shaping blocks, and field location. Doses from all treatment fields were summed and included the contribution of primary and scatter radiation [12] . If the surgical notes indicated an oophoropexy,

the dose to the ovary was reduced to approximately 10% of the in-beam dose. Doses to right and left ovaries were estimated separately.

Chemotherapy

Seven broad categories of drug classes of chemotherapy were identified from treatment records: alkylating agents, alkaloids, platinum-containing agents, antimetabolites, topoisomerase inhibitors, antibiotics, and steroids. The total exposure to alkylating agents was measured by calculating an alkylating agent score, accounting for both the number of drug exposures as well as the cumulative doses administered. Specifically, for each alkylating agent, the total dose in milligrams per square meter was calculated for each subject. The distribution of the doses received by all subjects in the CCSS cohort was determined for each alkylating agent. Each subject was assigned a score of 0, 1, 2, or 3 for each drug depending on whether the individual received no drug or fell into the lower, middle, or upper tertile of the distribution. The individual scores were summed, and the subjects were assigned an overall alkylating agent score of 0, 1, 2, or 3 depending on where the individual fell in the overall distribution [13] . Exposure to individual alkylating agents was also considered as separate dichotomous variables (yes or no).

Statistical analysis

Study participants were categorized into two groups: survivors with AOF and nonaffected survivors. Furthermore, survivors were divided into two age groups: subjects no more than 12 yr at diagnosis and those more than 12 yr at diagnosis. These age cutoffs were meant to correspond to survivors who were likely prepubertal (≤12 yr) or pubertal (>12 yr) at diagnosis. Cumulative doses of radiotherapy received by the ovaries were calculated and grouped as follows: less than 100, 100–999, 1000–1999, and 2000 cGy and above. Study subjects' ages at diagnosis and at completion of the menstrual history questionnaire were expressed as the mean ± SD; univariate comparisons between subjects with AOF and nonaffected survivors were made using Student's *t* test, and univariate associations of AOF and categorical variables were assessed by χ^2 test. Logistic regression was used to estimate the odds ratio (OR) with 95% confidence intervals (CI) for having AOF to account for the effect of the different patient characteristics, primary diagnoses, and treatment modalities. A multivariable logistic regression model was then constructed to estimate the effects of independent risk factors for AOF. We included interactions between age at diagnosis and treatment risk factors to investigate whether treatment-related risks varied with age at treatment. The Akaike information criterion was used as a guide in determining a final model that best explained the data [14] .

Results

Of a total of 3390 survivors included in the study, 215 cases (6.3%) developed AOF. The characteristics of patients with AOF and of the nonaffected survivors are summarized in Table 1 . Compared with survivors who did not develop AOF, survivors with AOF were older at diagnosis (9.8 ± 6.0 *vs.* 8.3 ± 6.0 yr; $P < 0.004$), were more likely to have been diagnosed with Hodgkin's lymphoma (30.7 *vs.* 15.3%; $P < 0.001$), and were more likely to have been exposed to an alkylating agent (67 *vs.* 48.6%; $P < 0.001$) and to abdominal/pelvic radiotherapy (75.3 *vs.* 21.1%; $P < 0.001$). Among survivors with AOF, 116 individuals (*i.e.* 54% of all cases of AOF and 72% of all cases treated with abdominal/pelvic radiation) had received an estimated dose of at least 1000 cGy to the ovary.

The univariate analysis showed that the following variables were all significantly associated with the occurrence of AOF: age at diagnosis above 12 yr; diagnoses of Hodgkin's lymphoma, non-Hodgkin's lymphoma, Wilms' tumor, and soft-tissue sarcoma; exposure of the ovaries to increasing doses of radiotherapy; and treatment with chemotherapy in general as well as exposure to various alkylating agents (Table 2). The multivariable logistic regression model revealed that the independent risk factors for AOF were age at diagnosis, exposure of the ovaries to radiotherapy, and exposure to cyclophosphamide and procarbazine. There were significant interactions between age at diagnosis and high

TABLE 1 -- Patient characteristics and treatment variables

	Survivors	Nonaffected

Characteristics	with AOF	survivors
Total population	215	3175
Mean age at diagnosis (yr)	9.8 (SD 6.0)	8.3 (SD 6.0) [b]
Mean age at study (yr)	32.9 (SD 6.8)	29.6 (SD 7.4) [a]
Age at diagnosis (yr), n (%)		
0–12	121 (56.2)	2221 (70.0)
13–20	94 (43.8)	954 (30.0) [a]
Diagnosis, n (%)		
Acute lymphoblastic leukemia	31 (14.4)	1001 (31.5)
Acute myeloblastic leukemia	12 (5.6)	87 (2.7) [a]
Hodgkin's lymphoma	66 (30.7)	487 (15.3) [a]
Non-Hodgkin's lymphoma	19 (8.8)	168 (5.3) [a]
Wilms' tumor	35 (16.3)	329 (10.4) [a]
Neuroblastoma	11 (5.1)	237 (7.5)
Soft-tissue sarcoma	27 (12.6)	290 (9.1) [a]
Other	14 (6.5)	576 (18.2)
Treatment, n (%)		
Chemotherapy ± surgery only	12 (5.6)	949 (30) [a]
RT ± surgery only	14 (6.5)	284 (8.9)
Chemotherapy + RT ± surgery	189 (87.9)	1623 (51.1) [a]
Exposure to AA	144 (67.0)	1540 (48.6) [a]
Exposure to cyclophosphamide	119 (55.3)	1336 (42.1) [a]
Exposure to procarbazine	53 (24.7)	276 (8.7) [a]
Abdominal/pelvic RT	162 (75.3)	670 (21.1) [a]
Abdominal/pelvic RT + AA	113 (52.6)	280 (8.8) [a]
ORT 1–99 cGy	40 (18.6)	1161 (36.6) [a]
ORT 100–999 cGy	38 (17.7)	260 (8.2) [a]
ORT 1000–1999 cGy	34 (15.8)	59 (1.9) [a]
ORT > 2000 cGy	82 (38.1)	18 (0.6) [a]
Stem cell transplantation	19 (8.8)	42 (1.3) [a]

Radiation dose to the ovaries was calculated only when treatment records were complete and of sufficient quality to permit an accurate assessment of exposure. RT, Radiotherapy; AA, alkylating agent; ORT, ovarian radiation therapy.

[b] $P = 0.004$.

[a] $P < 0.001$.

doses of radiotherapy to the ovary ($P = 0.03$ for dose ≥ 2000 cGy) and between age at diagnosis and treatment with cyclophosphamide ($P = 0.0006$), with this drug being a significant risk factor only for the older age group. Table 3 shows the treatment-related risk factors obtained by the multivariable model for each age group. Figure 1 illustrates the percentage of subjects who developed AOF according to age and radiation dose delivered to the ovaries. For subjects who developed AOF despite receiving radiation doses to the ovaries of less than 1000 cGy, 55% were older than age 12 yr at diagnosis and 72% had been exposed to alkylating agents.

Discussion

The precise incidence of therapy-related adverse effects and the chances that a particular individual will experience them are of critical importance to patients and families as they embark on cancer treatment. In the current study, we have characterized these parameters for AOF in childhood cancer survivors using data from the multicenter CCSS cohort.

AOF appears to occur in a small subset of childhood cancer survivors. The incidence of AOF in the CCSS cohort was 6.3%. This is substantially lower than the 12% previously reported by Stillman *et al.* [2] , who described data in a cohort of 182 childhood cancer survivors with a large percentage of survivors of Wilms' tumor (29%) and only a small number

TABLE 2 -- Risk factors associated with AOF: univariate associations

Characteristic	n	OR	95% CI	*P*
Age at diagnosis (yr)				
0–12	121	1.0		
13–20	94	1.8	1.4–2.4	<0.0001
Diagnosis				
HL	66	3.8	2.7–5.4	<0.0001
NHL	19	3.2	1.8–5.3	<0.0001
Wilms'	35	3.0	1.9–4.5	<0.0001
SST	27	2.6	1.6–4.1	<0.0001
Others	68	1.0		
Chemotherapy drugs				
None	14	1.0		
Any	201	3.3	2.0–6.1	<0.0001
Cyclophosphamide	119	1.7	1.3–2.3	0.0002
Busulfan	2	9.9	1.3–60.1	0.01
CCNU	10	4.1	1.9–8.1	<0.0001
Chlorambucil	6	7.6	2.6–19.7	<0.0001
Nitrogen mustard	20	1.7	1.0–2.6	0.04
Procarbazine	53	3.4	2.4–7.8	<0.0001
Alkylator score				
0	71	1.0		
1	41	1.5	1.0–2.2	0.05
2	33	1.7	1.1–2.6	0.01
3	42	2.9	1.9–4.3	<0.0001
Radiotherapy				
None	12	1.0		
Any	203	11.2	6.5–21.2	<0.0001
Pelvis or abdomen	162	25.4	14.7–48.6	<0.0001
Other sites	41	3.5	1.9–6.9	0.0002
Minimum ovarian irradiation dose (cGy)				
0	12	1.0		
1–99	40	3.7	2.0–7.3	<0.0001
100–999	38	15.5	8.2–31.3	<0.0001
1000–1999	34	61.0	30.8–128.4	<0.0001
≥2000	82	482.1	233.4–1082.9	<0.0001
Maximum ovarian irradiation dose (cGy)				

0	12	1.0		
1–99	39	3.6	1.9–7.2	0.0001
100–999	35	15.7	8.3–32.0	<0.0001
1000–1999	31	47.4	23.9–99.8	<0.0001
≥2000	89	195.6	103.9–399.1	<0.0001

Alkylating agent score and radiation dose to the ovaries were calculated only when treatment records were complete and of sufficient quality to permit an accurate assessment of exposure. Others (under *Diagnosis*) indicates reference group for the comparison among diagnoses. HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; SST, soft-tissue sarcoma.

of leukemia survivors (5%), a distribution quite different from that observed in the general pediatric population [15] . The higher incidence of AOF reported by this group may be due to the high doses of radiation received by the ovaries in girls treated for Wilms' tumor during this era. In a more recent study, Larsen *et al.* [10] reported on ovarian function of 100 childhood cancer survivors diagnosed and treated before the age of 15 yr. The distribution of cancer diagnoses was similar to that observed in the CCSS cohort; 8% of the survivors had AOF, if we apply our diagnostic criteria to that population.

Our data indicate that radiotherapy to the ovaries was the most significant risk factor for AOF, a finding that is consistent with previous reports [7] [16] [17] [18] [19] [20] . Of survivors who developed AOF, 75% had been previously exposed to abdominal-pelvic

TABLE 3 -- Risk factors associated with AOF: multivariable logistic regression model

Age at diagnosis [a]	Risk factor	OR	95% CI	*P*
0–12 yr	Exposure to procarbazine			
	No	1.0		
	Yes	3.2	1.3–7.3	0.01
	Exposure to cyclophosphamide			
	No	1.0		
	Yes	1.2	0.7–2.1	0.4
	Minimum ovarian irradiation dose (cGy)			
	0	1.0		
	1–99	3.7	1.6–10.2	0.005
	100–999	9.0	3.4–26.5	<0.0001
	1000–1999	55.3	22.3–157.8	<0.0001
	≥2000	950.1	352.9–3043.2	<0.0001
13–20 yr	Exposure to procarbazine			
	No	1.0		
	Yes	2.6	1.4–4.7	0.002

Exposure to cyclophosphamide			
No	1.0		
Yes	4.9	2.8–9.2	<0.0001
Minimum ovarian irradiation dose (cGy)			
0	1.0		
1–99	2.9	1.2–8.3	0.03
100–999	17.2	6.8–49.5	<0.0001
1000–1999	90.9	29.1–323.5	<0.0001
≥ 2000	171.2	55.8–609.8	<0.0001

Radiation dose to the ovaries was calculated only when treatment records were complete and of sufficient quality to permit an accurate assessment of exposure.

[a] Age at diagnosis main effect: 0–12 OR = 1.0; 13–20 OR = 0.9 (0.3–3.2); *P* = 0.9.

irradiation. Doses of radiotherapy to the ovary of at least 2000 cGy were associated with the highest risk of AOF; more than 70% of patients exposed to such doses developed AOF. Previous data indicate that radiation does affect the ovaries in a dose-dependent fashion [7] [17] [18] [19] [20] [21] . Several attempts were made in the past to define radiation dose thresholds for ovarian toxicity. Doses in the range of 1000–3000 cGy have been noted to cause AOF in the majority of patients treated during childhood and adolescence [3] [17] [23] . In the current study, smaller doses of radiotherapy to the ovaries were also found to be significant risk factors for AOF, albeit with a weaker statistical association than doses of at least 1000 cGy. Thus, doses of ovarian radiation of less than 1000 cGy are capable of inducing AOF in patients who have additional risk factors, namely concomitant exposure to alkylating agents and older age at diagnosis.

Among chemotherapeutic agents, alkylating agents,

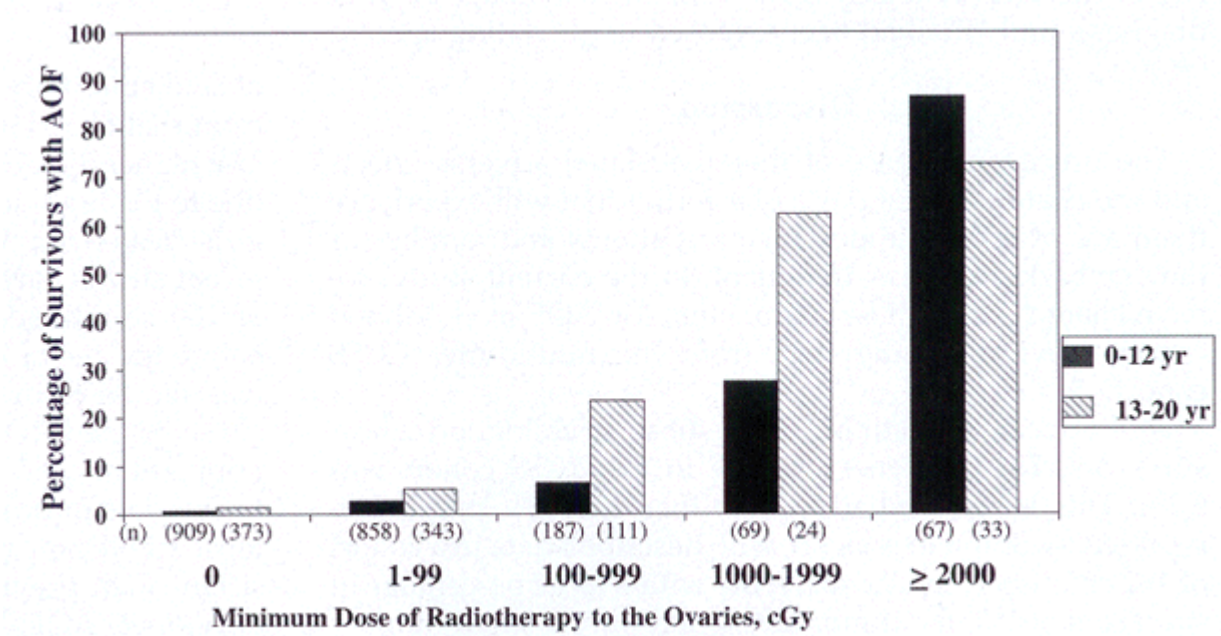

Figure 1. Percentage of subjects with AOF according to age at diagnosis of 0–12 yr (*solid bar*) and 13–20 yr (*striped bar*) *vs.* dose of radiation to the ovary.

which prevent cell division by interacting with DNA, are known to be associated with the occurrence of ovarian failure [5] [6] [23] [24] . In the current study, we showed that the alkylating agents cyclophosphamide and procarbazine were significant risk factors for AOF. Although exposure to procarbazine was an independent risk factor for AOF, regardless of age at treatment, cyclophosphamide significantly increased that risk only in subjects treated at an older age. As the number of oocytes declines with advancing age, the ovaries of older individuals become more vulnerable to gonadal toxins compared with that seen in younger subjects [3] [22] . Only a small number of patients in our study were exposed to other alkylating agents such as busulfan and chlorambucil, which may explain the weaker association of these agents with the development of AOF (Table 2). Myeloablative chemotherapy regimens, such as high-dose cyclophosphamide combined with busulfan, are being used increasingly as

preparation for stem cell transplantation. Several reports indicate a high incidence of AOF in patients exposed to such regimens [5] [6] [21] [24] . Thus, high-dose alkylating-agent chemotherapy may be a more prominent risk factor for AOF in patients treated on select contemporary regimens that incorporate these agents.

In this study, we report on the largest known cohort of female childhood cancer survivors suffering from AOF. However, there are limitations that need to be taken into account when interpreting the study results. The only criterion used to make a diagnosis of AOF was self-reported amenorrhea. Thus, it is possible that we may have included some cases of amenorrhea due to conditions other than primary ovarian failure (*e.g.* stress-related amenorrhea). Because treatment protocols have changed over time, the results of this study may not be strictly applicable to individuals who were treated more recently.

In conclusion, AOF appears to occur in a relatively small number of childhood cancer survivors. Exposure of the ovaries to irradiation, especially at doses of 1000 cGy and above, and exposure to the alkylating agents procarbazine and cyclophosphamide, at older ages, were identified as significant risk factors for AOF. These data will assist clinicians in counseling patients and their families at the time of diagnosis and before cancer therapy is initiated. Recently, successful pregnancies have been reported in cancer survivors after autotransplantation of cryopreserved ovarian tissue [25] [26] . Understanding which patients are at highest risk of developing AOF will help in defining those most likely to benefit from these novel treatments [9] .

Acknowledgments

This research used the CCSS, a resource supported by the National Cancer Institute to promote and facilitate research on long-term survivors of cancer diagnosed in childhood and adolescence. Investigators may apply to use the CCSS by proposing an analysis of existing data or proposing new initiatives that would use the cohort. Interested investigators are encouraged to visit the CCSS website at www.cancer. umn.edu/ccss to learn more about this unique resource.

Following is the list of CCSS institutions and investigators: University of California-San Francisco, CA: Robert Goldsby, M.D., [a] and Arthur Ablin, M.D. [b]; University of Alabama, Birmingham, AL: Roger Berkow, M.D. [d]; International Epidemiology Institute, Rockville, MD: John Boice, Sc.D. [c]; University of Washington, Seattle, WA: Norman Breslow, Ph.D. [b]; UT-Southwestern Medical Center at Dallas, TX: Gail Tomlinson, M.D. [d], Geroge R. Buchanan, M.D. [a]; Cincinnati Children's Hospital Medical Center, Cincinatti, OH: Stella Davies, M.D., Ph.D. [b]; Dana-Farber Cancer Institute, Boston, MA: Lisa Diller, M.D. [d], Holcombe Grier, M.D. [a], and Frederick Li, M.D. [b]; Texas Children's Center, Houston, TX: Zoann Dreyer, M.D. [d]; Children's Hospital and Medical Center, Seattle, WA: Debra Friedman, M.D., M.P.H., [d] and Thomas Pendergrass, M.D. [a]; Roswell Park Cancer Institute, Buffalo, NY: Daniel M. Green, M.D. [d], [b]; Hospital for Sick Children, Toronto, Ontario: Mark Greenberg, M.B., Ch.B. [d]; St. Louis Children's Hospital, St. Louis, MO: Robert Hayashi, M.D. [d], and Teresa Vietti, M.D. [a]; St. Jude Children's Research Hospital, Memphis, TN: Leslie L. Robison, Ph.D., [d], [b] and Melissa Hudson, M.D. [d], [b]; University of Michigan, Ann Arbor, MI: Raymond Hutchinson, M.D. [d]; Stanford University School of Medicine, Stanford, CA: Neyssa Marina, M.D., [d] Michael P. Link, M.D., [a] and Sarah S. Donaldson, M.D. [b]; Emory University, Atlanta, GA: Lillian Meacham, M.D. [d]; Children's Hospital of Philadelphia, Philadelphia, PA: Anna Meadows, M.D., [d], [b] and Bobbie Bayton [b]; Children's Hospital, Oklahoma City, OK: John Mulvihill, M.D. [b]; Children's Hospital, Denver, CO: Brian Greffe, M.D., [d] and Lorrie Odom, M.D. [a]; Children's Hospitals and Clinics of Minnesota, Minneapolis, MN: Joanna Perkins, M.D., [d] and Maura O'Leary, M.D. [a]; Columbus Children's Hospital, Columbus, OH: Amanda Termuhlen, M.D., [d] Frederick Ruymann, M.D., [a] and Stephen Qualman, M.D. [b]; Children's National Medical Center, Washington, DC: Gregory Reaman, M.D., [d] and Roger Packer, M.D. [b]; Children's Hospital of Pittsburgh, Pittsburgh, PA: A. Kim Ritchey, M.D., [d] and Julie Blatt, M.D. [a]; University of Minnesota, Minneapolis, MN: Ann Mertens, Ph.D., [b], [b] Joseph Neglia, M.D., M.P.H., [b] and Mark Nesbit, M.D. [b]; Children's Hospital Los Angeles, Los Angeles, CA: Kathy Ruccione, R.N., M.P.H. [d]; Memorial Sloan-Kettering Cancer Center, New York, NY: Charles Sklar, M.D., [d], [b] and Kevin Oeffinger, M.D. [b]; National Cancer Institute, Bethesda, MD: Barry Anderson, M.D., [b] and Peter Inskip, Sc.D. [b]; Mayo Clinic, Rochester, MN: Vilmarie Rodriguez, M.D., [d] W. Anthony Smithson, M.D., and Gerald Gilchrist, M.D. [a] University of Texas M.D. Anderson Cancer Center, Houston, TX: Louise Strong, M.D., [d], [b] and Marilyn Stovall, Ph.D. [b]; Riley Hospital for Children, Indianapolis, IN: Terry A. Vik, M.D., [d] and Robert Weetman, M.D. [a] Fred Hutchinson Cancer Research Center, Seattle, WA: Wendy Leisenring, Sc.D., [d], [b] and John Potter, M.D., Ph.D. [a] [b]; University of Alberta, Edmonton, Alberta: Yutaka Yasui, Ph.D. [a] [b]; and University of California-Los Angeles, Los Angeles, CA: Lonnie Zeltzer, M.D. [d], [b]

References

1. **Linet M, Ries LAG, Smith MA, Tarone RE, Devesa SS** 1999 Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. J Natl Cancer Inst 91:1051–1058 Abstract

2. **Stillman RJ, Schinfeld JS, Schiff I, Gelber RD, Greenberger J, Larson M, Jaffe N, Li FP** 1981 Ovarian failure in long term survivors of childhood malignancy. Am J Obstet Gynecol 139:62–66 Abstract

3. **Sklar CA** 1999 Reproductive physiology and treatment related loss of sex hormone production. Med Pediatr Oncol 33:2–8 Citation

4. **Byrne J** 1999 Infertility and premature menopause in childhood cancer survivors. Med Pediatr Oncol 33:24–28 Citation

5. **Bakker B, Oostdijk W, Bresters D, Walenkamp MJE, Vossen JM, Wit JM** 2004 Disturbances of growth and endocrine function after busulfan-based conditioning for haematopoietic stem cell transplantation during infancy and childhood. Bone Marrow Transplant 33:1049–1056 Abstract

6. **Afify A, Shaw PJ, Clavano-Harding A, Cowell CT** 2004 Growth and endocrine function in children with acute myeloid leukemia after bone marrow transplantation using busulfan/cyclophosphamide. Bone Marrow Transplant 25:1087–1092

7. **Wallace WH, Shalet SM, Crowne EC, Morris-Jones PH, Gattamaneni HR** 1989 Ovarian failure following abdominal irradiation in childhood: natural history and prognosis. Clin Oncol 1:75–79 Abstract

8. **Sklar CA** 2005 Maintenance of ovarian function and risk of premature menopause related to cancer treatment. J Natl Cancer Inst Monogr 34:25–27 Abstract

9. **Wallace WHB, Anderson RA, Irvine DS** 2005 Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol 6:209–218 Full Text

10. **Larsen EC, Muller J, Schmiegelow K, Rechnitzer C, Andersen AN** 2003 Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer. J Clin Endocrinol Metab 88:5307–5314 Full Text

11. **Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit ME, Packer RJ, Potter JD, Sklar CA, Smith MA, Stovall M, Strong LC, Yasui Y, Zeltzer LK** 2002 Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol 38:229–239 Abstract

12. **Stovall M, Donaldson SS, Weathers RE, Robison LL, Mertens AC, Winther JF, Olsen JH, Boice Jr JD** 2004 Genetic effects of radiotherapy for childhood cancer: gonadal dose reconstruction. Int J Radiat Oncol Biol Phys 60:542–552 Abstract

13. **Tucker MA, D'Angio GJ, Boice Jr JD, Strong LC, Li FP, Stovall M, Stone BJ, Green DM, Lombardi F, Newton W, Hoover RN, Fraumeni Jr JF** 1987 Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 317:588–593 Abstract

14. **Akaike H** 1974 A new look at the statistical identification model. IEEE Transact Automat Control 19:716–723

15. **Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR**

---

[a] Institutional principal investigator;

[b] former institutional principal investigator;

[d]

[c] member CCSS Steering Committee.

1999 Cancer incidence and survival among children and adolescents. United States SEER program 1975–1995. NCI SEER program. NIH publication no. 99–4649. Bethesda, MD: NIH, Department of Health and Human Services

16. **Wallace WHB, Shalet SM, Tetlow LJ, Morris-Jones PH** 1993 Ovarian function following the treatment of childhood acute lymphoblastic leukemia. Med Pediatr Oncol 21:333–339 Abstract

17. **Lushbaugh CC, Casarett GW** 1976 The effect of gonadal irradiation in clinical radiation therapy: a review. Cancer 37:1111–1120 Abstract

18. **Thibaud E, Ramirez M, Brauner R, Flamant F, Zucker JM, Fekete C, Rappaport R** 1992 Preservation of ovarian function by ovarian transposition performed before pelvic irradiation in childhood. J Pediatr 12:880–884 Abstract

19. **Green DM, Brecher ML, Lindsay AN, Yakar D, Voorhess ML, MacGillivray MH, Freeman AI** 1981 Gonadal function in pediatric patients following treatment for Hodgkin's disease. Med Pediatr Oncol 9:235–244 Abstract

20. **Wallace WH, Thomson AB, Saran F, Kelsey TW** 2005 Predicting age of ovarian failure after radiation to

a field that includes the ovaries. Int J Radiat Oncol Biol Phys 62:738–744 Abstract

21. **Couto-Silva AC, Trivin C, Thibaud E, Esperou H, Michon J, Brauner R** 2001 Factors affecting gonadal function after bone marrow transplantation during childhood. Bone Marrow Transplant 28:67–75 Abstract

22. **Sarafoglou K, Boulad F, Gillio A, Sklar C** 1997 Gonadal function after bone marrow transplantation for acute leukemia during childhood. J Pediatr 130: 210–216 Full Text

23. **Balis FM, Poplack DG** 1993 Cancer chemotherapy. In: Nathan DG, Oski FA, eds. Hematology of infancy and childhood. 4th ed. Philadelphia: Saunders; 1223–1229

24. **Michel G, Socie G, Gebhard F, Bernaudin F, Thuret I, Vannier JP, Demeocq F, Leverger G, Pico JL, Rubie H, Mechinaud F, Reiffers J, Gratecos N, Troussard X, Jouet JP, Simonin G, Gluckman E, Maraninchi D** 1997 Late effects of allogeneic bone marrow transplantation for children with acute myeloblastic leukemia in first complete remission: the impact of conditioning regimen without total-body irradiation. A report from the Société Française de Greffe de Moelle. J Clin Oncol 15:2238–2246 Abstract

25. **Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, Martinez-Madrid B, van Langendonckt A** 2004 Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 16:364:1405–1410

26. **Meirow D, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, Schiff E, Dor J** Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med 353:318–321

