

Ovarian tissue cryopreservation in young females through the Oncofertility Consortium's National Physicians Cooperative

Austin G Armstrong¹, Bruce F Kimler², Brigid M Smith³, Teresa K Woodruff³, Mary Ellen Pavone³ & Francesca E Duncan^{*,3}

¹University of Kansas School of Medicine, Wichita, KS 67214, USA

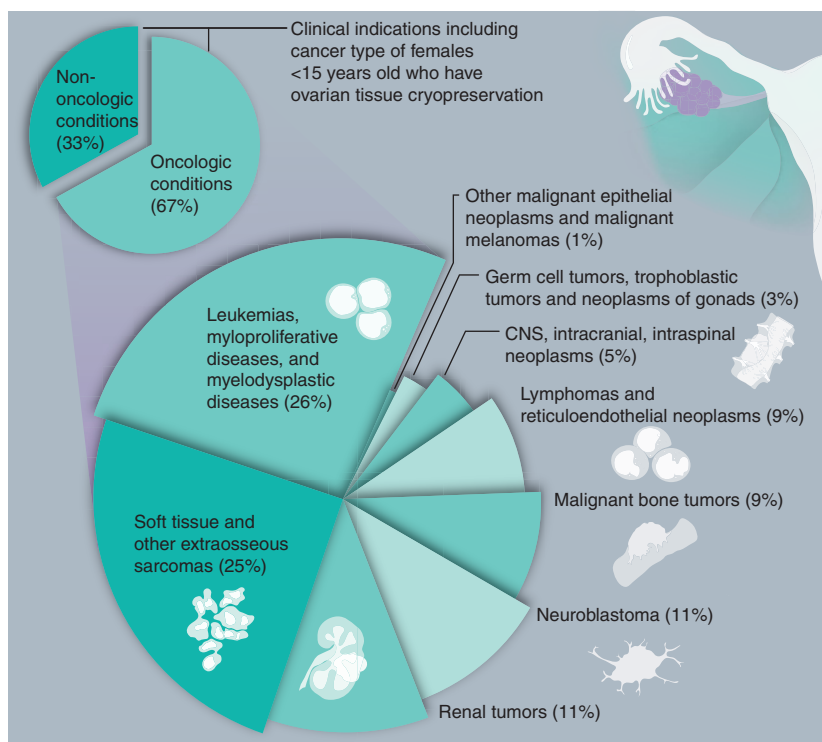
²Radiation Oncology, University of Kansas Medical Center, Kansas City, KS 66160, USA

³Department of Obstetrics & Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

* Author for correspondence: Tel.: +1 312 503 2172; f-duncan@northwestern.edu

Aim: To characterize the clinical indications of females (<15 years old) undergoing ovarian tissue cryopreservation (OTC) through the Oncofertility Consortium's National Physicians Cooperative (OC-NPC). **Patients & methods:** The clinical indications of 114 females who underwent OTC were classified, and their incidence was compared with childhood cancer databases. **Results:** Leukemias/myeloproliferative diseases/myelodysplastic diseases and hemoglobinopathies were the most prevalent oncologic and nononcologic indications for OTC, respectively. The frequencies of malignant bone tumors and soft tissue and other extrasosseous sarcomas were higher in the OC-NPC cohort relative to the general population, while CNS/intracranial/intraspinal neoplasms, retinoblastoma and hepatic tumors were lower. **Conclusion:** Those opting for OTC through the OC-NPC are at highest fertility risk, indicating that the appropriate patient populations are being identified.

Graphical abstract



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Cancer survivorship has steadily risen over the past four decades as treatments have become increasingly successful [1]. There are over 10,000 new cases of childhood cancer diagnosed per year, with a child <15 years of age in the USA having a 1 in 408 chance of receiving a cancer diagnosis [2]. Adult survival has improved by roughly 20% since the 1970s, with a current 5-year survival incidence of 69% [3]. Even more impressive are the changes in those with childhood cancer, in which the 5-year survival incidence in this population has improved from 58 to 83% since the 1970s [4]. As the population of cancer survivors increases, focus on long-term health and quality of post-treatment life is imperative. Unfortunately, the therapeutic regimens of chemotherapy and radiation have a deleterious effect on reproductive organs and increase a patient's risk for future infertility [5]. For example, women are born with a finite number of primordial follicles, which dictates their reproductive lifespan [6]. Radiation and chemotherapy can damage the follicular reserve resulting in compromised fertility and early menopause [7]. Alkylating drugs, total-body radiation and radiation below the diaphragm pose the highest risk for iatrogenic premature ovarian insufficiency (POI) [8].

The field of oncofertility was developed to help patients faced with potentially sterilizing treatments or conditions to identify appropriate fertility-preservation options [9,10]. The current accepted standards for fertility preservation in females are banking of either oocytes or embryos [11]. Both procedures involve hyperstimulation of the ovary to induce the growth of multiple follicles [12]. Following retrieval, mature oocytes or embryos obtained by *in vitro* fertilization (IVF), are cryopreserved and stored for the patient's future use [13]. These standard options, however, are not possible for those patients who cannot delay gonadotoxic treatment to undergo assisted reproduction technologies (ART) or prepubertal females. For these patient populations, ovarian tissue cryopreservation (OTC) with the potential for retransplantation is an emerging fertility-preservation method in which cortical ovarian tissue is removed, cryopreserved and transplanted to restore endocrine function and fertility [14]. In fact, there have been an estimated 86 live births and nine ongoing pregnancies worldwide following ovarian tissue transplantation [15]. The actual efficacy of OTC, however, is speculative as the total number of transplants attempted relative to the positive outcomes is typically not reported, and it cannot be proven that the restoration of reproductive function is due exclusively to the transplanted tissue [16]. In addition to OTC, *in vitro* growth of ovarian follicles is another promising fertility-preservation strategy, but it has not yet been used clinically [17].

OTC is the only fertility-preservation option for prepubertal girls because oocyte and embryo cryopreservation rely on a mature hypothalamic–pituitary–ovarian (HPO) axis, ovarian hyperstimulation and/or a sperm donor [11,18]. OTC followed by transplantation has also been used to restore endocrine function and fertility [19,20]. OTC can restore endocrine function that is impaired in POI. For example, normal endocrine function is possible after transplantation of cortical tissue for 5–7 years, and cortical strips have allowed patients to conceive naturally with normal endocrine function [21,22]. A live birth has been reported from tissue that was frozen prior to puberty but transplanted after [23]. There is also the potential of using ovarian tissue transplantation to induce puberty. However, concerns about this application exist due to the finite lifespan of the implanted tissue, limited and valuable nature of the tissue, and the abnormal variation of hormones in the HPO axis following transplant [24,25]. Nevertheless, this growing evidence provides tangible hope for young girls that endogenous hormone production through OTC will delay the deleterious health effects of menopause imposed by POI while also potentially restoring fertility.

The Oncofertility Consortium's National Physicians Cooperative (OC-NPC) was established in 2007 to address fertility challenges faced by cancer treatment or other fertility-threatening conditions. The OC-NPC includes 38 member institutions in 20 states across the USA that offer, or have one time offered, OTC through Institutional Review Board-approved protocols (Figure 1A). Of the 20 states, 16 have member institutions that enroll pediatric ages ranging from 0 to 17 years into their OTC protocols (Figure 1A). The OC-NPC also has partner institutions in 35 countries across the globe, which together comprise the Oncofertility Consortium's Global Partners Network (Figure 1B). Use of OTC through the OC-NPC has been steadily increasing over the last decade, especially in young females [26]. The goal of this study was to gain further insight into the profile of participants (<15 years of age) who are accessing OTC through the OC-NPC by comparing the frequency of malignancies in this cohort to

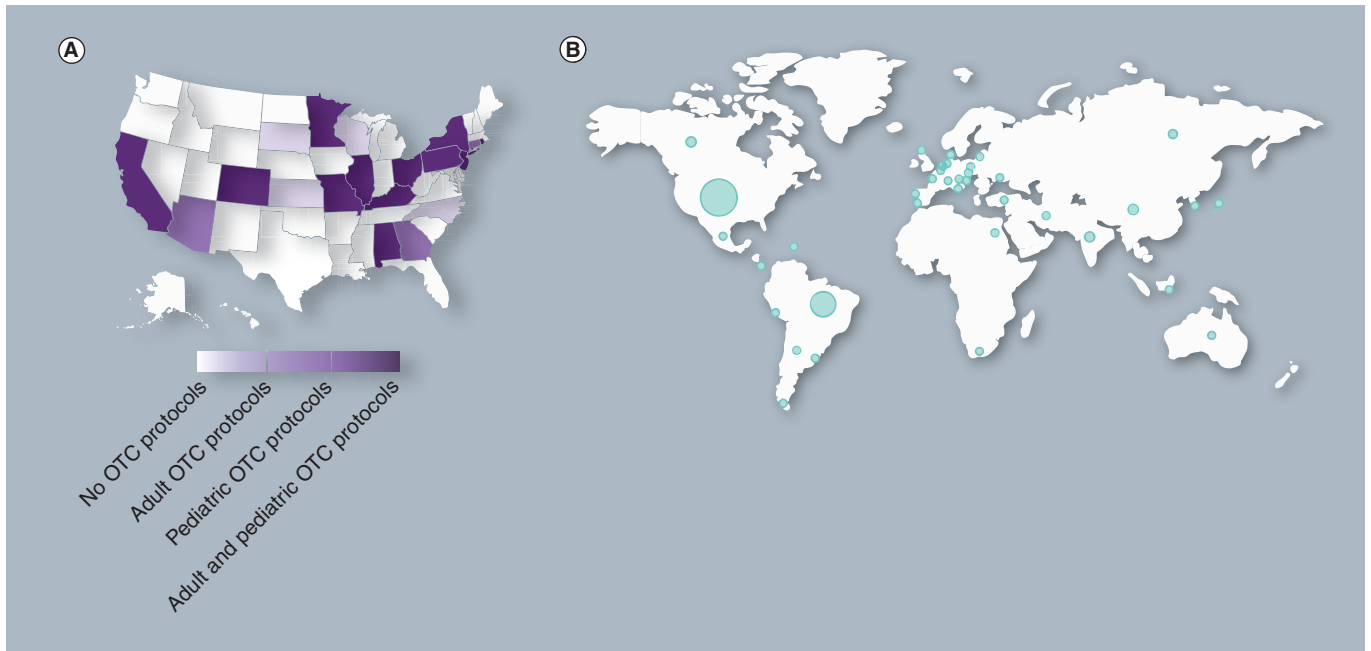


Figure 1. The Oncofertility Consortium's National Physicians Cooperative presence in the USA and globally. (A) The distribution of Oncofertility Consortium's National Physicians Cooperative sites within the USA according to which types of ovarian tissue cryopreservation protocols they currently have or have had approved. **(B)** The distribution of National Physicians Cooperative partner institutions across the globe. The circle width is proportional to the relative number of sites. OTC: Ovarian tissue cryopreservation.

the general population. This age limit was selected so that we could directly compare OC-NPC data to existing databases for childhood cancers that report data in the same age cohort.

Materials & methods

Data acquisition & ethical conduct of research

At OC-NPC sites that offer OTC, ovarian tissue is harvested from individuals under Institutional Review Board-approved protocols and following informed consent or assent. Eighty percent of the tissue is cryopreserved for the participant's future clinical use to restore endocrine function and/or fertility and the remaining 20% can be donated for basic research [26]. Basic demographic and clinical information for each participant is collected and de-identified including age, clinical diagnosis and treatment history prior to OTC. We obtained de-identified clinical data from the OC-NPC database for females <15 years old who underwent OTC. From a total of 330 OTC cases that occurred between the inception of the OC-NPC through May 2016, 117 were from participants <15 years of age. Three of the 117 cases were excluded from further analysis due to incomplete data availability. The collected data from the remaining 114 OC-NPC cases are summarized in Tables 1 & 2. We then compared the OC-NPC data with that available for the same age cohorts in two existing databases, including the Surveillance, Epidemiology and End Results Program (SEER), a cancer surveillance program in the USA [27], and the Automated Childhood Cancer Information System (ACCIS), which reports cancer incidence in children and adolescents in Europe [28–30].

Data analysis

The OC-NPC cases were classified into two broad categories: oncologic and nononcologic. Oncologic conditions were further divided into the 12 categories specified by the International Classification of Childhood Cancer (ICCC; ICD-O-3; Tables 2 & 3) [31]. Nononcologic conditions were grouped into broad disease categories including hemoglobinopathies, DNA-repair diseases and bone marrow failure (Table 1). The frequency of malignancies between the OC-NPC cohort was compared with that in the general population obtained through the ACCIS and SEER databases. These two databases were selected due to their use of ICCC categories and reporting malignancy incidence for each category in individuals <15 years of age.

Table 1. Age and clinical diagnoses of Oncofertility Consortium’s National Physicians Cooperative participants who underwent ovarian tissue cryopreservation due to a nononcologic condition.

OC-NPC ID#	Age (years)	Race	Ethnicity	Diagnosis	Treatment
Hemoglobinopathies					
NPC-2013-150	2	White	Non-Hispanic	β-thalassemia intermedia	Chemotherapy
NPC-2015-238	2	African–American/black	Non-Hispanic	Sickle cell anemia	None
NPC-2014-210	3	Not reported	Non-Hispanic	β-thalassemia	None
NPC-2014-168	6	African–American/black	Non-Hispanic	Sickle cell disease	Chemotherapy
NPC-2014-193	6	Not reported	Non-Hispanic	β-thalassemia	None
NPC-2015-252	6	Black	Non-Hispanic	Sickle cell disease	None
NPC-2014-182	7	Not reported	Non-Hispanic	β-thalassemia	None
NPC-2013-144	8	White	Non-Hispanic	Thalassemia	Chemotherapy
NPC-2015-253	8	White	Non-Hispanic	Sickle cell disease	None
NPC-2014-200	10	African–American/black	Non-Hispanic	Sickle cell anemia going to BMT	None
NPC-2011-80	10.5	African–American/black	Non-Hispanic	Sickle cell anemia going to BMT	Chemotherapy
NPC-2013-147	11	African–American/black	Non-Hispanic	Sickle cell anemia	None
NPC-2015-244	11	Not reported	Non-Hispanic	β-thalassemia	BMT
NPC-2015-247	11	African–American/black	Non-Hispanic	Sickle cell disease	None
NPC-2016-192	12	Not reported	Non-Hispanic	β-thalassemia major	None
NPC-2016-278	12	African–American/black	Non-Hispanic	Sickle cell	None
NPC-2015-259	12	Not reported	Non-Hispanic	β-thalassemia major	None
NPC-2014-175	13	African–American/black	Non-Hispanic	Sickle cell disease	None
DNA-repair disease					
NPC-2013-128	5	Not reported	Not reported	Diamond–Blackfan anemia	None
NPC-2014-192	5	African–American/black	Non-Hispanic	Fanconi’s anemia	None
NPC-2013-151	7	White	Non-Hispanic	Fanconi’s anemia	None
NPC-2016-277	9	White	Non-Hispanic	Fanconi’s anemia	None
NPC-2013-145	11	White	Non-Hispanic	Fanconi’s anemia	None
NPC-2015-266	12	White	Non-Hispanic	Fanconi’s anemia	BMT
Bone marrow failure					
NPC-2015-241	5	White	Non-Hispanic	Aplastic anemia	None
NPC-2014-180	7	White	Non-Hispanic	Aplastic anemia	None
NPC-2015-214	8	White	Non-Hispanic	Acquired aplastic anemia since 2008, developed clonal evolution consistent with hypocellular myelodysplastic syndrome, with megakaryocytic dysplasia	None
NPC-2015-254	11	White	Non-Hispanic	Aplastic anemia	None
NPC-2013-153	13	White	Non-Hispanic	Aplastic anemia	None
NPC-2014-207	14	White	Hispanic	Aplastic anemia	None
Other					
NPC-2015-220	0.5	Not reported	Non-Hispanic	Hemophagocytic lymphohistiocytosis	Chemotherapy
NPC-2015-256	0.6	White	Non-Hispanic	Hemophagocytic lymphohistiocytosis	Chemotherapy
NPC-2016-276	0.9	Not reported	Non-Hispanic	IFN-γ deficiency	None
NPC-2016-286	1	White	Non-Hispanic	Hemophagocytic lymphohistiocytosis	Chemotherapy
NPC-2016-279	1.2	White	Non-Hispanic	Hemophagocytic lymphohistiocytosis	Chemotherapy
NPC-2013-133	2	White	Non-Hispanic	Hurler’s syndrome	None
NPC-2012-116	5	White	Non-Hispanic	Idiopathic hypereosinophilic syndrome	Other
NPC-2013-143	10	White	Non-Hispanic	Turner’s syndrome	None
BMT: Bone marrow transplant; OC-NPC: Oncofertility Consortium’s National Physicians Cooperative.					

Table 2. Age and clinical diagnoses of Oncofertility Consortium’s National Physicians Cooperative participants who underwent ovarian tissue cryopreservation due to an oncologic condition.

OC-NPC ID#	Age (years)	Race	Ethnicity	Diagnosis	Treatment
I: Leukemias, myeloproliferative diseases and myelodysplastic neoplasms					
NPC-2012-110	3.8	White	Non-Hispanic	Chronic myeloid leukemia going to BMT	Chemotherapy
NPC-2015-219	4	Not reported	Hispanic	Low-risk CNS-negative acute myeloid leukemia	Chemotherapy
NPC-2016-294	4	White	Non-Hispanic	Chronic myeloid leukemia	None
NPC-2013-149	5	White	Non-Hispanic	JJMML	Chemotherapy and HSCT
NPC-2013-136	6	White	Non-Hispanic	B-cell precursor acute lymphoblastic leukemia	Chemotherapy and radiation
NPC-2015-225	6	African–American/black	Non-Hispanic	AML with WBC 39,000 and 55% blasts on smears and large paraspinal and intraspinal chloroma with spinal cord compression	Chemotherapy
NPC-2015-273	6	White	Non-Hispanic	Pre B acute lymphoblastic leukemia	Chemotherapy
NPC-2011-82	8	White	Non-Hispanic	Acute myeloid leukemia	Chemotherapy
NPC-2013-130	8	White	Non-hispanic	T-cell acute lymphoblastic leukemia	Chemotherapy and HSCT
NPC-2016-300	8	White	Non-Hispanic	Acute lymphoblastic leukemia (Ph + ALL)	Chemotherapy
NPC-2012-123	8	White	Non-Hispanic	Very high-risk acute lymphoblastic leukemia due to cytogenetics	Chemotherapy
NPC-2012-125	9	White	Non-Hispanic	Fanconi anemia; myelodysplastic syndrome	None
NPC-2015-255	9	White	Non-Hispanic	Trisomy 8 myelodysplastic syndrome	None
NPC-2014-204	10	White	Non-Hispanic	Acute myeloid leukemia after acute lymphoblastic leukemia going to BMT	Chemotherapy
NPC-2012-119	12	African–American/black	Non-Hispanic	Acute lymphoblastic leukemia in March 2012 (hypoploidy; which puts her at very high risk for relapse during chemotherapy); will go to BMT with thiotepa, cytoxan, TBI	Chemotherapy
NPC-2014-178	12	White	Non-Hispanic	Acute myeloid leukemia	Chemotherapy
NPC-2011-73	14	Other	Non-Hispanic	Acute myeloid leukemia going to BMT	Chemotherapy
NPC-2013-139	14	White	Non-Hispanic	Very high-risk acute lymphoblastic leukemia (hypodiploid)	Chemotherapy
NPC-2009-24	14.5	White	Non-Hispanic	Myelodysplastic syndrome + trisomy 8	None
NPC-2011-85	14.6	White	Non-Hispanic	Myelodysplastic syndrome, go for transplantation	None
II: Lymphomas and reticuloendothelial neoplasms					
NPC-2014-167	12	White	Non-Hispanic	Primary mediastinal B-cell lymphoma, localized to her chest	Chemotherapy
NPC-2012-124	13	White	Non-Hispanic	Hodgkin disease, stage II	None
NPC-2014-166	13	White	Non-Hispanic	Primary mediastinal B-cell lymphoma, localized to her chest	Chemotherapy
NPC-2016-284	13	White	Non-Hispanic	Hodgkin’s lymphoma	Chemotherapy
NPC-2016-288	13	White	Non-Hispanic	Hodgkin’s lymphoma	Chemotherapy
NPC-2009-29	13.9	White	Non-Hispanic	Lymphoma	None
NPC-2014-197	14	White	Hispanic	Natural killer cell lymphoma	Chemotherapy
III: CNS and miscellaneous intracranial and intraspinal neoplasms					
NPC-2016-280	2	White	Hispanic	Primitive neuroectodermal tumor-metastatic	Chemotherapy
NPC-2016-282	8	White	Non-Hispanic	Medulloblastoma	None
NPC-2011-66	12.5	White	Non-Hispanic	Pineoblastoma	None
NPC-2015-217	14	White	Non-Hispanic	Optic pathway pilocytic astrocytoma	Chemotherapy
AML: Acute myeloid leukemia; BMT: Bone marrow transplant; HSCT: Hematopoietic stem-cell transplantation; JJMML: Juvenile myelomonocytic leukemia; OC-NPC: Oncofertility Consortium’s National Physicians Cooperative; TBI: Total body irradiation; WBC: White blood cell count.					

Table 2. Age and clinical diagnoses of Oncofertility Consortium’s National Physicians Cooperative participants who underwent ovarian tissue cryopreservation due to an oncologic condition (cont.).

OC-NPC ID#	Age (years)	Race	Ethnicity	Diagnosis	Treatment
IV: Neuroblastoma and other peripheral nervous cell tumors					
NPC-2011-65	2	White	Non-Hispanic	Neuroblastoma	Chemotherapy and surgery
NPC-2014-205	4	White	Hispanic	Neuroblastoma	Chemotherapy and radiation
NPC-2014-185	5	African–American/black	Non-Hispanic	Neuroblastoma	None
NPC-2016-281	5	Not reported	Non-Hispanic	High-risk neuroblastoma	Chemotherapy and HSCT
NPC-2015-262	7	White	Non-Hispanic	Neuroblastoma	Chemotherapy
NPC-2015-272	9	White	Non-Hispanic	High-risk neuroblastoma, stage IV	Chemotherapy
NPC-2014-165	10	White	Non-Hispanic	High-risk neuroblastoma	Chemotherapy and surgery
NPC-2010-43	11.4	Not reported	Not reported	High-risk neuroblastoma	Chemotherapy
VI: Renal tumors					
NPC-2015-240	1.9	White	Non-Hispanic	Stage III Wilms tumor, CNS relapse	Chemotherapy and radiation
NPC-2014-203	3	White	Non-Hispanic	Relapsed Wilms tumor	Chemotherapy
NPC-2015-222	4	White	Non-Hispanic	Stage IV favorable histology Wilms tumor	Chemotherapy
NPC-2015-224	4	White	Non-Hispanic	Wilms tumor, bilateral multifocal	Chemotherapy
NPC-2015-239	4	White	Non-Hispanic	Clear cell sarcoma of the left kidney	None
NPC-2008-17	8.5	Not reported	Not reported	Wilms tumor	Chemotherapy and radiation
NPC-2011-78	10	White	Non-Hispanic	Wilms tumor	Chemotherapy and radiation
NPC-2015-216	10	White	Non-Hispanic	History of Wilms tumor stage III now secondary pancreatic mass consistent with Ewing sarcoma	Chemotherapy and radiation
VIII: Malignant bone tumors					
NPC-2015-250	7	White	Non-Hispanic	Ewing sarcoma, right clavicle	None
NPC-2015-257	8	White	Non-Hispanic	Osteosarcoma	None
NPC-2014-194	9	White	Non-Hispanic	Ewing sarcoma	None
NPC-2015-246	10	Not reported	Non-Hispanic	Ewing sarcoma	None
NPC-2012-112	11.7	White	Non-Hispanic	Ewing sarcoma, localized superficial disease right thigh	None
NPC-2014-162	13	N/A	Non-Hispanic	Ewings; sarcoma	None
NPC-2014-187	13	White	Non-Hispanic	Ewing sarcoma left foot	None
IX: Soft tissue and other extrasosseous sarcomas					
NPC-2010-40	1.4	White	Non-Hispanic	Rhabdomyosarcoma	Chemotherapy
NPC-2015-275	1.5	White	Non-Hispanic	Vaginal rhabdomyosarcoma	None
NPC-2015-231	1.8	White	Non-Hispanic	Rhabdomyosarcoma (right chest wall: liver)	None
NPC-2013-155	3	Not reported	Not reported	Rhabdomyosarcoma	None
NPC-2014-183	3	African–American/black	Non-Hispanic	Vaginal embryonal rhabdomyosarcoma	Chemotherapy
NPC-2016-304	3	White	Non-Hispanic	Rhabdomyosarcoma	None
NPC-2014-161	4	>1	Non-Hispanic	Alveolar rhabdomyosarcoma	Chemotherapy and radiation
NPC-2016-295	4	Asian	Non-Hispanic	Stage IV embryonal rhabdomyosarcoma, primary abdominal tumor	Chemotherapy
NPC-2015-232	5	African–American/black	Non-Hispanic	Pelvic rhabdomyosarcoma	None
NPC-2015-263	7	White	Non-Hispanic	Alveolar rhabdomyosarcoma	Chemotherapy
NPC-2016-291	7	White	Non-Hispanic	Embryonal rhabdomyosarcoma	Chemotherapy
AML: Acute myeloid leukemia; BMT: Bone marrow transplant; HSCT: Hematopoietic stem-cell transplantation; JJMML: Juvenile myelomonocytic leukemia; OC-NPC: Oncofertility Consortium’s National Physicians Cooperative; TBI: Total body irradiation; WBC: White blood cell count.					

Table 2. Age and clinical diagnoses of Oncofertility Consortium’s National Physicians Cooperative participants who underwent ovarian tissue cryopreservation due to an oncologic condition (cont.).

OC-NPC ID#	Age (years)	Race	Ethnicity	Diagnosis	Treatment
NPC-2015-249	9	Not reported	Not reported	Embryonal sarcoma	None
NPC-2011-72	9.6	White	Non-Hispanic	Vaginal rhabdomyosarcoma	Chemotherapy
NPC-2014-189	10	White	Non-Hispanic	Synovial sarcoma abdomen	Chemotherapy
NPC-2008-10	12	Not reported	Not reported	Rhabdomyosarcoma	None
NPC-2015-268	12	White	Non-Hispanic	Parameningeal embryonal rhabdomyosarcoma	None
NPC-2016-283	12	White	Non-Hispanic	Synovial cell sarcoma	Chemotherapy
NPC-2014-202	14	White	Non-Hispanic	Embryonal rhabdomyosarcoma	Chemotherapy
NPC-2015-223	14	White	Non-Hispanic	Nasal rhabdomyosarcoma (alveolar subtype)	None
X: Germ cell tumors, trophoblastic tumors and neoplasms of gonads					
NPC-2015-218	6	White	Non-Hispanic	Sacroccygeal germ cell tumor	Chemotherapy and HSCT
NPC-2016-293	14	White	Non-Hispanic	Bilateral ovarian tumors, elevated AFP	None
XI: Other malignant epithelial neoplasms and malignant melanomas					
NPC-2014-169	13	White	Non-Hispanic	Small cell carcinoma of ovary	None

AML: Acute myeloid leukemia; BMT: Bone marrow transplant; HSCT: Hematopoietic stem-cell transplantation; JJMML: Juvenile myelomonocytic leukemia; OC-NPC: Oncofertility Consortium’s National Physicians Cooperative; TBI: Total body irradiation; WBC: White blood cell count.

Table 3. Categories of pediatric malignancies per the WHO’s International Classification of Childhood Cancer system.

ICCC category	Malignancies
I	Leukemias, myeloproliferative diseases and myelodysplastic diseases
II	Lymphomas and reticuloendothelial neoplasms
III	CNS and miscellaneous intracranial and intraspinal neoplasms
IV	Neuroblastoma and other peripheral nervous cell tissues
V	Retinoblastoma
VI	Renal tumors
VII	Hepatic tumors
VIII	Malignant bone tumors
IX	Soft tissue and other extraosseous sarcomas
X	Germ cell tumors, trophoblastic tumors and neoplasms of gonads
XI	Other malignant epithelial neoplasms and malignant melanomas
XII	Other and unspecified malignant neoplasms

ICCC: International Classification of Childhood Cancer.

Results

Profile of OC-NPC participants (<15 years old) who underwent ovarian tissue cryopreservation

In the cohort of OC-NPC participants we examined, the age ranged from 0.5 to 14.6 years, with a mean age of 8.1 years and a median age of 8 years (Figure 2A). The average age of menarche in the USA is 12.5 years, and only 18% of participants in this cohort were older than this [32]. Thus, we believe that the majority of the females in our study were likely to be premenarchal, which is significant because OTC would be the only fertility-preservation option available in this cohort. For patients where race was reported 81% were white, 16% were African-American/black, 1% Asian, 1% were more than one race and 1% were other. Ninety percent of these patients were non-Hispanic. Reported previous treatment history for patients utilizing OTC varied, with 49% having had no prior treatment, 37% having undergone chemotherapy, 6% having been treated with chemotherapy and radiation, 3% with chemotherapy and hematopoietic stem-cell transplantation (HSCT), 2% treated with chemotherapy and surgery, 2% with bone marrow transplant and 1% other (Tables 1 & 2).

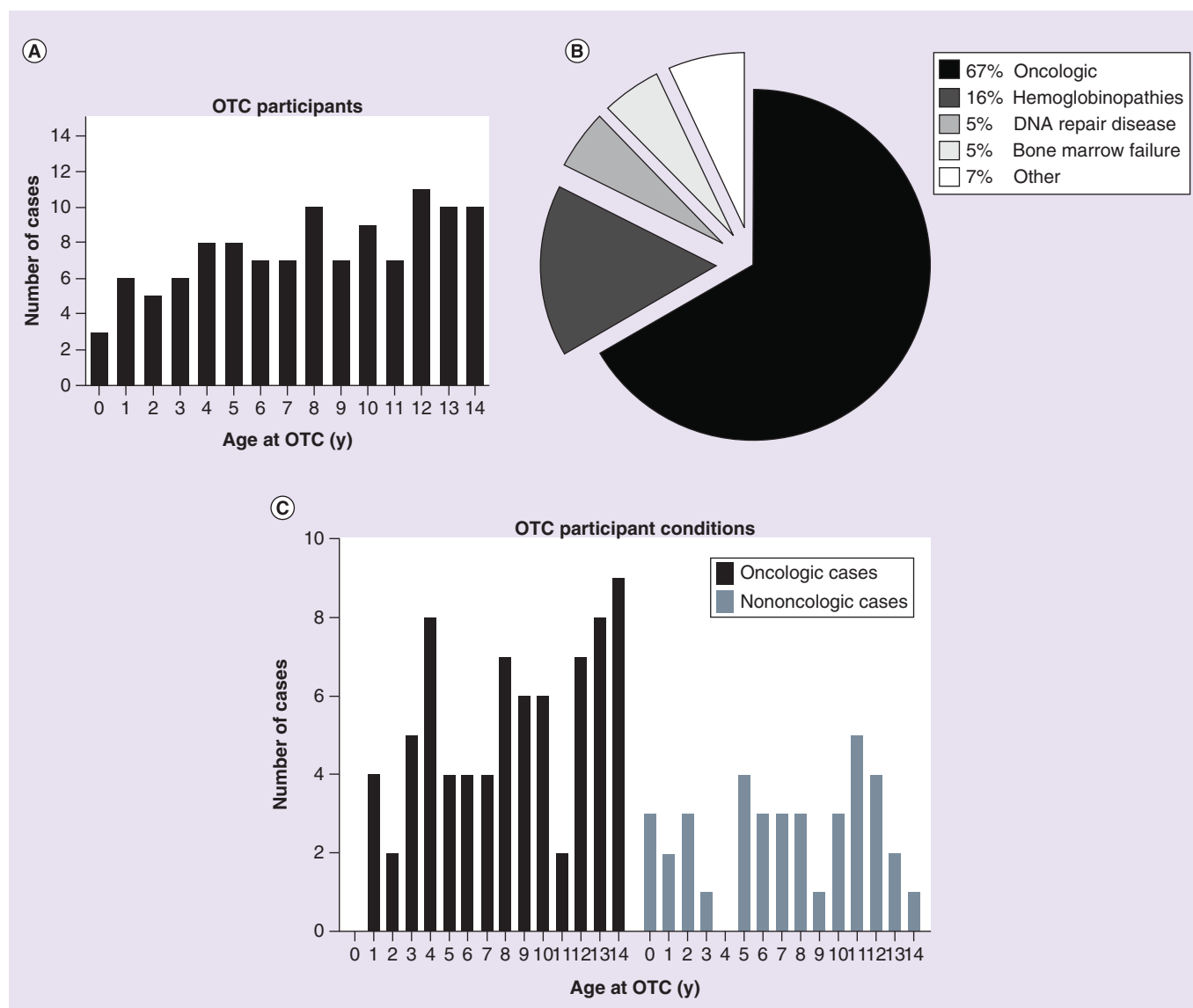


Figure 2. Characteristics of participants <15 years old who have undergone ovarian tissue cryopreservation through the Oncofertility Consortium's National Physicians Cooperative. (A) The age distribution in years of OC-NPC participants who have undergone OTC. The number of cases at each age is shown. **(B)** Distribution of clinical indications for OTC in the OC-NPC cohort. Oncologic conditions are clustered together. Nononcologic conditions are subdivided, and the relative percentages of each condition are noted. Additional details are in Tables 1 & 2. **(C)** The age distribution in years of participants who have undergone OTC for oncologic and nononcologic conditions. The number of cases at each age is shown. OC-NPC: Oncofertility Consortium's National Physicians Cooperative; OTC: Ovarian tissue cryopreservation; y: Years.

The largest indication for OTC was oncologic conditions, comprising 67% of cases (Figure 2B). Nononcologic conditions comprised the remainder of the cases and included hemoglobinopathies (16%; sickle cell anemia and β -thalassemia); DNA-repair diseases (5%; Diamond–Blackfan anemia and Fanconi anemia); bone marrow failure (5%; aplastic anemia); and other (7%) (Figure 2B & Table 1). The majority of African–American/black participants underwent OTC for nononcologic versus oncologic conditions (67 vs 33%; Tables 1 & 2). This is not surprising given the higher prevalence of sickle cell anemia in this population [33]. Both oncologic and nononcologic conditions were distributed across ages (Figure 2C).

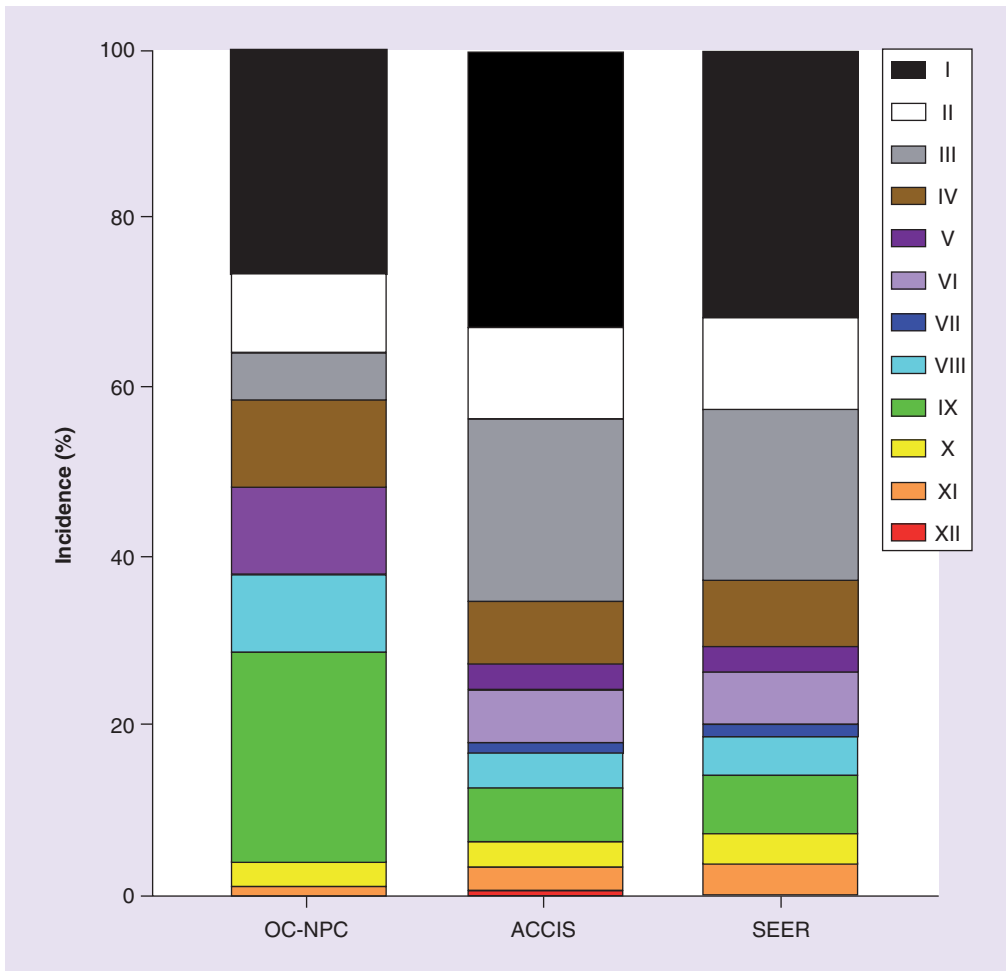


Figure 3. The incidence of International Classification of Childhood Cancer malignancy categories in the Oncofertility Consortium’s National Physicians Cooperative cohort compared with the general population. The percent incidence of malignancies in individuals <15 years old in each category was plotted from the three databases (OC-NPC cohort, ACCIS, and SEER Program). More detail on each International Classification of Childhood Cancer category is in Table 3.

ACCIS: Automated Childhood Cancer Information System; OC-NPC: Oncofertility Consortium’s National Physicians Cooperative; SEER: Surveillance, Epidemiology and End Results Program.

Characterization & evaluation of the OC-NPC cohort according to the ICCC malignancy categories

The oncologic conditions in the OC-NPC cohort were classified according to the 12 established categories of the ICCC system, which categorizes malignancies according to histological characteristics as opposed to primary site (Tables 2 & 3). The ICCC was utilized due to its acceptance within the international community for epidemiological studies and cancer registries, such as the SEER and ACCIS databases [34]. The breakdown of the OC-NPC cohort according to ICCC categories is shown in Figure 3. Leukemias, myeloproliferative diseases and myelodysplastic diseases (category I) were the largest oncologic indication (26%) in the OC-NPC cohort and included myeloid leukemia, lymphoid leukemia and myelodysplastic syndrome. Soft tissue and other extraosseous sarcomas (category IX), such as rhabdomyosarcoma and synovial sarcoma, were the second largest indication for OTC in the OC-NPC cohort (25%). Neuroblastoma (category IV) and renal tumors (category VI), including Wilms tumor and clear cell sarcoma, both accounted for 11% of oncologic cases. Lymphomas and reticuloendothelial neoplasms (category II), including Hodgkin lymphoma, non-Hodgkin lymphoma and B-cell lymphoma, and malignant bone tumors (category VIII), including Ewing sarcoma and osteosarcoma, each accounted for 9% of the OC-NPC oncologic cases. Five percent of the OC-NPC cases were CNS, intracranial and intraspinal neoplasms (category III) consisting of medulloblastoma, pineoblastoma, astrocytoma and primitive neuroectodermal tumors. Three percent of cases

Table 4. Categories with lower and higher frequency in the Oncofertility Consortium's National Physicians Cooperative cohort than the general population.

ICCC category	OC-NPC (%)	ACCIS (%)	SEER (%)
Lower frequency categories			
III	5	21.5	20.2
V	No cases	2.9	3.1
VII	No cases	1.1	1.3
Higher frequency categories			
VIII	9	4.1	4.5
IX	25	6.3	7.0

ACCIS: Automated Childhood Cancer Information System; ICCC: International Classification of Childhood Cancer; OC-NPC: Oncofertility Consortium's National Physicians Cooperative; SEER: Surveillance, Epidemiology and End Results.

were germ cell tumors, trophoblastic tumors and neoplasms of gonads (category X). The one case in the other malignant epithelial neoplasms and malignant melanomas (category XI) case was small cell carcinoma of the ovary. There were no cases of retinoblastoma (category V), hepatic tumors (category VII) or other and unspecified malignant neoplasms (category XII; Table 2 & Figure 3).

Within each ICCC category, the ages of the OC-NPC cohort were displayed in histograms (Figure 4A). Participants with leukemias, myeloproliferative diseases and myelodysplastic diseases (category I); CNS, intracranial and intraspinal neoplasms (category III); renal tumors (category VI); and soft tissue and other extraosseous sarcomas (category IX), were distributed across the age spectrum. However, lymphomas and reticuloendothelial neoplasms (category II) and malignant bone tumors (category VIII) were more prevalent in older aged participants (Figure 4A). The OC-NPC participants with malignancies in category II were 12 years or older, and those in category VIII were 7 years or older. These findings are consistent with epidemiologic data, as lymphomas and reticuloendothelial neoplasms occur at a higher incidence in children >10 years, especially those with Hodgkin's disease [27]. Epidemiologic data for malignant bone tumors (category VIII) show rising incidence in individuals age 5–10 years, with an increased incidence associated with growth peaking at age 13 [27]. There were no OC-NPC participants that had retinoblastoma (category V), hepatic tumors (category VII) or unspecified malignant neoplasms (category XII). Limited numbers of OC-NPC cases had malignancies in category X (germ cell tumors, trophoblastic tumors and neoplasm of gonads) or category XI (malignant epithelial neoplasms and malignant melanomas). For nononcologic conditions, those with hemoglobinopathies were distributed across ages, whereas those with DNA-repair diseases and bone marrow failure were noted to be in females above 5 years of age (Figure 4B). However, this dataset is limited.

We next compared the incidence of ICCC malignancy categories between the OC-NPC cohort and the general population. To do this, we examined the frequency of each ICCC malignancy category for data obtained from three separate databases: the OC-NPC; ACCIS; and SEER (Figure 3). ACCIS and SEER are databases for childhood cancer, and as expected, there was concordance in the frequency distribution of malignancy categories between these two databases (Figure 3). However, when comparing the malignancy incidence within the OC-NPC cohort to the general population (ACCIS and SEER), differences in five main categories were observed (Figure 3). Categories III, V and VII (CNS/intracranial/intraspinal malignancies, retinoblastoma and hepatic tumors) were under-represented in the OC-NPC cohort relative to the general population (Table 4). In contrast, categories VIII and IX (malignant bone tumors and soft tissue/extraosseous sarcomas) were over-represented in the OC-NPC cohort (Table 4).

A limitation of comparing the OC-NPC data to that in the ACCIS and SEER databases is that the male and female malignancy incidences are combined. We therefore examined whether there were sex-specific differences in malignancy incidences in the general population. In the SEER database, malignancy incidences are separated by sex and reported for individuals <15 and <20 years old. For the majority of malignancy categories, the male-to-female ratio was close to one (Figure 5). The sex-specific incidence for category XII was not reported due to a low number of cases but was not highlighted as having a sex bias. Thus overall, these malignancies appear to have similar incidences between males and females (Figure 5). However, category II (non-Hodgkin lymphoma) had a higher incidence in males (M:F ratio: 3.0), and category XI (malignant epithelial neoplasms) had a higher incidence in females (M:F ratio: 0.5; Figure 5). Importantly, the malignancy categories that appeared different between the OC-NPC cohort

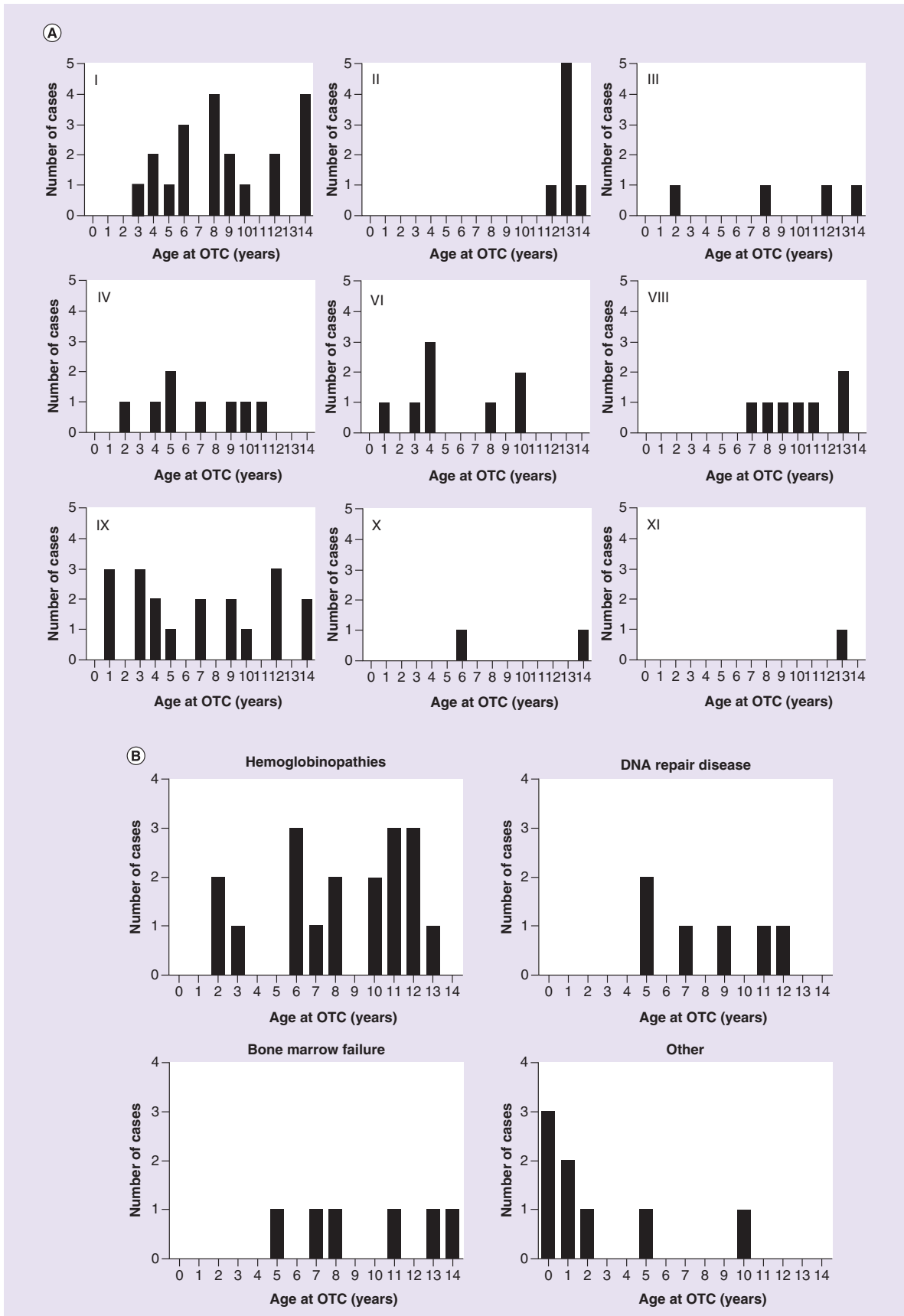


Figure 4. Age histogram of the Oncofertility Consortium’s National Physicians Cooperative cohort according to clinical condition. (A) The number of OTC cases at each age is shown for the oncologic conditions specified by the relevant International Classification of Childhood Cancer malignancy categories and **(B)** the nononcologic conditions. OTC: Ovarian tissue cryopreservation.

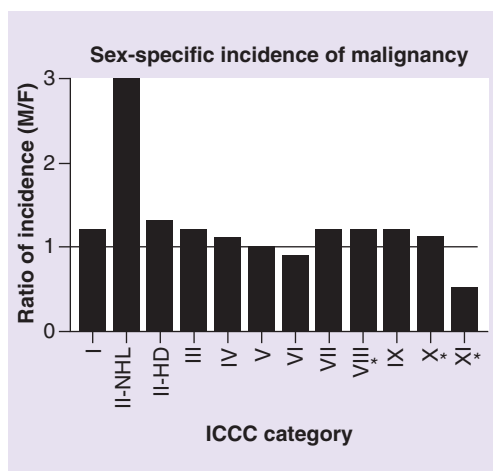


Figure 5. The sex-specific incidence of malignancies according to International Classification of Childhood Cancer categories. Malignancy incidences were separated by sex and reported for individuals <15 or <20 (marked with asterisk) years old in the Surveillance, Epidemiology and End Results Program database. For each International Classification of Childhood Cancer category, the data are shown as a ratio of male-to-female incidence. Specific numerical data were not available for category XII. The horizontal line highlights equal incidence or a ratio of one. F: Female; ICC: International Classification of Childhood Cancer; M: Male.

and the ACCIS and SEER populations (categories III, V, VII, VIII and IX) did not exhibit sex-specific differences in incidence (Figure 5 & Table 4).

Discussion

The OC-NPC represents the largest formal fertility-preservation network in the USA, and we previously documented that usage of OTC has steadily increased among young females (<18 years old) relative to the adult female population in this network [26]. The purpose of this study was to further investigate the characteristics of this young cohort that has utilized OTC. However, we narrowed our focus to females <15 years old so that we could directly compare our data to existing databases of cancer incidences. Understanding how OTC is used among patients has broad implications because the usage of this technique is widespread and increasing globally. A recent study of OTC in Danish girls <18 years of age reported a similar increased frequency in indications in both malignant (malignant bone tumors and soft tissue/other extraosseous sarcomas) and nonmalignant conditions (hemoglobinopathies, bone marrow failure, DNA-repair diseases), with a peak incidence in hematologic malignancies [35]. This is reassuring that our data regarding indications for OTC coincides with this study, though the Danish study investigated a wider age group in a single country. The experimental label and restrictions placed on OTC have been challenged in Israel, indicating that this procedure may become an even more prevalent fertility-preservation option [36].

In our cohort, the largest indication for OTC was oncologic conditions, with the top two malignancy classifications being leukemias, myeloproliferative diseases and myelodysplastic diseases (category I) and soft tissue and other extraosseous sarcomas (category IX). This is expected due to the fertility risk of the therapy regimens involved in treating these malignancies, including alkylating chemotherapy, radiation of tumors and radioablation in preparation for HSCT [37,38]. Importantly, studies suggest that over 60% of patients undergoing HSCT experience POI [39]. It is also clear from our analysis that OTC in young females is performed for indications beyond the setting of oncofertility. A third of patients had nononcologic conditions that required fertility preservation due to either the sterilizing nature of the disease treatment or the disease process itself. For example, patients with hemoglobinopathies, DNA-repair diseases, bone marrow failure and inborn errors of metabolism can all be treated with HSCT [40–44]. Thus, fertility-preservation options are offered in these scenarios. In the case of sickle cell anemia, there has been a successful birth from a patient utilizing her cryopreserved cortical grafts that were preserved a decade prior, before she had entered puberty [23]. These results are encouraging and underscore the importance of OTC as a fertility-preservation option for both oncologic as well as nononcologic conditions. Leukemias comprised the largest indication for OTC in our cohort; autotransplantation of ovarian tissue from patients with hematologic malignancies imparts a risk of re-seeding malignancy [45]. A recent study describes autotransplantation of ovarian tissue from a small number of patients with leukemia with no detection of malignant cells within the sample tissue or reoccurrence of malignancy, though this tissue was harvested after adjuvant chemotherapy prior to HSCT and conditioning regimens [36]. Careful counseling of patients with hematologic malignancies before OTC is needed because of the risk of re-seeding malignancy and investigation of tissue for malignant cells is still required. Other possible methods to decrease risk of re-seeding malignancies include the isolation of follicles from cryopreserved

ovarian tissue and utilizing an artificial ovary or *in vitro* follicle growth [17,46,47]. These methods, however, are still experimental and have not been translated clinically.

When we compared the types and incidence of malignancies in the OC-NPC cohort who underwent the OTC procedure relative to the age-matched general population, we observed that several disease categories were either relatively over- or under-represented. These discrepancies appear to correlate with the fertility risk of these specific conditions or their treatment. For example, conditions with higher incidence within the OC-NPC cohort were malignant bone tumors and soft tissue and other extraosseous sarcomas. Standard treatment for bone tumors and rhabdomyosarcoma utilizes alkylating agent chemotherapy (cisplatin, cyclophosphamide, and ifosfamide) and radiation in excess of 30 Gy, which may be targeted to the pelvis for vaginal rhabdomyosarcoma [38,48,49]. Because these categories use therapies that impose the highest risk to fertility, it is expected and reassuring that these patients are being educated about fertility preservation and electing to undergo OTC. In contrast, conditions that were under-represented in the OC-NPC cohort relative to the general population included CNS/intracranial/intraspinal malignancies, retinoblastoma and hepatic tumors. Of note, there were no cases of retinoblastoma or hepatic tumors reported in the OC-NPC cohort. CNS/intracranial/intraspinal malignancies are typically treated with a combination of surgical resection and radiation, which could damage the HPO axis [50]. However, this exposure would not directly damage the ovaries and, therefore, OTC would not necessarily be indicated. Some cases involve spinal irradiation or alkylating agent chemotherapy, both of which would warrant discussion of the fertility preservation [51]. Patients with CNS/intracranial/intraspinal malignancies may require fertility preservation depending on their treatment modality, though it is likely that these fertility-threatening regimens were not utilized in the OC-NPC patients within this category due to a low observed incidence. Retinoblastoma affects the retina and is typically treated via enucleation, though 20% of retinoblastoma cases are metastatic and involve alkylating agents and radiation [52]. Retinoblastoma has a 5-year recurrence rate of 62% [53]. In most cases, OTC is not relevant for this condition, and this may explain why we did not observe any individuals with this diagnosis in the OC-NPC cohort. On the other hand, hepatic tumors are treated with alkylating agent chemotherapy, which represents a high risk to fertility [54]. Although patients with hepatic tumors may be candidates for OTC, the incidence of this malignancy is low during childhood, accounting for 1.1% of all malignancies in children <20 years of age [27]. This low frequency could account why this population was not represented in the OC-NPC cohort.

Ovarian tissue should only be removed from individuals that are at the highest risk of sterilization. This study provides important insight into the profile of young girls who have undergone OTC for fertility preservation for oncologic and nononcologic conditions. Although our sample size is small, it appears that the fertility risk imparted by disease treatments corresponds to the disease categories of individuals that have undergone OTC. Our findings indicate that the physicians in the OC-NPC are correctly identifying and extending OTC to young patients with the highest risk of POI imposed by their treatment. These findings provide evidence that providers and patients are aware of fertility-preservation options. One limitation of our study is that we do not know, of the patients who were counseled, how many elected to undergo fertility preservation. Although not electing to pursue OTC is a valid decision, these patients may have also been correctly identified as the highest need for fertility preservation but would not have been included in our analysis. Our analysis is also confined to the OC-NPC, which is comprised of large interdisciplinary teams primarily at large academic centers that are trained and committed to providing fertility preservation to men, women and children in the USA [9,55]. Whether these findings can be extrapolated from this biased population across larger populations warrants additional investigation. In addition, it is simply a matter of years before those who banked their ovarian tissue during childhood return to use it for transplantation. Global efforts are needed to monitor transplantation efficiency and outcomes in these individuals and to develop novel methods to restore fertility and endocrine function with these tissues [56].

Conclusion

The population of those surviving and experiencing long-term health effects of cancer treatment is increasing. Fertility preservation is an important option for cancer patients, which allows restoration of endocrine function and/or fertility in those whose disease or treatment may have the unintended consequence of compromised reproductive function. OTC followed by transplantation is an experimental procedure that has successfully restored fertility (86 live births) and hormone production (up to 7 years). Importantly, OTC is the only fertility-preservation method suitable for prepubertal girls. Nearly 25% of OTC cases that have been done through the OC-NPC network were in girls <15 years of age. Removal of ovarian tissue, especially in young individuals, is experimental, must be done under appropriate ethical approvals, and represents a drastic fertility-preservation measure. Thus, it is

imperative that physicians are educated to appropriately identify only those patients at highest risk of reproductive failure as candidates for OTC. By examining the malignancy categories that are predominant in the OC-NPC cohort relative to the general population, we observed congruence between the diagnoses of participants who underwent OTC and the relative fertility risk associated with the treatment for their condition. This finding validates that the physicians in the OC-NPC are correctly identifying and extending OTC to young patients at the highest risk and in most need of fertility preservation.

Summary points

- Between the inception of the Oncofertility Consortium's National Physicians Cooperative (OC-NPC) in 2007 and May 2016, 330 individuals have undergone ovarian tissue cryopreservation (OTC), and 117 of these individuals were <15 years old.
- A third of the girls (<15 years old) that have undergone OTC through the OC-NPC have done so for nononcologic conditions that have a high risk of infertility due to the conditions themselves or their treatment.
- The top two oncologic indications for OTC through the OC-NPC in girls (<15 years old) include the International Classification of Childhood Cancer categories of leukemias, myeloproliferative diseases, and myelodysplastic diseases (I) and soft-tissue and other extraosseous sarcomas (IX).
- Differences exist in malignancy distribution between the general population and girls (<15 years old) who have undergone OTC through the OC-NPC. These differences can be traced to the relative fertility risk imparted by the specific conditions and/or their treatment.
- OC-NPC physicians are correctly identifying and extending fertility preservation to patients at highest risk and in most need of fertility preservation.

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