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FERTILITY PRESERVATION

History of cancer and fertility treatment outcomes: a registry linkage study in Massachusetts

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Abstract

Purpose To investigate assisted reproductive technology (ART) outcomes among adolescent and young-adult female cancer survivors.

Methods The Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) data were linked to the Massachusetts Cancer Registry for 90,928 ART cycles in Massachusetts to women ≥ 18 years old from 2004 to 2013. To estimate relative risks (RR) and 95% confidence intervals (CI), we used generalized estimating equations with a log link that accounted for multiple cycles per woman and a priori adjusted for maternal age and cycle year. The main outcomes of interest were ART treatment patterns; number of autologous oocytes retrieved, fertilized, and transferred; and rates of implantation, clinical intrauterine gestation (CIG), live birth, and pregnancy loss.

Results We saw no difference in number of oocytes retrieved (aRR: 0.95 (0.89–1.02)) or proportion of autologous oocytes fertilized (aRR: 0.99 (0.95–1.03)) between autologous cycles with and without a history of cancer; however, cancer survivors required a higher total FSH administered (aRR: 1.12 (1.06–1.19)). Among autologous cycle starts, cycles in women with a history of cancer were less likely to result in CIG compared to no history of cancer (aRR: 0.73 (0.65–0.83)); this relationship was absent from donor cycles (aRR: 1.01 (0.85–1.20)). Once achieving CIG, donor cycles for women with a history of cancer were two times more likely to result in pregnancy loss (aRR: 1.99 (1.26–3.16)).

Conclusions Our analysis suggests that cancer may influence ovarian stimulation response, requiring more FSH and resulting in lower CIG among cycle starts.

Keywords Cancer · ART · Infertility · Survivorship

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Background

In the last five decades, the probability of mortality for children, adolescents, and young adults diagnosed with cancer has declined by nearly two thirds [1, 2]. Due to these improvements in survival among women who experience cancer early in life, there is increasing interest in the long-term reproductive outcomes related to their diagnosis and treatment [3–7]. The American Society for Clinical Oncology has identified fertility as an important issue among cancer survivors [8] as early-life cancer survivors have been shown to be less fecund [9, 10], having 40% fewer children than individuals without a history of cancer [11]. Research also suggests that cancer survivors may be more likely to experience infertility and to utilize fertility treatments compared to women without a history of cancer [10, 12, 13].

Research into the outcomes of fertility treatments for cancer survivors has been limited, but prior research has suggested that women with a history of cancer may require different treatment modalities, experience different treatment responses [14–17], and have a different probability of live birth [15, 18] compared to women without a history of cancer. Research has suggested that women with a history of cancer are more likely to have their cycles canceled [14, 15] and require higher doses of gonadotropins [14, 19]. To date, the majority of research on this topic has been limited to individual clinics or hospital systems or to studies with short duration between cancer incidence and fertility treatment utilization. Therefore, the goal of this study was to describe utilization patterns of assisted reproductive technology (ART) procedures and investigate differences in ART outcomes among early-life female cancer survivors utilizing a large dataset formed by linking the Massachusetts Cancer Registry and Massachusetts ART cycles from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS).

Methods

Data sources

Massachusetts Cancer Registry (MCR)

The MCR was established in 1980 (MAs General Law, Chapter 111, Sect. 111B) and collects information on all cancer diagnoses within the state of MA. Health care facilities are required by law to report newly diagnosed cancer or benign brain tumor cases that were diagnosed, evaluated, and/or treated at the facility/office. The MCR has received Gold Certification from the North American Association of Central Cancer Registries (NAACCR) every year from 1997 to 2018, indicating that they have achieved the highest standard for complete, accurate, and timely data collection. Additionally, the MCR has been recognized by the Centers for Disease Control and Prevention (CDC) and the National Program for Cancer Registries (NPCR) for achievement of the NPCR standards for data completeness, timeliness, and quality data since 2002.

The Society for Assisted Reproductive Technology Clinical Outcome Reporting System (SART CORS)

The SART CORS collects national, cycle-specific ART data under the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493). Information is collected about patient demographics, treatment parameters, and pregnancy outcomes. These data are validated annually, and some clinics have in-person visits for chart review where data reported by the clinic is compared with information recorded in patients' charts. In 2014, the 10 data fields selected for validation were found to have discrepancy rates of $\leq 6\%$ [20].

Data linkage

SART CORS data were matched with MCR data using Match*Pro1, a software developed by Information Management Services, Inc. (IMS), to conduct probabilistic record linkages. MCR data from 1995 to 2013 were linked to SART CORS cycles 2004 and 2013, using first name, last name, date of birth, and zip code. In situations where the last name disagreed, results were individually reviewed for matching by birth date, first name, and zip code. We included new cancers diagnosed by biopsy or CT scan. Recurrences of a cancer or metastatic occurrence of a cancer were not included. This research has been approved by the Massachusetts Department of Public Health (Title: Massachusetts Outcomes Study of Assisted Reproductive Technology (MOSART): Linkage of data from the Society for Reproductive Technology Clinical Outcomes Reporting System (SART CORS) to the PELL Data System; IRB #: 2,498,696).

Study population

Our study population included ART cycles from the SART CORS database in Massachusetts that took place between July 1, 2004, and December 31, 2013, to women ≥ 18 years of age (Fig. 1). Women whose date of cancer diagnosis from the MCR was before their first ART cycle in SART CORS were considered to have a history of cancer for this analysis. ART cycles in women who did not have a diagnosis of

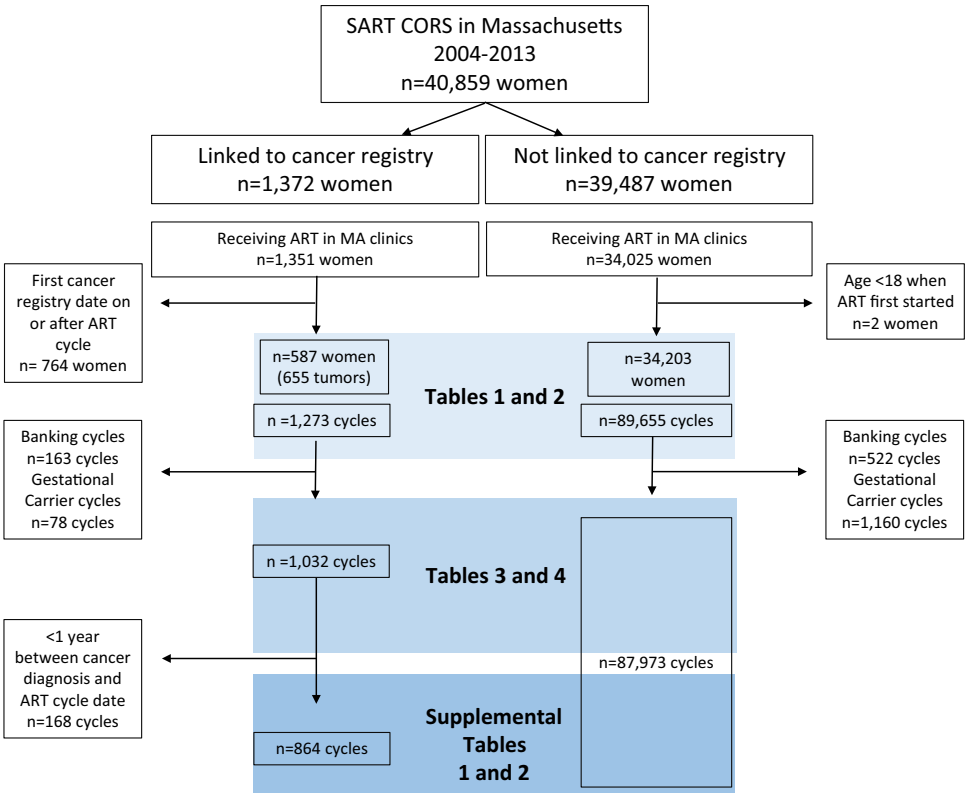

Fig. 1 Flow diagram of SART CORS population under study for analysis in MA 2004-2013

cancer in the MCR were considered to be without a history of cancer for this analysis. Women whose date of cancer diagnosis from MCR was after their first ART cycle were excluded. This resulted in 587 women with a history of cancer and 34,203 women without a history of cancer in our population and 90,928 ART cycles. Our main statistical analyses (Tables 3 and 4; Supplemental Tables 1, 2) excluded embryo banking and gestational carrier cycles resulting in 89,005 cycles, 1,032 ART cycles in women with a history of cancer, and 87,973 ART cycles in women without a history of cancer. Oocyte banking was rarely performed, and information was very limited in SART CORS prior to 2012 where it was collected solely under the category of research cycles. We do not have access to the limited data from those cycles. A woman could contribute multiple cycles to the analysis. Subsequent cycles would define the previous cycle as a prior cycle and these cycles may have included embryo banking, but any gestational carrier cycles or embryo banking cycles would have been excluded in our main analyses. We have separately run analyses among gestational carrier cycles.

Outcomes

Our main outcomes of interest were ART treatment parameters including autologous vs. donor cycles, number of embryos cryopreserved, reason for ART, total FSH dose (IU), number of autologous oocytes retrieved and fertilized, proportion of embryos fertilized, and number of embryos transferred. Information on the number of oocytes retrieved was limited to autologous oocytes. Information on fertilization was further restricted to cycles with at least one oocyte retrieved. The number of mature oocytes is not available from SART CORS.

For treatment outcomes, implantation rate and probability of biochemical pregnancy and clinical intrauterine gestation (CIG) were investigated. Implantation rate was defined as the number of fetal hearts (number of gestational sacs is not available) on an ultrasound divided by the number of embryos transferred to the uterus. Pregnancy outcomes of live birth and pregnancy loss were restricted to cycles with a successful clinical intrauterine gestation. We investigated autologous and donor cycles combined and then separately for treatment and pregnancy outcomes. We also investigated outcomes among all cycle starts and restricted to cycles with embryos transferred. In supplemental analyses, we investigated differences in embryo grade, total embryo grade score, average embryo grade score per cycle, and cycles without "good" graded embryos among embryos transferred (maximum 5 embryos). Embryo grade has been recorded in SART CORS as of 2010 for transferred embryos only. The grade is recorded as good, fair, or poor according to previously published criteria [21]. For analysis, grades were given numeric values with good being equal to 3, fair to 2, and poor to 1.

Statistical methods

We modeled the risks for cycle outcomes using log-binomial regression to yield relative risks and 95% confidence intervals. Generalized estimating equations with an exchangeable correlation structure were used to take into account multiple ART cycles per woman [22]. Log-Poisson models were utilized when dependent variables were counts or proportions and when log-binomial models failed to converge [23, 24]. Our analysis of FSH utilized a gamma distribution. All models were adjusted a priori for maternal age (18–29, 30–34, 35–40, 40 +) and year of cycle start (2004–2007, 2008–2010, 2011–2013). We did not adjust for race as this information is missing for approximately 2/3 of SART CORS cycles. In order to disentangle women who underwent fertility preservation after cancer diagnosis but prior to cancer treatment from women who pursued fertility treatment after cancer treatment, the main analyses were restricted to non-embryo banking cycles (Tables 3 and 4). Moreover, we conducted sensitivity analyses where we restricted our study population to women with > 1 year between cancer diagnosis and first cycle start date. Additionally, we separately ran analyses among gestational carrier cycles.

Results

In our population of 34,790 women, 587 (1.7%) had a history of cancer prior to their first ART cycle (Table 1). Women without a history of cancer were less likely to be nulligravida (51.5% vs. 62.7%) compared to women with a history of cancer. Women without a history of cancer were more likely to have had a prior pregnancy resulting in a full-term birth (25.2% vs. 20.1%) compared to women with a history of cancer.

Among women with a history of cancer, 25.9% were between the ages of 20 and 29, 33.9% were between the ages of 30 and 34, and 29.5% were between the ages of 35 and 39 at cancer diagnosis (Table 2). Approximately 40% of women with cancer had their first ART cycle < 1 year after their cancer diagnosis, with 22.2% having fertility treatment 1–2 years after their cancer diagnosis, 13.3% 3–4 years after their cancer diagnosis, and 24.4% having their first IVF cycle ≥ 5 years after their cancer diagnosis. The vast majority of embryo banking cycles (88.4%) were reported in the group with cancer diagnoses at < 1 year between diagnosis and first ART cycle. The most common cancer diagnoses in our population were breast cancer (32.5%), thyroid cancer (16.5%), and melanoma (14.5%).

We observed variation in clinical characteristics of ART cycles by cancer history. Cycles in women with a history of cancer were more likely to be banking cycles (12.8% vs 0.6%) or to utilize a gestational carrier (6.1% vs.

Table 1 Characteristics of women who utilized ART by history of cancer in MA 2004–2013[1]

	No cancer		History of cancer diagnosed in women prior to first ART cycle	
	n	%	*n*	%
Total	34,203	98.3	587	1.7
Age when 1st cycle started				
Mean (SD)	35.4 (4.8)		35.6 (5.4)	
Race/ethnicity[2]				
Hispanic	610	1.8	11	1.9
Non-Hispanic White	9,973	29.2	225	38.3
Non-Hispanic Black	715	2.1	14	2.4
Non-Hispanic Asian	1,600	4.7	19	3.2
Other non-Hispanic	53	0.2	< 11	-
Missing data	21,285	62.2	316	53.8
Gravidity				
0	17,611	51.5	368	62.7
1	8,319	24.3	125	21.3
2	4,250	12.4	47	8.0
3–11	3,936	11.5	44	7.5
Missing data	87	0.3	< 11	-
History of full-term birth				
Yes	8,624	25.2	118	20.1
History of preterm birth				
Yes	459	1.3	< 11	-
History of spontaneous abortion				
Yes	9,061	26.5	116	19.8
History of Biochemical Pregnancies				
Yes	432	1.3	< 11	-
Pregnancy outcome				
Live birth	10,619	31.0	91	15.5
Pregnancy loss	2,125	6.2	23	3.9
Stillbirth	42	0.1	0	0.0
First cycle resulted in embryo banking	158	0.5	148	25.2
Year of ART cycle started				
2004	5,374	15.7	57	9.7
2005	3,499	10.2	46	7.8
2006	3,053	8.9	56	9.5
2007	2,821	8.2	46	7.8
2008	2,972	8.7	48	8.2
2009	3,469	10.1	61	10.4
2010	3,200	9.4	43	7.3
2011	3,239	9.5	76	12.9
2012	3,315	9.7	65	11.1
2013	3,261	9.5	89	15.2

[1]Based on first ART cycle for each woman in SART CORS

[2]Patients may be in more than one race category

Table 2 Cancer characteristics among women with a history of cancer who utilized ART in MA 2004–2013 ($n = 587$ women)

Characteristics		
	n 587 women	%
Age at first cancer diagnosis (range 10–56)		
10–19	10	1.7
20–29	152	25.9
30–34	199	33.9
35–39	173	29.5
≥ 40	53	9.0
Years between first cancer diagnosis and first ART cycle start date		
< 1 year	236	40.2
1–2 years	130	22.1
3–4 years	78	13.3
≥ 5 years	143	24.4
	n 655 tumors	%
Primary cancer type[1]		
Breast	213	32.5
Brain and other nervous system	14	2.1
Lymphoma	66	10.1
Leukemia	17	2.6
Bone and soft tissue tumors	11	1.7
Thyroid	108	16.5
Melanoma	95	14.5
Female genital organs[2]	87	13.3
Other	44	6.7
Cancer treatment[3]		
Radiation	201	30.7
Chemotherapy	265	40.5
Surgery	547	83.5
Hormone	485	74.0
Biologic response modifiers	638	97.4
Year of initial treatment for that tumor[4]		
1995–2000	79	12.1
2001–2005	175	26.7
2006–2010	214	32.7
2011–2013	134	20.5
2014–2016	17	2.6

[1]Based on SEER cancer type

[2]Uterus, cervix, ovaries, vagina, vulva

[3]Initial cancer treatments are not mutually exclusive

[4]Initial year of radiation, chemotherapy, or surgery

1.3%). We observed no statistically significant difference in risk of cancelation between women with and without a history of cancer overall (RR: 1.24, 95% CI: 0.99–1.55) (Table 3), and in sensitivity analyses, when banking cycles were included (RR: 1.19, 95% CI: 0.96–1.48). Women with a history of cancer in non-banking cycles were also more likely to cryopreserve a greater number of embryos (mean = 4.6) compared to women without a history of cancer (mean = 3.7) (aRR: 1.22 (1.10–1.35)) (Table 3). This relation attenuated and was no longer statistically significant in sensitivity analyses restricted to cycles > 1 year after cancer diagnoses (aRR: 1.04) (Supplemental Table 2). Cycles in women with a history of cancer were less likely to have had a prior fresh ART cycle (aRR: 0.92 (0.86–0.98)). Cycles in women with cancer had a statistically significantly higher risk of having the infertility diagnosis "Other" (aRR: 2.41 (2.12–2.73)), which would have included the diagnosis of cancer being the reason for undergoing ART. When restricted to cycles > 1 year after cancer diagnosis, women with a history of cancer were more likely to have the diagnosis of "Diminished Ovarian Reserve" in addition to the diagnosis of "Other" (Supplemental Table 1). Cycles in women with a history of cancer required a greater amount of FSH to be administered for ovulation stimulation (aRR: 1.12 (1.06–1.19)); however, in autologous cycles, we saw no statistically significant difference in the number of autologous oocytes retrieved (aRR: 0.95 (0.89–1.02)), proportion of oocytes fertilized (aRR: 0.99 (0.95–1.03)) among cycles with at least one oocyte retrieved, or number of embryos transferred (aRR: 1.02 (0.97–1.06)) between cycles in women with and without a history of cancer.

Among cycle starts, cycles in women with a history of cancer were less likely to result in a CIG (aRR: 0.78, (0.71–0.87)) compared to cycles in women without a history of cancer (Table 4). This reduced probability of CIG was 27% lower in autologous cycles (aRR CIG: 0.73 (0.65–0.83)), but not in donor cycles (aRR CIG: 1.01 (0.85–1.20)). Among autologous and donor cycles with embryos transferred, we found no statistically significant associations between cancer history and probability of CIG. Among donor cycles, cycles in women with a history of cancer were two times more likely to result in pregnancy loss once clinical pregnancy was achieved (aRR: 1.99 (1.26–3.16)). Sensitivity analyses restricted to cycles > 1 year after cancer diagnosis did not meaningfully change results of treatment outcomes (Supplemental Table 2). Among gestational carrier cycles, the overall probability of CIG was higher among both cycles in women with (55.1%) and without (46.8%) a history of cancer when compared to autologous cycles (34.1% among women with a history of cancer; 40.1% among women without a history of cancer). Nevertheless, among gestational carrier cycles, we observed no difference between cycles in women with and without a history of cancer for implantation (RR: 0.94, 95% CI: 0.71–1.25), CIG (RR: 1.15, 95% CI: 0.91–1.47), live birth (RR: 0.94, 95% CI: 0.81–1.09), or pregnancy loss (RR: 1.46, 95% CI: 0.87–2.44).

We observed no difference in embryo quality for cycles in women with and without a history of cancer (Supplemental Table 3). We observed no meaningful difference in the

Table 3 Characteristics of ART cycles by cancer history, MA 2004–2013 (excluding embryo banking and gestational carrier cycles)

	No cancer ($n=87,973$)		History of cancer ($n=1,032$)		Crude		Multivariable adjusted[2]	
	N	%	*N*	%	RR[1]	95% CI	RR[1]	95% CI
Autologous oocyte	81,515	92.7	912	88.4	1.00 (Ref)		1.00 (Ref)	
Donor oocyte	6,453	7.3	120	11.6	1.56	1.21–2.00	1.05	0.82–1.35
Canceled cycle	6084	6.9	94	9.1	1.35	1.08–1.69	1.24	0.99–1.55
Prior fresh cycle[3]								
Yes	51,977	59.1	578	56.0	0.94	0.87–1.00	0.92	0.86–0.98
Number embryos cryopreserved								
Range	1–20		1–19					
Mean (SD)	3.73 (3.16)		4.58 (3.84)		1.23	1.11–1.36	1.22	1.10–1.35
Reason for ART[4]								
Male	27,175	30.9	219	21.2	0.62	0.51–0.75	0.62	0.51–0.75
Endometriosis	6,264	7.1	37	3.6	0.56	0.36–0.89	0.53	0.32–0.87
PCOS	10,294	11.7	79	7.7	0.65	0.47–0.89	0.67	0.48–0.93
DOR	14,122	16.1	237	23.0	1.37	1.15–1.62	1.15	0.97–1.37
Tubal factor	11,762	13.4	69	6.7	0.54	0.39–0.75	0.55	0.40–0.76
Uterine	3,227	3.7	43	4.2	1.16	0.76–1.78	1.14	0.74–1.74
Unexplained	21,028	23.9	228	22.1	0.79	0.66–0.95	0.81	0.68–0.98
Other	11,701	13.3	307	29.7	2.49	2.20–2.81	2.41	2.12–2.73
Total FSH (IU)								
Range	0–19,200		46–14,400					
Mean (SD)	3361.9 (1925.7)		3783.2 (2146.2)		1.15	1.09–1.21	1.12	1.06–1.19
Oocytes retrieved[5]								
Mean (SD)	11.49 (7.23)		10.73 (7.87)		0.93	0.86–1.00	0.95	0.89–1.02
Total oocytes fertilized[6]								
0 or null	22,214	35.1	263	38.9				
1–60	41,005	64.9	413	61.1				
Range	1–60		1–33					
Mean (SD)	7.18 (4.96)		6.43 (4.82)		0.98	0.93–1.04	0.98	0.94–1.04
Proportion of oocytes fertilized[6]								
Range	0.03–1.00		0.05–1.00					
Mean (SD)	0.62 (0.22)		0.62 (0.23)		0.99	0.95–1.03	0.99	0.95–1.03
Number of embryos transferred[7]								
0	12,932	14.7	275	26.6				
1–13	75,041	85.3	757	73.4				
Range	1–13		1–10					
Mean (SD)	2.19 (1.07)		2.35 (1.20)		1.08	1.03–1.13	1.02	0.97–1.06

[1]General estimating equations with a log link, exchangeable correlation structure were used to estimate relative risks and 95% confidence intervals. A binomial, gamma, or Poisson distribution was specified depending on the nature of the data

[2]Models were adjusted for maternal age (18–29, 30–34, 35–40, 40+) and year of cycle started (2004–2007, 2008–2010, 2011–2013)

[3]Women could contribute multiple cycles to the study sample and thus some women will have reported a prior cycle in this dataset

[4]Categories not mutually exclusive

[5]Limited to autologous oocytes

[6]Limited to autologous oocytes with at least one oocyte retrieved

[7]Limited to transfers of at least one embryo

probability of transferred embryos being graded as "good" for cycles in women with and without a history of cancer (57.9% vs 58.7%) or in the average (SD) embryo grade score per cycle (mean = 2.48 (0.62) vs. mean = 2.51 (0.59)). Cycles in women with a history of cancer were slightly more likely to result in no transferred embryos being graded as "good" compared to cycles in women without a history of cancer (5.61% vs. 4.79%).

Table 4 Treatment outcomes from ART cycles by cancer history, MA 2004–2013, among cycle starts and among embryos transferred (excluding embryo banking and gestational carrier cycles)

	No cancer ($n=87,973$)		History of cancer ($n=1,032$)		Crude risk ratio		Multivariable adjusted[2] risk ratio	
	N	%	*N*	%	RR[1]	95% CI	RR[1]	95% CI
Implantation rate								
Among embryo transfers								
Range	0–3		0–1.5					
Mean (SD)	0.26 (0.38)		0.22 (0.34)		0.81	0.71–0.91	0.89	0.79–1.01
Treatment outcomes								
Among all cycle starts								
Biochemical	6,313	7.2	66	6.4	0.88	0.69–1.13	0.87	0.68–1.11
CIG	30,755	35.0	277	26.8	0.75	0.68–0.83	0.78	0.71–0.87
Autologous cycles								
Biochemical	5,805	7.1	56	6.1	0.85	0.65–1.12	0.84	0.64–1.11
CIG	27,743	34.0	220	24.1	0.69	0.61–0.78	0.73	0.65–0.83
Donor cycles								
Biochemical	508	7.9	< 11	-	-	-	-	-
CIG	3,012	46.6	57	47.5	1.01	0.85–1.20	1.01	0.85–1.20
Among embryo transfers								
Biochemical	6,302	8.4	66	8.7	1.03	0.82–1.31	1.02	0.81–1.29
CIG	30,723	40.9	277	36.6	0.89	0.81–0.99	0.94	0.85–1.04
Autologous cycles								
Biochemical	5,796	8.4	56	8.7	1.03	0.79–1.34	1.02	0.78–1.32
CIG	27,714	40.1	220	34.1	0.85	0.76–0.95	0.92	0.82–1.03
Donor cycles								
Biochemical	506	8.6	< 11	-	-	-	-	-
CIG	3,009	50.9	57	51.4	0.99	0.84–1.17	0.99	0.84–1.17
Pregnancy outcomes (restricted to clinical pregnancy)								
Live birth	24,815	80.7	214	77.3	0.95	0.89–1.02	0.99	0.93–1.05
Pregnancy loss	5,678	18.5	62	22.4	1.24	0.98–1.57	1.11	0.88–1.39
Autologous cycles								
Live birth	22,264	80.3	173	78.6	0.98	0.91–1.05	1.02	0.96–1.08
Pregnancy loss	5,233	18.9	46	20.9	1.12	0.86–1.47	0.98	0.76–1.26
Donor cycles								
Live birth	2,551	84.7	41	71.9	0.84	0.71–1.01	0.84	0.71–1.01
Pregnancy loss	445	14.8	16	28.1	1.96	1.23–3.11	1.99	1.26–3.16

[1]General estimating equations with a binominal distribution, log link, exchangeable correlation structure were used to estimate relative risks and 95% confidence intervals. Poisson distribution was specified for testing on the implantation rates

[2]Models were adjusted for maternal age (18–29, 30–34, 35–40, 40+) and year of cycle started (2004–2007, 2008–2010, 2011–2013)

Discussion

In one of the largest studies to investigate ART treatment outcomes among cancer survivors with prolonged follow-up between cancer diagnosis and ART initiation, we found that ART cycles in women with a history of cancer had different treatment utilization patterns and probability of success compared to women without a history of cancer. Specifically, we observed that women with a history of cancer were more likely to use embryo banking or use gestational carriers. Among non-banking cycles/non gestational carrier cycles in women with a history of cancer, more total FSH was prescribed for ovarian stimulation, but we observed no difference in the number of oocytes retrieved, proportion of oocytes fertilized when restricted to cycles with at least one oocyte retrieved, or number of embryos transferred. Nevertheless, these women with a history of cancer were less likely to have cycles that resulted in clinical intrauterine gestation among autologous cycles and were more likely to result in pregnancy loss among donor cycles. We observed no meaningful difference in embryo quality from the data obtained in the current SART registry parameters.

Our study is in agreement with prior research that suggested that women with a history of cancer may utilize different fertility services than women without a history of cancer. Several, but not all [17], clinic-based studies have found that women with a history of cancer were given higher total gonadotropin doses compared to women with no history cancer [14, 15, 17]. We observed that women with a history of cancer were administered a higher total dosage of FSH (mean = 3,783 IU) compared to women without a history of cancer (mean = 3,362). Nevertheless, among the participants who had an embryo transfer, we observed no statistically significant difference in number of oocytes retrieved in autologous cycles between women with (mean = 10.7) and without (mean = 11.5) a history of cancer. Our findings are in agreement with a prior study that observed no difference in the number of oocytes retrieved [14]. However, other prior studies found that a smaller number of oocytes were retrieved in cycles in women with a history of cancer [15, 19, 25, 26]. Our findings may be influenced by the fact that our sample was restricted to individuals who had oocyte retrieval and embryo transfer and therefore, may be better responders than those individuals who were not included because their cycle was canceled.

Differences in treatment utilization and ART cycle outcomes may be related to changes in clinical practice and timing of stimulation and oocyte retrieval in relation to cancer diagnosis. Current guidelines suggest that fertility preservation should be proposed before starting systemic cancer treatment [8, 27, 28]. Indeed, some of the prior work has investigated fertility treatment response among women recently diagnosed with cancer undergoing embryo banking cycles prior to cancer treatment [14, 16, 26]. However, there are many women who undergo fertility treatment after their cancer treatment has ended [17, 18]. Women who undergo fertility preservation prior to cancer treatment and those whose cancer diagnosis and treatment was prior to undergoing ART may represent two distinct groups in terms of ART treatment options offered, response to stimulation, and ART treatment outcomes. To minimize the impact of these different groups, our main analyses excluded banking and gestational carrier cycles (Tables 3 and 4). Furthermore, to try to tease apart what remained of these potentially disparate groups with respect to the impact of cancer on ART outcomes, we conducted sensitivity analyses restricted to non-banking cycles > 1 year after cancer diagnosis. In these sensitivity analyses, we found similar overall patterns of treatment utilization and treatment outcomes, but no difference in the number of embryos cryopreserved between women with and without a history of cancer.

Given the small population size for the majority of research in this area, there has been limited research that has been able to investigate pregnancy outcomes after ART among women with a history of cancer [18, 26, 29]. Recent research combining state-level data from New York, Illinois, and Texas by Luke et al. found that women with a history of cancer within the last 5 years, who utilized autologous ART treatment, had reduced odds of conception (aOR: 0.34 95% CI: 0.27–0.87) and live birth (aOR: 0.36 95% CI: 0.28–0.46) compared to women without a history of cancer [18]. However, when their analysis was restricted to cycles that achieved conception, they observed no difference in livebirth between women with and without a history of cancer (aOR: 1.21 (0.69–2.11)). Similar to Luke et al., we observed that autologous cycles in women with a history of cancer were less likely to result in CIG (aRR: 0.73 95% CI: 0.65–0.83), and among cycles that achieved CIG, we observed no association between history of cancer and live birth. Among donor cycles, we observed reduced odds of live birth and greater risk of pregnancy loss for cycles in women with a history of cancer compared to cycles in women with no history of cancer. Our findings are in agreement with prior research that suggests that women with a history of cancer are less likely to achieve CIG with their own eggs; however, once analyses are restricted to conception, the probability of live birth is equivalent between women with and without a history of cancer in autologous cycles [18].

To our knowledge, this is the largest study with information on women with a history of cancer that includes women with cancer diagnoses > 5 years prior to ART treatment. However, there are several important limitations that must be considered. As is true of all state-level linkage studies, information will be missing if women received cancer treatment or fertility treatment outside the state of MA. We expect that cancer survivors who moved out of state prior to fertility treatment would not be different with respect to adverse outcomes from the cancer survivors who stayed in MA. Thus, this misclassification would, if anything, most likely attenuate our reported relationships. Additionally, SART CORS, and thus ART treatment data, is not available for cycles that took place prior to 2004. Approximately, 12.1% of our participants started their cancer treatment prior to 2001 and 26.7% prior to 2006 (Table 2). Therefore, our results may not reflect ART treatment patterns prior to 2004 and thus may have limited generalizability to fertility treatment outcomes before that time. Information on some important covariates (i.e., body mass index, details of medically assisted reproduction that is not IVF, entire cancer treatment history) are not available in these data. Given the timeframe of our study, oocyte banking cycles were rare. We were, furthermore, unable to determine whether these were in the cancer or non-cancer cohort or whether they were from donor egg cycles. Nevertheless, we would expect the impact of these cycles to be minimal on our findings given their rarity and dilution among the large number of non-oocyte banking cycles. Due to low numbers, we were unable to disentangle the influence of different cancer diagnoses, which may have different

treatment patterns and may have a different influence on IVF outcomes. Lastly, we were not able to link information on the cancer history of the male partner for ART cycles and this information may be influential. With regard to embryo morphology, which is determined subjectively, we are aware that different clinics may assess morphology differently which could have obscured differences.

In summary, women with a history of cancer who utilized ART were more likely to use banking cycles or gestational surrogacy. We observed differences of increased total FSH prescribed but no difference in oocytes retrieved for women with a history of cancer. Autologous cycles in women with a history of cancer were less likely to result in clinical intrauterine gestation. We saw no overall difference in probability of live birth, but donor cycles with a history of cancer were more likely to result in pregnancy loss and less likely to result in live birth. To our knowledge, this is the largest study that includes prolonged follow-up between cancer incidence and fertility treatment utilization. While these findings offer a unique contribution to the field, future research with detailed information on both previous cancer history and fertility treatment for both male and female cancer survivors is necessary to better counsel survivors of cancer regarding their family building goals.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10815-021-02376-x.

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References

1. American Cancer Society. Cancer facts and figures 2019. Atlanta: American Cancer Society; 2019.
2. Fidler MM, Gupta S, Soerjomataram I, Ferlay J, Steliarova-Foucher E, Bray F. Cancer incidence and mortality among young adults aged 20–39 years worldwide in 2012: a population-based study. Lancet Oncol. 2017;18(12):1579–89. https://doi.org/10.1016/s1470-2045(17)30677-0.
3. Peate M, Meiser B, Hickey M, Friedlander M. The fertility-related concerns, needs and preferences of younger women with breast cancer: a systematic review. Breast Cancer Res Treat. 2009;116(2):215–23. https://doi.org/10.1007/s10549-009-0401-6.
4. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst. 2012;104(5):386–405. https://doi.org/10.1093/jnci/djr541.
5. Zebrack BJ, Casillas J, Nohr L, Adams H, Zeltzer LK. Fertility issues for young adult survivors of childhood cancer. Psychooncology. 2004;13(10):689–99. https://doi.org/10.1002/pon.784.
6. Hawkins Bressler L, Mersereau JE, Anderson C, Rodriguez JL, Hodgson ME, Weinberg CR, et al. Fertility-related experiences after breast cancer diagnosis in the Sister and Two Sister Studies. Cancer. 2019;125(15):2675–83. https://doi.org/10.1002/cncr.32126.
7. Anderson RA, Clatot F, Demeestere I, Lambertini M, Morgan A, Nelson SM, et al. Cancer survivorship: Reproductive health outcomes should be included in standard toxicity assessments. Eur J Cancer (Oxford,England: 1990). 2021;144:310–6. https://doi.org/10.1016/j.ejca.2020.11.032.
8. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018;36(19):1994–2001. https://doi.org/10.1200/jco.2018.78.1914.
9. Green DM, Sklar CA, Boice JD Jr, Mulvihill JJ, Whitton JA, Stovall M, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27(14):2374–81. https://doi.org/10.1200/jco.2008.21.1839.
10. Armuand G, Skoog-Svanberg A, Bladh M, Sydsjo G. Reproductive patterns among childhood and adolescent cancer survivors in Sweden: a population-based matched-cohort study. J Clin Oncol. 2017;35(14):1577–83. https://doi.org/10.1200/jco.2016.71.0582.
11. Anderson RA, Brewster DH, Wood R, Nowell S, Fischbacher C, Kelsey TW, et al. The impact of cancer on subsequent chance of pregnancy: a population-based analysis. Hum Reprod. 2018;33(7):1281–90. https://doi.org/10.1093/humrep/dey216.
12. Stensheim H, Klungsoyr K, Skjaerven R, Grotmol T, Fossa SD. Birth outcomes among offspring of adult cancer survivors: a population-based study. Int J Cancer. 2013;133(11):2696–705. https://doi.org/10.1002/ijc.28292.
13. Barton SE, Najita JS, Ginsburg ES, Leisenring WM, Stovall M, Weathers RE, et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol. 2013;14(9):873–81. https://doi.org/10.1016/s1470-2045(13)70251-1.
14. Dolinko AV, Farland LV, Missmer SA, Srouji SS, Racowsky C, Ginsburg ES. Responses to fertility treatment among patients with cancer: a retrospective cohort study. Fertility research and practice. 2018;4:3. https://doi.org/10.1186/s40738-018-0048-2.
15. Barton SE, Missmer SA, Berry KF, Ginsburg ES. Female cancer survivors are low responders and have reduced success compared with other patients undergoing assisted reproductive technologies. Fertil Steril. 2012;97(2):381–6. https://doi.org/10.1016/j.fertnstert.2011.11.028.
16. Knopman JM, Noyes N, Talebian S, Krey LC, Grifo JA, Licciardi F. Women with cancer undergoing ART for fertility preservation: a cohort study of their response to exogenous gonadotropins. Fertil Steril. 2009;91(4 Suppl):1476–8. https://doi.org/10.1016/j.fertnstert.2008.07.1727.
17. Das M, Shehata F, Son WY, Tulandi T, Holzer H. Ovarian reserve and response to IVF and in vitro maturation treatment following chemotherapy. Hum Reprod. 2012;27(8):2509–14. https://doi.org/10.1093/humrep/des143.
18. Luke B, Brown MB, Missmer SA, Spector LG, Leach RE, Williams M, et al. Assisted reproductive technology use and outcomes among women with a history of cancer. Hum Reprod. 2016;31(1):183–9. https://doi.org/10.1093/humrep/dev288.
19. Robertson AD, Missmer SA, Ginsburg ES. Embryo yield after in vitro fertilization in women undergoing embryo banking for fertility preservation before chemotherapy. Fertil Steril. 2011;95(2):588–91. https://doi.org/10.1016/j.fertnstert.2010.04.028.
20. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive

Technology. 2014 Assisted reproductive technology fertility clinic success rates report Atlanta (GA): US dept of health and human services; 2016.
21. Racowsky C, Vernon M, Mayer J, Ball GD, Behr B, Pomeroy KO, et al. Standardization of grading embryo morphology. J Assist Reprod Genet. 2010;27(8):437–9. https://doi.org/10.1007/s10815-010-9443-2.
22. Dodge LE, Farland LV, Correia KFB, Missmer SA, Seidler EA, Wilkinson J, et al. Choice of statistical model in observational studies of ART. Hum Reprod. 2020;35(7):1499–504. https://doi.org/10.1093/humrep/deaa050.
23. Christopher JWZ. Generalized estimating equation models for correlated data: a review with applications. Am J Polit Sci. 2001;45(2):470–90. https://doi.org/10.2307/2669353.
24 Williamson T, Eliasziw M, Fick GH. Log-binomial models: exploring failed convergence. Emerg Themes Epidemiol. 2013;10(1):14. https://doi.org/10.1186/1742-7622-10-14.
25. Klock SC, Zhang JX, Kazer RR. Fertility preservation for female cancer patients: early clinical experience. Fertil Steril. 2010;94(1):149–55. https://doi.org/10.1016/j.fertnstert.2009.03.028.
26. Cardozo ER, Thomson AP, Karmon AE, Dickinson KA, Wright DL, Sabatini ME. Ovarian stimulation and in-vitro fertilization outcomes of cancer patients undergoing fertility preservation compared to age matched controls: a 17-year experience. J Assist Reprod Genet. 2015;32(4):587–96. https://doi.org/10.1007/s10815-015-0428-z.
27. Lambertini M, Peccatori FA, Demeestere I, Amant F, Wyns C, Stukenborg JB, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines(†). Annals of oncology : official journal of the European Society for Medical Oncology. 2020;31(12):1664–78. https://doi.org/10.1016/j.annonc.2020.09.006.
28 Anderson RA, Amant F, Braat D, DAngelo A, Chuva de Sousa Lopes SM, Demeestere I, et al. ESHRE guideline: female fertility preservation. Human reproduction open. 2020;2020(4):52. https://doi.org/10.1093/hropen/hoaa052.
29. Farland LV, Stern JE, Hwang SS, Liu CL, Cabral H, Knowlton R, et al. Early-life cancer, infertility, and risk of adverse pregnancy outcomes: a registry linkage study in Massachusetts. Cancer Causes Control. 2020. https://doi.org/10.1007/s10552-020-01371-4.