Time to cancer treatment and reproductive outcomes after fertility preservation among adolescent and young adult women with cancer

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Funding information
St. Baldrick's Foundation, Grant/Award Number: Scholar Award 523803; National Institute of Environmental Health Sciences, Grant/Award Number: P30 ES010126; National Cancer Institute, Grant/Award Numbers: F31 CA260787, R01 CA204258, R01 CA211093, T32 CA057726; University of North Carolina

Abstract

Background: Fertility preservation (FP) may be underused after cancer diagnosis because of uncertainty around delays to cancer treatment and subsequent reproductive success.

Methods: Women aged 15 to 39 years diagnosed with cancer between 2004 and 2015 were identified from the North Carolina Central Cancer Registry. Use of assisted reproductive technology (ART) after cancer diagnosis between 2004 and 2018 (including FP) was assessed through linkage to the Society for Assisted Reproductive Technology. Linear regression was used to examine time to cancer treatment among women who did (n = 95) or did not (n = 469) use FP. Modified Poisson regression was used to estimate risk ratios (RRs) and 95% CIs for pregnancy and birth based on timing of ART initiation relative to cancer treatment (n = 18 initiated before treatment for FP vs n = 26 initiated after treatment without FP).

Results: The median time to cancer treatment was 9 to 33 days longer among women who used FP compared with women who did not, matched on clinical factors. Women who initiated ART before cancer treatment may be more likely to have

a live birth given pregnancy compared with women who initiated ART after cancer treatment (age-adjusted RR, 1.47; 95% CI, 0.98-2.23), though this may be affected by the more frequent use of gestational carriers in the former group (47% vs 20% of transfer cycles, respectively).

Conclusions: FP delayed gonadotoxic cancer treatment by up to 4.5 weeks, a delay that would not be expected to alter prognosis for many women. Further study of the use of gestational carriers in cancer populations is warranted to better understand its effect on reproductive outcomes.

KEYWORDS
assisted reproductive technology, cancer survivors, reproduction, survivorship, time to treatment

INTRODUCTION

Nearly nine in 10 adolescent and young adult (AYA) women with cancer will survive at least 5 years after diagnosis, highlighting the importance of better addressing their survivorship challenges.[1] Treatment-related risks to fertility are particularly relevant to AYAs[1] because they may not have completed building their families and may receive cancer therapies that compromise future reproductive function.[2,3]

However, women with cancer report forgoing fertility preservation (FP) because of a concern of delaying cancer treatment.[4–9] Oncologists similarly cite an unwillingness to delay treatment as a reason for not engaging in fertility discussions or referring patients to reproductive specialists.[10–13] Existing evidence regarding the delay to cancer treatment after FP is based exclusively on studies conducted at single medical institutions, which have lacked control for important confounding variables (e.g., stage, race), and that have largely been limited to women with breast cancer.[8,14–24]

Furthermore, evidence of FP success within cancer populations is limited.[13,25] Pregnancy rates using thawed oocytes or embryos from the general population are often used to counsel patients with cancer who are considering FP, though the validity of extrapolating those rates to women with a cancer diagnosis is unclear.[3,26,27] Even fewer studies have assessed reproductive outcomes in women who initiate assisted reproductive technology (ART) after cancer treatment.[28]

To address these limitations, we used a statewide sample of AYA women diagnosed with cancer to examine time to cancer treatment following FP and reproductive outcomes based on timing of ART initiation relative to cancer treatment.

METHODS

Study population

AYA women (aged 15-39 years) diagnosed with a first primary invasive cancer in North Carolina between 2004 and 2015 were identified from the North Carolina Central Cancer Registry (CCR) (n = 15,998). Women were probabilistically linked to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS) for fertility services received between 2004 and 2018 using social security number, date of birth, full name, and zip code. SART CORS is a database of ART cycles performed at SART-member fertility clinics (available to researchers from 2004 onward), and accounted for 96% to 100% of all ART cycles performed in North Carolina during the study years.[29] This study was approved by the institutional review board at the University of North Carolina at Chapel Hill.

Assisted reproductive technology

ART involves the handling of oocytes or embryos to attempt pregnancy, including oocyte and embryo cryopreservation and embryo transfer. Women were classified as initiating ART before or after potentially gonadotoxic cancer treatment—defined as chemotherapy for any cancer, radiation for gynecologic cancers or hematologic malignancies, or any surgical treatment for gynecologic cancers. Women who first initiated ART for oocyte/embryo cryopreservation (without transfer) after the date of cancer diagnosis but before the date of first gonadotoxic treatment were defined as using FP. Women who first initiated ART for oocyte/embryo cryopreservation or embryo transfer after gonadotoxic treatment were defined as using ART without fertility preservation. Women who did not receive gonadotoxic cancer treatment (n = 7909) or who had used ART before cancer diagnosis (n = 29) were excluded from all analyses.

Time to cancer treatment

Type and dates of first-course cancer treatment were identified from the North Carolina CCR, which have been validated against insurance claims for AYA women diagnosed with lymphoma, breast, thyroid, or gynecologic cancer. Among cancer types combined, sensitivity of the North Carolina CCR data (vs administrative claims data as the gold

standard) ranged from 74% for radiation to 86% for chemotherapy; positive predictive values ranged from 82% for chemotherapy to 83% for radiation; and agreement in date of treatment initiation (defined as within 30 days) ranged from 63% for chemotherapy to 93% for radiation.[30]

Women who were diagnosed with cancer during pregnancy were excluded from analysis of time to treatment, including one woman who used FP. AYA women with cancer who used FP ("exposed"; $n = 95$) were matched to five women with cancer who did not ("unexposed") by cancer characteristics that were *a priori* confounders: years of diagnosis (2004-2009, 2010-2015); cancer type (exact match); summary stage (localized, regional, distant); and first gonadotoxic treatment (Figure 1). Timing of chemotherapy (neoadjuvant or adjuvant) was an additional matching factor for women with breast cancer or cancers other than hematologic or gynecologic because chemotherapy could be administered before or after non-gonadotoxic radiation or surgery. Three women who used FP only had two to four matches but were retained in analysis. Time to treatment was defined as the days between cancer diagnosis and receipt of first gonadotoxic treatment.

Pregnancy and live birth with ART

For analysis of reproductive outcomes with ART, women who initiated ART before cancer treatment (i.e., cryopreserved oocytes or embryos for FP) and underwent embryo transfer after cancer treatment ($n = 18$) were compared with women who did not use FP but underwent embryo transfer after cancer treatment ($n = 26$). None of the 18 women who used FP and attempted embryo transfer had additional oocyte retrieval after receipt of gonadotoxic treatment. Inclusion in both groups was limited to women who had received gonadotoxic treatment; the comparator group was not a subset of the matched unexposed group from the time to treatment analysis, though women could be included in both analyses (Figure 1). Clinical pregnancy was defined as the presence of at least one gestational sac within the uterus confirmed by ultrasound. Clinical pregnancy, live birth, and ART cycle characteristics were obtained from SART CORS.

Covariates

Cancer and individual-level characteristics were obtained from the North Carolina CCR, except for parity, which was defined using North Carolina birth certificates. Vital status was available from the North Carolina CCR through mid-2017. Area-level characteristics were obtained through linkage of Federal Information Processing System codes at the census tract using home address at the time of diagnosis. Rural-urban commuting area codes were used to categorize census tracts as urban or nonurban.[31] The Yost Socioeconomic (SES) index was used to categorize census tracts as low (quintiles 1-3) or high SES (quintiles 4 and 5).[32]

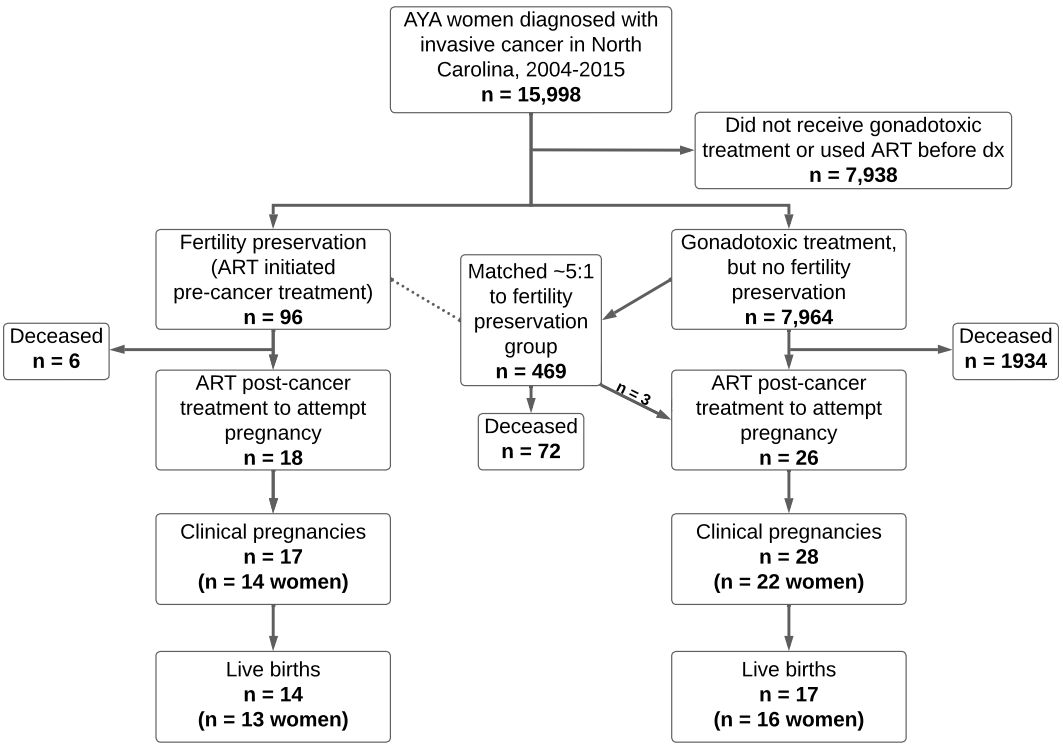

FIGURE 1 Study sample flow diagram. One woman who used fertility preservation was excluded in time to cancer treatment analysis because she was diagnosed with cancer during pregnancy. ART indicates assisted reproductive technology

Statistical analysis

Time to cancer treatment

All comparisons of time to treatment by FP use were adjusted for year of diagnosis, cancer type, stage, and treatment by design because of the matching of exposure groups by those clinical factors. The association between FP and time to treatment was further examined using linear regression for cancer type and treatment groups with sufficient sample sizes, which were breast (time to adjuvant chemotherapy), hematologic (time to chemotherapy or radiation), and "other invasive" cancers, which included gastrointestinal tract, osseous and chondromatous, soft-tissue sarcoma, other carcinomas of the head and neck, and other invasive cancers not otherwise specified (time to adjuvant therapy). The analytic sample was limited to women who received gonadotoxic treatment, and thus there was no censoring. To address the observed heteroscedasticity and nonnormality of the residuals—assumptions of the model that, when violated, may bias regression coefficients and CIs[33]—two separate regression analyses were conducted for each cancer type/treatment group: (1) outliers were excluded (i.e., observations with a Studentized residual $>\pm 2$); and (2) time to treatment was natural log transformed.[33] *A priori* confounders were identified using a directed acyclic graph and included race and ethnicity, rurality, and SES. Because of lack of positivity (i.e., lack of both exposed and unexposed women across all levels of the covariate distribution), rurality could not be included in adjusted regression.

Pregnancy and live birth with ART

Reproductive outcomes with ART were compared based on timing of ART initiation relative to cancer treatment (with or without FP). Modified Poisson regression models with robust error variance were used to estimate unadjusted and age-adjusted risk ratios (RRs) and 95% CIs.[34] For outcomes at the transfer cycle or pregnancy level, generalized estimating equations with a Kauermann-Carroll small-sample correction of standard errors was used to account for within-subject correlation.[35–37] Adjustment for other *a priori* confounders (year of ART initiation, race and ethnicity, parity, and cancer treatment) was not possible given small sample sizes. Our *a priori* analytic strategy was to assess reproductive outcomes comparing women who used ART with versus without fertility preservation. However, some women who had used fertility preservation subsequently used donor oocytes to attempt pregnancy, rather than use of their previously cryopreserved oocytes/embryos. Thus, reproductive outcomes were also examined separately for autologous transfers only (i.e., using a woman's own oocytes/embryos), as well as for transfers without a gestational carrier, though unadjusted and age-adjusted models could not be presented for all outcomes given lack of model convergence. Though our sample size limited detailed analysis of reproductive outcomes by cancer type and treatments, we were able to stratify outcomes by receipt of gynecologic surgery, which can be a risk factor for pregnancy loss.[38] All analyses were conducted in SAS 9.4.

RESULTS

Sample characteristics

Ninety-six women cryopreserved oocytes or embryos for FP (one of whom was diagnosed with cancer during pregnancy and was excluded from time to treatment analysis) and 18 (19%) attempted at least one embryo transfer cycle at a median of 2.9 years after diagnosis. Twenty-six women who did not use FP had at least one embryo transfer at a median of 3.6 years after diagnosis (Figure 1). Compared with women who did not use FP, women who used FP were younger at diagnosis, and more likely to be non-Hispanic White, unmarried, nulliparous, have private insurance, or live in areas that were urban or higher SES (Table 1).

Time to cancer treatment

The median time to treatment was longer among women who used FP across all cancer types (Figure 2). Compared with women who did not use FP—matched on cancer clinical factors—women with breast cancer who used FP received chemotherapy a median of 15.5 (neoadjuvant) or 14 (adjuvant) days later; women with hematologic malignancies or gynecologic cancers who used FP received gonadotoxic treatment a median of 9 or 28.5 days later, respectively; and women with other invasive cancers who used FP received chemotherapy a median of 31 (neoadjuvant) or 33.5 (adjuvant) days later.

Differences in time to treatment were further examined using linear regression for cancer type/treatment groups with sufficient sample sizes. In fully adjusted analysis that excluded outliers, FP was associated with a longer time to treatment among women with breast cancer who received adjuvant chemotherapy ($\beta = 15.5$ days; 95% CI, 6.5-24.5), women with hematologic malignancies ($\beta = 13.8$ days; 95% CI, 7.1-20.4), and women with other invasive cancers who received adjuvant chemotherapy ($\beta = 27.5$ days; 95% CI, 9.5-45.5) (Table 2).

In fully adjusted analysis that used a natural log transformation of the outcome (no exclusion of outliers), delays in treatment were similarly observed, though because of the outcome transformation, the scale of the interpretation changes to relative. FP was associated with a 25.2% (95% CI, 4.0-50.7) increase in days to treatment among women with breast cancer who received adjuvant chemotherapy; a 66.9% (95% CI, 18.8-134.2) increase in days to treatment among women with hematologic malignancies; and a 52.0% (95% CI, 9.1-111.9) increase in days to treatment among women with other invasive cancers who received adjuvant chemotherapy.

Six women (6.3%) who used FP died by the end of survival follow-up (mid-2017), compared with 72 women (15.4%) in the

TABLE 1 Cancer and sociodemographic characteristics among adolescent and young adult women with cancer in North Carolina, 2004-2015, by use of oocyte or embryo cryopreservation for fertility preservation

	Used fertility preservation, *n* = 95		Did not use fertility preservation,[a] *n* = 469	
	No.	%[b]	No.	%[b]
Median (IQR) follow-up for survival, y	3.9	(3.6)	4.7	(4.1)
Median (IQR) age at diagnosis, y	30.0	(7.0)	34.0	(8.0)
Age at diagnosis, y				
15-24	12	12.6	56	11.9
25-29	34	35.8	70	14.9
30-34	29	30.5	125	26.7
35-39	20	21.1	218	46.5
Year of cancer diagnosis, matched				
2004-2009	18	18.9	90	19.2
2010-2012	24	25.3	201	42.9
2013-2015	53	55.8	178	37.9
Cancer type (first gonadotoxic treatment), matched				
Breast (neoadjuvant chemotherapy)[c]	<11	<11.5	**	**
Breast (adjuvant chemotherapy)	48	50.5	240	51.2
Gynecologic (radiation or surgery)[c]	<11	<11.5	**	**
Hematologic (chemotherapy or radiation)	21	22.1	102	21.7
Other (neoadjuvant chemotherapy)[c]	<11	<11.5	**	**
Other (adjuvant chemotherapy)	13	13.7	62	13.2
Summary stage, matched				
Localized	36	37.9	177	37.7
Regional	49	51.6	242	51.6
Distant[c]	<11	<11.5	50	10.7
Unstaged/unknown/unspecified[c]	<11	<11.5	0	0
Race and ethnicity				
Hispanic[c]	<11	<11.5	29	6.3
Non-Hispanic Black	13	13.7	124	26.8
Non-Hispanic White	74	77.9	290	62.8
Non-Hispanic all other races[c,d]	<11	<11.5	19	4.1
Missing	0	0.0	7	1.5
Marital status at diagnosis				
Never married or widowed, divorced, or separated	43	60.6	172	44.9
Married or domestic partner	28	39.4	211	55.1
Missing	24	25.3	86	18.3
Parity at diagnosis				
Nulliparous[e]	80	84.2	232	49.5
Parous	15	15.8	237	50.5

(Continues)

TABLE 1 (Continued)

	Used fertility preservation, $n = 95$		Did not use fertility preservation,[a] $n = 469$	
	No.	%[b]	No.	%[b]
Insurance status at diagnosis				
Private	77	81.9	246	53.8
Medicaid[c]	<11	<11.5	85	18.6
Other government[c,f]	<11	<11.5	24	5.3
Insurance, not otherwise specified[c]	<11	<11.5	53	11.6
Not insured[c]	<11	<11.5	39	8.5
Missing	1	1.0	12	2.6
Rurality at diagnosis				
Urban	89	96.7	362	77.3
Large rural city/town[c]	<11	<11.5	67	14.3
Small rural town[c]	<11	<11.5	20	4.3
Isolated small town rural[c]	<11	<11.5	19	4.1
Missing	3	3.2	1	0.2
Yost SES index at diagnosis[g]				
Quintiles 1-3 (lowest)	27	29.7	279	60.7
Quintile 4-5 (highest)	64	70.3	181	39.3
Missing	4	4.2	9	1.9

Abbreviations: IQR, interquartile range; SES, socioeconomic status.

[a]The no fertility-preservation group was matched approximately 5:1 to the fertility preservation group by year of cancer diagnosis, cancer type, summary stage, and cancer treatment. Three women who used fertility preservation only had two to four matches but were retained in analysis.

[b]Percentages exclude missing values.

[c]Exact number not reported because the North Carolina Central Cancer Registry requires cell sizes <11 to be suppressed. **Indicates a nonreportable size because of the ability to derive a cell size <11 if that cell was reported.

[d]Non-Hispanic all other races includes American Indian, Aleutian, or Eskimo; Asian or Pacific Islander; and other race, not otherwise specified.

[e]Assumes that women without a record of a live birth in North Carolina during 2000-2015 were nulliparous at diagnosis, which may misclassify women if they had a birth in North Carolina before 2000, or in another state at any time and did not have a birth in North Carolina during 2000-2015.

[f]Other government includes Medicare, TRICARE, military, Veterans Affairs, and Indian/Public Health Service.

[g]Yost SES index: a time-dependent composite score constructed from the following census tract variables: median household income, median house value, median rent, percent below 150% of poverty line, education index, percent working class, and percent unemployed.

unexposed matched comparator group, though the comparator group had a longer follow-up time after diagnosis (median of 4.7 vs 3.9 years).

Pregnancy and live birth with ART

A majority of women (81%) who used FP did not attempt transfer by the end of SART CORS follow-up (2018) (Table 3). Women who used ART to attempt pregnancy with or without FP were similar in median age at diagnosis, most women were non-Hispanic White, and nulliparous at diagnosis (Table 3). Most women in the FP group had breast cancer (72.2%), whereas the no FP group had 50% of women with gynecologic cancer. Both groups had received gonadotoxic cancer treatment; all women in the FP group received chemotherapy and none underwent gynecologic surgery, compared with 65.4% who received chemotherapy and 50% who underwent gynecologic surgery in the no FP group.

Compared with women who initiated ART after cancer treatment, women who initiated ART before cancer treatment for FP underwent fewer embryo transfer cycles, initiated ART at a younger age, and had a shorter median time from diagnosis to first embryo transfer. A larger proportion of transfer cycles in the FP group were autologous, fewer used fresh embryo transfer cycles (i.e., used oocytes or embryos that had never been cryopreserved), and more used a gestational carrier (Table 3).

Eighteen women who initiated ART before cancer treatment for FP and attempted transfer had a total of 30 transfer cycles, resulting in 17 clinical pregnancies among 14 women (77.8% pregnancy rate per woman) and 14 live births among 13 women (72.2% live birth rate per woman) (Table 4). Twenty-six women who initiated ART after cancer treatment without FP had a total of 55 transfer cycles,

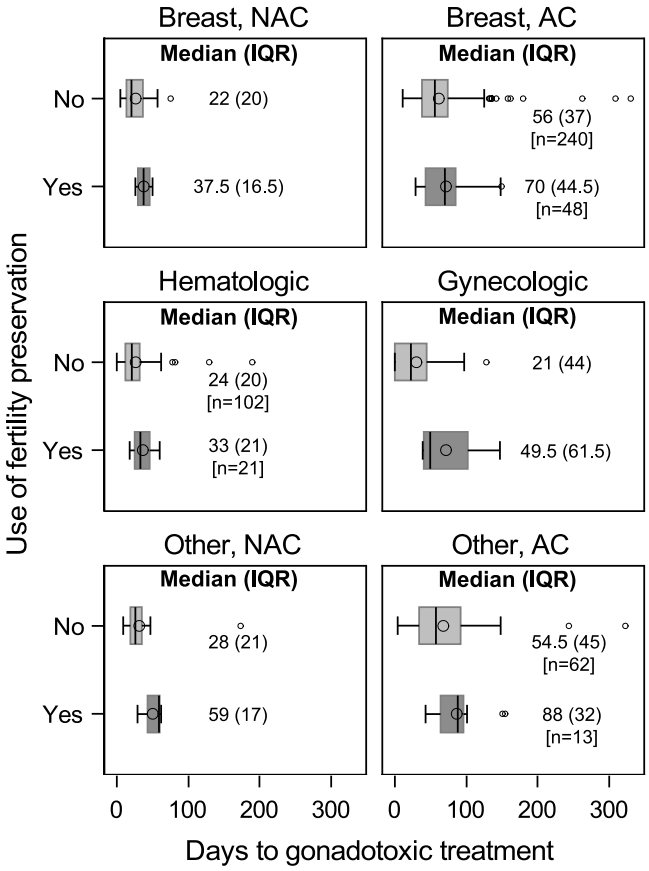

FIGURE 2 Time to receipt of first gonadotoxic treatment after oocyte or embryo cryopreservation for fertility preservation among adolescent and young adult women with cancer in North Carolina, 2004-2015, by cancer type and treatment.[a] Abbreviations: AC indicates adjuvant chemotherapy; IQR, interquartile range; NAC, neoadjuvant chemotherapy. [a] The no fertility-preservation group was matched approximately 5:1 to the fertility preservation group by year of cancer diagnosis, cancer type, summary stage, and cancer treatment. Three women who used fertility preservation only had two to four matches but were retained in analysis. Other invasive cancers included gastrointestinal tract, osseous and chondromatous, soft-tissue sarcoma, other carcinomas of the head and neck, and other invasive cancers not otherwise specified. Not all sample sizes are reported because the North Carolina Central Cancer Registry requires cell sizes <11 to be suppressed.

resulting in 28 clinical pregnancies among 22 women (84.6% pregnancy rate per woman) and 17 live births among 16 women (61.5% live birth rate per woman).

In age-adjusted regression, although imprecise, no differences were observed by FP use for pregnancy after the first transfer cycle, per transfer cycle, or per woman (Table 4). Similarly, no differences between groups were observed for live birth after the first transfer cycle, per transfer cycle, or per woman, though there was suggestive evidence of a higher rate of live birth given pregnancy among women who used FP (age-adjusted RR, 1.47; 95% CI, 0.98-2.23). Relatedly, pregnancy loss per woman after having achieved pregnancy was more than two times lower among women who had used FP, though this difference was not statistically significant (age-adjusted RR, 0.41; 95% CI, 0.14-1.15). Regression models were also conducted separately for autologous transfer cycles only and transfers without a gestational carrier. No substantive differences were observed compared to all transfer cycles combined, though sample sizes were small and should be interpreted as exploratory only (Table 4). Similarly, no substantive differences in clinical pregnancy or live birth were observed when outcomes were stratified by receipt of gynecologic surgery, though more transfer cycles among women who received gynecologic surgery resulted in pregnancy loss (46.7% of transfers resulted in pregnancy loss among women who did not use FP and received gynecologic surgery vs 30.8% among women who did not use FP and did not receive gynecologic surgery vs 17.6% among women who used FP and did not receive gynecologic surgery) (Table 4).

DISCUSSION

AYA women diagnosed with cancer in North Carolina who cryopreserved oocytes or embryos for FP experienced up to a 4.5-week delay in receipt of first gonadotoxic cancer treatment (independent of year of diagnosis and stage), the magnitude of which depended on cancer type and treatment. Additionally, our study provides suggestive evidence that FP may increase the likelihood of live birth after achieving pregnancy relative to women who initiated ART after cancer treatment, though further examination of how the use of gestational carriers may affect this association is warranted. With more detailed analysis of ART cycle-level factors in larger studies, such data can contribute to more personalized and informed decision-making around fertility after a cancer diagnosis.

Examination of delay to cancer treatment after FP in our study adds novel, statewide data to the existing evidence from prior studies conducted at single institutions. Most prior studies have been limited to women with breast cancer, finding up to an additional 13 days to chemotherapy.[14,15,18,19,21,22,24] All but two of these previous studies reported unadjusted analyses only,[22,24] whereas we were able to match exposure groups on cancer-related characteristics and further adjust certain analyses for race and ethnicity and SES.

The clinical introduction in 2010 of random-start ovarian stimulation that can be initiated independent of menstrual cycle phase theoretically shortens the time to cancer treatment by decreasing the ovarian stimulation process from 4 to 6 weeks to roughly 2 weeks.[39,40] Such shortening of the FP process could warrant the use of additional cycles of ovarian stimulation in certain patients to yield more oocytes or embryos for cryopreservation and potentially improve FP outcomes.[41–44] Unfortunately, we lacked data on specific ovarian stimulation protocol and had inadequate sample sizes to stratify analyses by calendar year of diagnosis as a proxy for the extent to which random-start protocols may contribute to an expedited time to cancer treatment.

Only two studies, to our knowledge, have assessed reproductive success by timing of ART initiation relative to cancer treatment. One study of Japanese women with breast cancer reported a higher pregnancy rate among two women who used FP (100%) compared

TABLE 2 Linear regression examining the association between fertility preservation use and time to cancer treatment among adolescent and young adult women with cancer in North Carolina, 2004-2015

			Fertility preservation		
Linear regression model	**No., FP**	**No., no FP (matched)[a]**	**β**	**95% CI**	**SE**
Breast (time to adjuvant chemotherapy)					
Outliers excluded[b]					
Unadjusted (exposure groups matched by clinical factors)	45	212	12.65	3.88-21.43	4.46
Adjusted for matching variables only	45	212	12.81	4.26-21.37	4.34
Adjusted for race/ethnicity and SES	45	212	15.48	5.88-25.09	4.87
Adjusted for matching variables, race/ethnicity, and SES	45	212	15.52	6.53-24.51	4.57
Natural log transformation of outcome					
Unadjusted (exposure groups matched by clinical factors)	45	220	0.164	−0.018 to 0.346	0.092
Adjusted for matching variables only	45	220	0.165	−0.013 to 0.342	0.090
Adjusted for race/ethnicity and SES	45	220	0.220	0.031-0.410	0.096
Adjusted for matching variables, race/ethnicity, and SES	45	220	0.225	0.039-0.410	0.094
Hematologic (time to chemotherapy or radiation)					
Outliers excluded[b]					
Unadjusted (exposure groups matched by clinical factors)	21	92	13.34	6.76-19.91	3.32
Adjusted for matching variables only	21	92	13.23	6.73-19.73	3.28
Adjusted for race/ethnicity and SES	21	92	14.00	7.36-20.65	3.35
Adjusted for matching variables, race/ethnicity and SES	21	92	13.76	7.13-20.39	3.34
Natural log transformation of outcome[c]					
Unadjusted (exposure groups matched by clinical factors)	21	94	0.490	0.151-0.828	0.171
Adjusted for matching variables only	21	94	0.480	0.146-0.813	0.168
Adjusted for race/ethnicity and SES	21	94	0.520	0.179-0.862	0.172
Adjusted for matching variables, race/ethnicity, and SES	21	94	0.512	0.172-0.851	0.171
Other invasive cancer[d] (time to adjuvant chemotherapy)					
Outliers excluded[b]					
Unadjusted (exposure groups matched by clinical factors)	13	58	28.29	10.72-45.85	8.80
Adjusted for matching variables only	13	58	26.53	9.92-43.15	8.31
Adjusted for race/ethnicity and SES	13	58	29.44	10.53-48.36	9.48
Adjusted for matching variables, race/ethnicity, and SES	13	58	27.53	9.54-45.52	9.00
Natural log transformation of outcome					
Unadjusted (exposure groups matched by clinical factors)	13	61	0.373	0.048-0.698	0.163
Adjusted for matching variables only	13	61	0.362	0.047-0.676	0.157
Adjusted for race/ethnicity and SES	13	61	0.438	0.097-0.778	0.171
Adjusted for matching variables, race/ethnicity, and SES	13	61	0.419	0.087, 0.751	0.166

Abbreviations: FP, fertility preservation; SES, socioeconomic status.

[a]Matching variables were year of cancer diagnosis, cancer type, summary stage, and first potentially gonadotoxic cancer treatment. Women with breast cancer and other invasive cancers were additionally matched on timing of chemotherapy (neoadjuvant or adjuvant).

[b]Outliers excluded among women with breast cancer who received adjuvant chemotherapy included eight women in the no FP group (time to cancer treatment ranged from 159 to 387 days). Outliers excluded among women with hematologic malignancies included four women in the no FP group (time to cancer treatment ranged from 97 to 158 days). Outliers excluded among women with other invasive cancers included three women in the no FP group (time to cancer treatment ranged from 148 to 244 days).

[c]In the log-transformed analysis among women with hematologic malignancies, two women in the no FP group with a time to treatment of 0 days were excluded.

[d]Other invasive cancers included gastrointestinal tract, osseous and chondromatous, soft-tissue sarcoma, other carcinomas of the head and neck, and other invasive cancers not otherwise specified.

with 19 women with breast cancer who did not use FP (no FP and chemotherapy-naïve: 45.5%; no FP and chemotherapy-exposed: 37.5%).[45] In a second study of Swedish women with breast cancer, a 12% lower live birth rate after ART was observed among 10 women who did not use FP compared with 48 women who did (30% vs 42%, respectively).[46]

These studies, including our own, are primarily limited in their relatively small sample sizes. These small samples yielded imprecise

TABLE 3 Cancer, sociodemographic, and ART use characteristics among adolescent and young adult women with cancer in North Carolina, 2004-2015, who used ART after cancer diagnosis

Cancer and sociodemographic characteristics		Fertility preservation but no transfer, *n* = 78 No. (%)	ART with fertility preservation, *n* = 18 No. (%)	ART without fertility preservation, *n* = 26 No. (%)
Median (IQR) age at diagnosis, y		29.0 (7.0)	32.0 (6.0)	31.5 (5.0)
Median (IQR) calendar year of diagnosis		2013 (3.0) [range, 2008-2015]	2011.5 (4.0) [range, 2006-2015]	2008.5 (5.0) [range, 2004-2014]
Breast cancer[a]		40 (51.3)	13 (72.2)	<11 (<42.3)
Gynecologic cancer[a]		<11 (<14.1)	0 (0)	13 (50.0)
Localized stage[a]		28 (35.9)	<11 (<61.1)	17 (65.4)
Chemotherapy		75 (96.2)	18 (100.0)	17 (65.4)
Radiation for gynecologic or hematologic cancers[a]		<11 (<14.1)	0 (0)	<11 (<42.3)
Gynecologic surgery[a]		<11 (<14.1)	0 (0)	13 (50.0)
Non-Hispanic White		60 (76.9)	15 (83.3)	20 (76.9)
Nulliparous at diagnosis		67 (85.9)	14 (77.8)	25 (96.2)
At least one spontaneous (non-ART) birth conceived after diagnosis between 2004 and 2016[a]		<11 (<14.1)	<11 (<61.1)	<11 (<42.3)
Median (IQR) follow-up time after diagnosis, years		5.4 (3.3) [range, 3.0 – 11.0]	7.2 (4.6) [range, 3.5 – 12.6]	10.0 (5.4) [range, 4.3 – 15.0]
ART use characteristics			**Median (IQR)**	**Median (IQR)**
Age at ART initiation, years	--		32.0 (6.0) [range, 22-39]	34.5 (7.0) [range, 28-40]
Calendar year of ART initiation	--		2011.5 (5.0) [range, 2006-2015]	2012.5 (7.0) [range, 2006-2017]
Follow-up after ART initiation, y	--		7.1 (4.8) [range, 3.4-12.5]	6.1 (7.4) [range, 1.8-12.8]
ART transfer cycle characteristics			**No. (%)**	**No. (%)**
Total thaw cycles with no transfer		1	0	1
Total transfer cycles		--	30	55
Mean (SD) transfer cycles per woman		--	1.7 (1.0) [range, 1-5]	2.1 (1.9) [range, 1-7]
Median (IQR) years from diagnosis to first transfer		--	2.9 (2.6) [range, 1.3-6.4]	3.6 (3.5) [range, 0.2-12.6]
Reason for ART[b]		--		
Male infertility		--	2 (6.7)	12 (21.8)
Endometriosis		--	0 (0)	2 (3.6)
Polycystic ovaries		--	0 (0)	4 (7.3)
Diminished ovarian reserve		--	0 (0)	16 (29.1)
Tubal factor, other than ligation or hydrosalpinx		--	0 (0)	8 (14.5)
Uterine		--	0 (0)	4 (7.3)
Unexplained		--	2 (6.7)	1 (1.8)
Other		--	28 (93.3)	13 (23.6)
Autologous transfers (woman's own oocytes or embryos)[c]		--	26 (86.7)	37 (67.3)

(Continues)

TABLE 3 (Continued)

ART transfer cycle characteristics		No. (%)	No. (%)
Fresh embryo transfers (oocytes or embryos that had never been cryopreserved)[d]	--	2 (6.7)	22 (40.0)
Transfer cycles using gestational carrier[c]	--	14 (46.7)	11 (20.0)

Abbreviations: ART, assisted reproductive technology; IQR, interquartile range.

[a]Exact number not reported because the North Carolina Central Cancer Registry requires cell sizes <11 to be suppressed.

[b]Categories are not mutually exclusive.

[c]Autologous transfers and transfer cycles using a gestational carrier are not mutually exclusive. All autologous transfers in the ART with fertility preservation group used previously cryopreserved oocytes or embryos (no fresh embryo transfers).

[d]Both of the fresh embryo transfer cycles in the ART with fertility preservation group used fresh donor oocytes. Five of the fresh embryo transfer cycles in the ART without fertility preservation group used fresh donor oocytes.

estimates for some analyses and precluded more detailed assessment of cycle-level factors and analysis by cancer type and treatments. Further study of how gestational carriers may affect the association between timing of ART initiation and reproductive success is particularly warranted given the more frequent use of gestational carriers among women who initiated ART before cancer treatment in our study.

Our study has several limitations. We did not capture women who used ART at non-SART member fertility clinics, women who were diagnosed with cancer in NC but used ART in a different state, women who used fertility preservation in NC but attempted pregnancy using ART outside of NC, or were diagnosed in more recent years and had not yet attempted pregnancy using ART. However, we did capture 96% to 100% of all ART cycles in North Carolina during the study years, and though the AYA population is mobile relative to other age groups, only 10.4% to 10.7% of AYAs moved out of state between 2005 and 2015,[47,48] meaning our study population was relatively stable over the study period (though we may slightly underestimate the number of women who used ART after cancer diagnosis). Though the North Carolina CCR has demonstrated moderate to high sensitivity in receipt of treatment and moderate agreement in dates of treatment,[30] there may still be some level of misclassification of gonadotoxic treatment receipt or time to cancer treatment. Although we are unable to quantify the specific impact of unknown misclassification on the analysis, the prior work comparing the North Carolina CCR to administrative claims provides additional confidence in our findings.

We lacked more detailed cancer-related characteristics and longer follow-up to assess whether the observed delays affected cancer outcomes, though a few weeks of delay is not expected to affect recurrence or survival for many women.[8,16,24] It is also unclear to what extent residual confounding by disease severity affected time to treatment: groups were matched on summary stage, though stage is just one indicator of prognosis that may span a clinically meaningful range of disease severity; women who used FP may have been a lower risk population at baseline who did not need to start treatment as urgently. Future studies should consider controlling for other prognostic factors as data allow, including histologic subtype and genomic profiling. Additionally, we were limited to broad treatment category from the North Carolina CCR, potentially leading to misclassification of certain cancer treatments as gonadotoxic, including types of gynecologic surgery and chemotherapeutic agents that are not expected to harm fertility. Relatedly, we could not assess how specific cancer treatments (e.g., type of gynecologic surgery, chemotherapy regimen, specific radiation field and dose) correlated with reproductive outcomes.

The strengths of our study include the use of a statewide sample of AYA women with cancer. Previous studies examining how FP may affect timing of cancer treatment initiation and reproductive outcomes have primarily been limited to single institutions and to women with breast cancer. The linkage between the population-based North Carolina CCR and SART CORS allowed for the comprehensive capture of cancer-related characteristics and use of ART across an entire state. Additionally, linkage with SART CORS enabled us to examine not only live birth, but also clinical pregnancy, which is not available in vital records and is more difficult to accurately assess.

CONCLUSIONS

Our study shows that FP may delay cancer treatment by up to 4.5 weeks—a delay that is acceptable without expected effect on prognosis for many women with cancer—and that more than 70% of women who used FP had a live birth with ART after cancer treatment. These data add to the relatively sparse evidence base for young women with cancer and clinicians regarding how FP may affect cancer care delivery and the likelihood of reproductive success after FP.

AUTHOR CONTRIBUTIONS

Clare Meernik: Conceptualization; methodology; formal analysis; visualization; writing—original draft; and writing—review and editing. **Stephanie M. Engel:** Writing—review and editing. **Christopher D. Baggett:** Resources; data curation; and writing—review and editing. **Ally Wardell:** Data curation and writing—review and editing. **Xi Zhou:** Data curation and writing—review and editing. **Kathryn J. Ruddy:** Writing—review and editing. **Ethan Wantman:** Writing—review and editing. **Valerie L. Baker:** Writing—review and editing. **Barbara Luke:** Writing—review and editing. **Jennifer E. Mersereau:** Writing—review and editing. **Jianwen Cai:** Writing—review and editing. **Andrew F. Olshan:** Writing—review and editing. **Andrew B. Smitherman**: Writing—review and editing. **Hazel B. Nichols**: Funding

TABLE 4 Clinical pregnancy, live birth, and pregnancy loss with the use of ART, based on timing of ART initiation relative to cancer treatment (with or without prior fertility preservation), among adolescent and young adult women with cancer in North Carolina, 2004-2015

	ART with FP, $n = 18$	ART without FP, $n = 26$ [Referent]	Unadjusted RR (95% CI)[a]	Age-adjusted RR (95% CI)[a,b]
Clinical pregnancy				
Per woman	77.8% (14/18)	84.6% (22/26)	0.92 (0.68-1.24)	0.92 (0.70-1.22)
After first transfer cycle	44.4% (8/18)	57.7% (15/26)	0.77 (0.42-1.42)	0.70 (0.38-1.29)
Per transfer cycle[c]	56.7% (17/30)	50.9% (28/55)	1.10 (0.73-1.65)	0.96 (0.66-1.41)
Per transfer cycle: autologous transfers[c,d]	50.0% (13/26)	48.7% (18/37)	1.03 (0.60-1.77)	Not estimable
Per transfer cycle: no gestational carrier[c]	56.3% (9/16)	45.5% (20/44)	1.14 (0.63-2.06)	0.99 (0.54-1.81)
Per transfer: gynecologic surgery received	0 women	55.6% (15/27)	NA	NA
Per transfer: no gynecologic surgery[c]	56.7% (17/30)	46.4% (13/28)	1.21 (0.68-2.13)	1.07 (0.64-1.80)
Live birth				
Per woman	72.2% (13/18)	61.5% (16/26)	1.17 (0.77-1.78)	1.31 (0.88-1.95)
After first transfer cycle	38.9% (7/18)	34.6% (9/26)	1.12 (0.51-2.46)	1.19 (0.52-2.71)
Per transfer cycle[c]	46.7% (14/30)	30.9% (17/55)	1.56 (0.88-2.75)	1.51 (0.79-2.86)
Per transfer cycle: autologous transfers[c,d]	46.2% (12/26)	27.0% (10/37)	1.68 (0.82-3.46)	1.64 (0.76-3.58)
Per transfer cycle: no gestational carrier[c]	50.0% (8/16)	27.3% (12/44)	Not estimable	Not estimable
Per transfer: gynecologic surgery received	0 women	29.6% (8/27)	NA	NA
Per transfer: no gynecologic surgery	46.7% (14/30)	32.1% (9/28)	1.53 (0.76-3.08)	1.47 (0.68-3.21)
Given pregnancy[c]	82.4% (14/17)	60.7% (17/28)	1.38 (0.95-2.01)	1.47 (0.98-2.23)
Pregnancy loss				
Per clinical pregnancy[c]	17.6% (3/17)	39.3% (11/28)	0.46 (0.16-1.31)	0.37 (0.12-1.17)
Per clinical pregnancy: gynecologic surgery received	0 women	46.7% (7/15)	NA	NA
Per clinical pregnancy: no gynecologic surgery	17.6% (3/17)	30.8% (4/13)	0.60 (0.19-1.89)	0.40 (0.08-2.05)
Per woman (given clinical pregnancy)	21.4% (3/14)	45.5% (10/22)	0.47 (0.16-1.42)	0.41 (0.14-1.15)

Abbreviations: ART, assisted reproductive technology; FP, fertility preservation; NA, not available; RR, risk ratio.

[a]Referent group is women who initiated ART after cancer treatment without fertility preservation.

[b]Adjusted for age at ART initiation (linear).

[c]Estimate from Poisson regression model using generalized estimating equations and a Kauermann-Carroll small-sample correction to account for clustering at the woman level. Women who initiated ART for FP before cancer treatment had a mean of 1.7 transfer cycles. Women who initiated ART after cancer treatment without FP had a mean of 2.1 transfer cycles (see Table 3).

[d]All autologous transfers in the ART with fertility preservation group used previously cryopreserved oocytes or embryos (no fresh embryo transfers).

acquisition; conceptualization; methodology; writing—review and editing; and supervision.

ACKNOWLEDGMENT

This research was supported in part by R01 CA204258, R01 CA211093, St. Baldrick's Foundation Scholar Award 523803, and P30 ES010126. Clare Meernik was supported by the University of North Carolina Lineberger Cancer Control Education Program (T32 CA057726) and the National Cancer Institute (F31 CA260787). The other authors made no disclosures.

CONFLICTS OF INTEREST

Ethan Wantman: Redshift is the data vendor for SART.

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How to cite this article: Meernik C, Engel SM, Baggett CD, et al. Time to cancer treatment and reproductive outcomes after fertility preservation among adolescent and young adult women with cancer. *Cancer*. 2023;129(2):307-319. doi:10.1002/cncr.34520