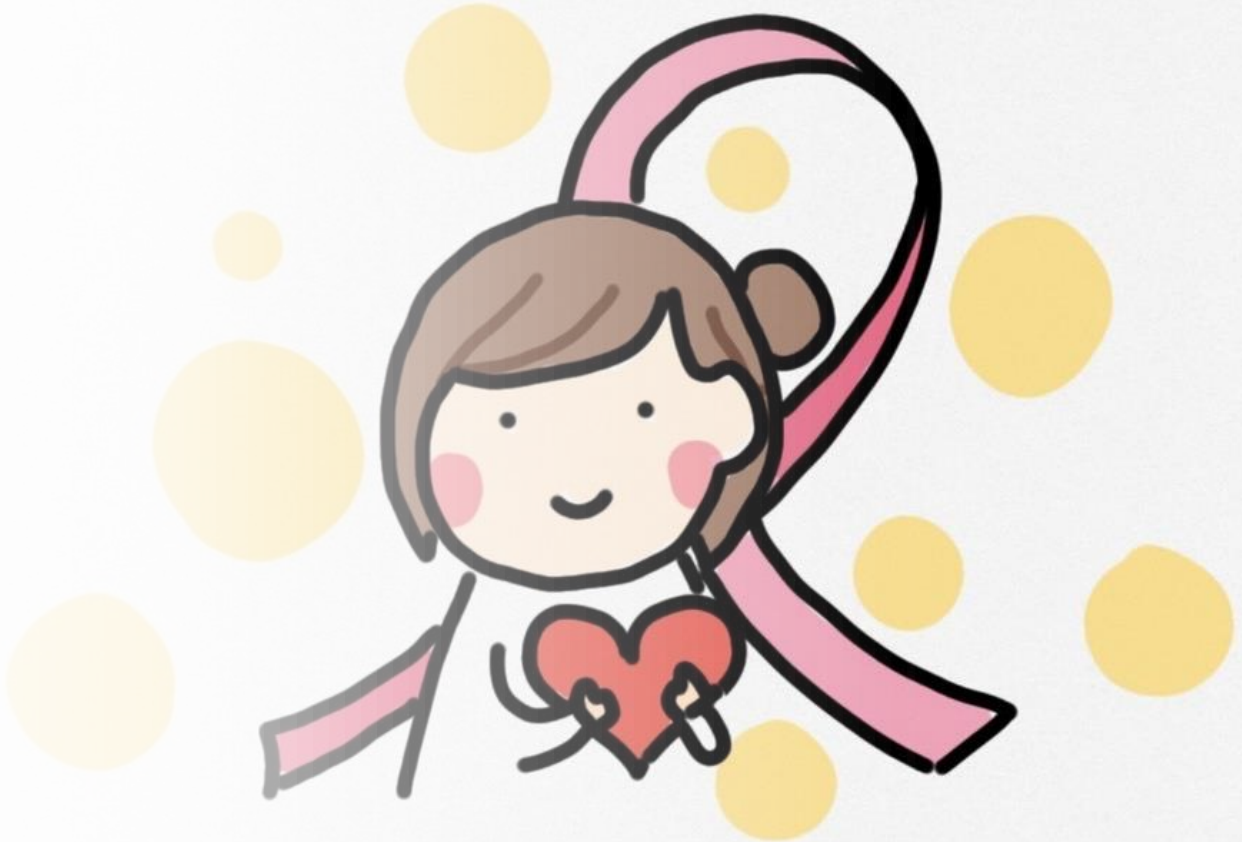
The era of increasing cancer survivorship: Trends in fertility preservation and challenges



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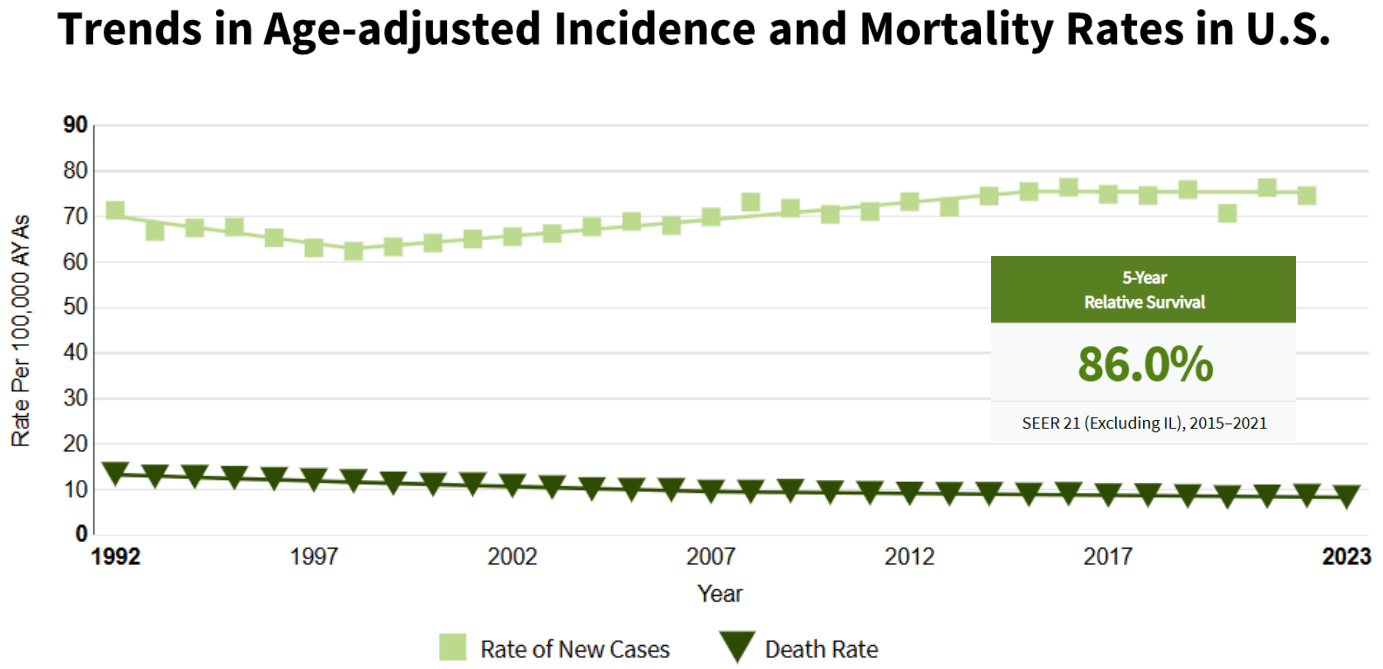
2025.05.07

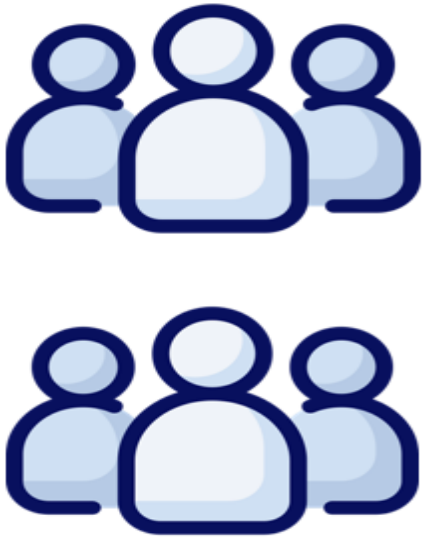
The fertility challenges faced by adolescent and young adult(AYA)

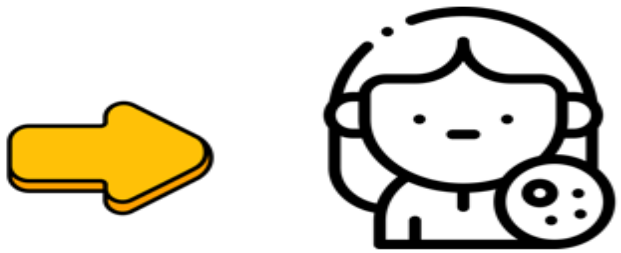
- Cancer remains a public health problem worldwide that also includes young adults. Cancer in adolescents and young adults is defined by the National Cancer Institute as diagnoses occurring among those aged 15 to 39 years(hereafter, “AYA ”).



1.https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21637.2.https://seer.cancer.gov/statfacts/html/aya.html

- According to the 2022 Cancer Registry Report from the Ministry of Health and Welfare, approximately 120,000 new cancer cases were reported, with about 16% of patients between the ages of 15 and 49.
- For female AYA cancer survivors, chronic diseases, including cancer, increase the risk of pregnancy and childbirth complications. Radiotherapy and chemotherapy can also harm cardiovascular, endocrine, liver, kidney, and reproductive functions.





One in every six newly diagnosed cancer patients being of reproductive age

Key Considerations for Fertility Preservation in Cancer Patients

1. Informed consent and autonomy
2. Availability and accessibility of fertility preservation techniques
3. Timing of Fertility Preservation Treatments and Balancing Risks and Benefits

De Paola, L., Napoletano, G., Gullo, G., Circosta, F., Montanari Vergallo, G. & Marinelli, S. (2025). The era of increasing cancer survivorship: Trends in fertility preservation, medico-legal implications, and ethical challenges. Open Medicine, 20(1), 20251144. https://doi.org/10.1515/med-2025-1144

Paper 1

Reproductive Outcomes After Breast Cancer in Women With vs Without Fertility Preservation

Anna Marklund, MD; Frida E. Lundberg, PhD; Sandra Eloranta, PhD; Elham Hedayati, MD, PhD; Karin Pettersson, MD, PhD; Kenny A. Rodriguez-Wallberg, MD, PhD

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CATEGORY
ONCOLOGY

12/322

JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
2023	12/322	Q1	96.4

Anna Marklund, PhD

She is a postdoctoral researcher at Karolinska Institutet, focusing on fertility preservation in cancer patients, especially those with breast and cervical cancer.

- **Knowledge gap**

Most studies on breast cancer(BC) survivors focus on short-term outcomes, with limited data on long-term reproductive results, especially among women with fertility preservation (FP). Large-scale comparisons of live birth and Assisted Reproductive Technology(ART) rates between women with and without FP are lacking.

- **Aim**：

1. To evaluate the likelihood of post-BC live births and ART treatments in women with vs without a history of fertility preservation (FP).
2. To assess whether fertility preservation impacts overall survival after BC.

- **Hypothesis**：FP in women with BC is associated with increased rates of live births and ART use post-diagnosis, without compromising overall survival.

Study Design

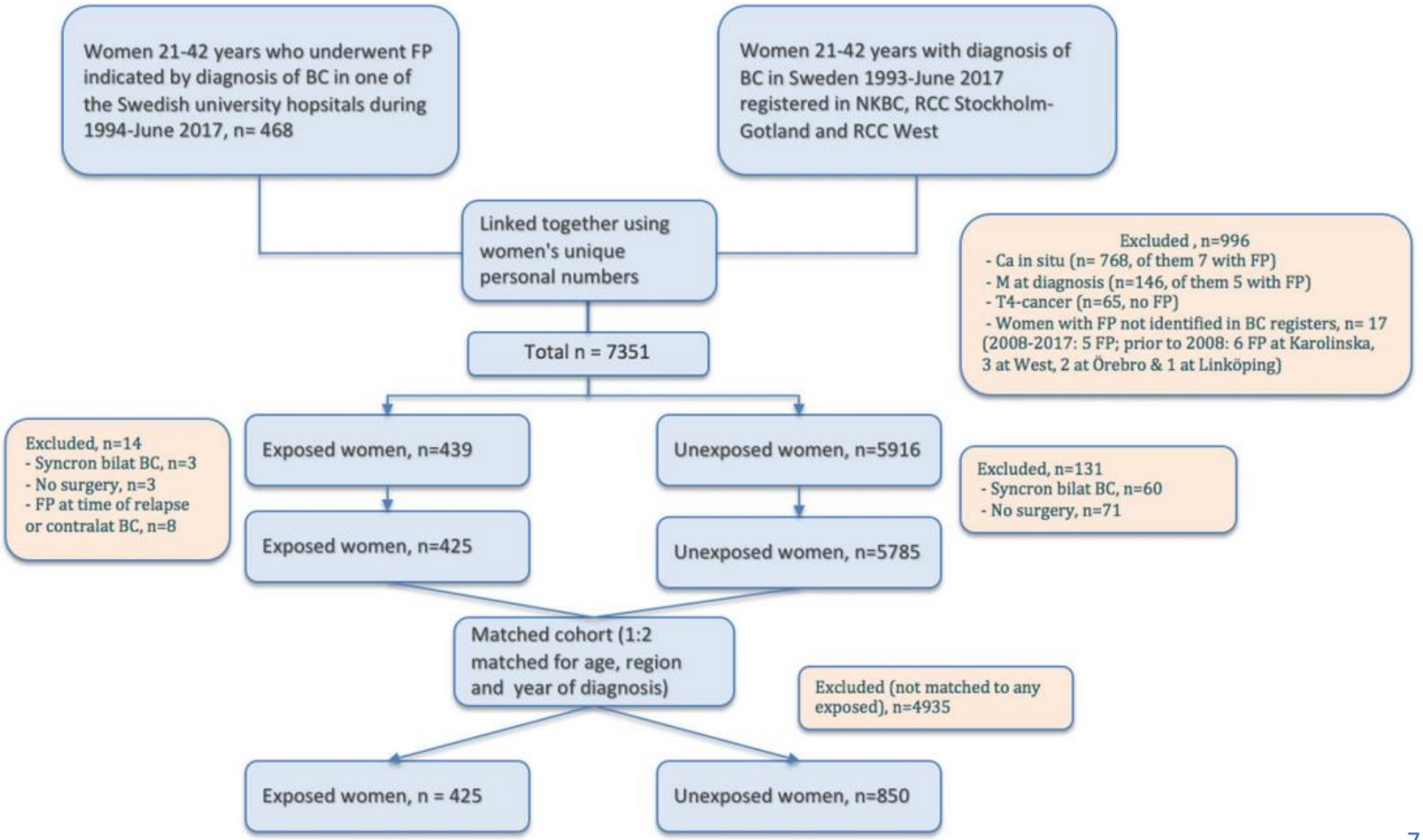
- Retrospective cohort study: Data were collected by linking Swedish quality registers for breast cancer with national population-based registers (1994–2017).
- Inclusion:

1. Women with BC who underwent FP at 1 of 7 Swedish university hospitals between January 1, 1994, and June 30, 2017.

- Exclusion：

1. Women with cancer in situ, distant metastasis at diagnosis, T4 tumors, synchronic bilateral BC, and without surgery for their BC, and those who could not be identified in any BC register.

Figure 1. Study Diagram.



- Covariates of interest：

1. Age at diagnosis
2. Calendar period of diagnosis
3. Country of birth
4. Education level
5. Parity at diagnosis
6. Tumor size
7. Lymph node metastases
8. Estrogen receptor status
9. Chemotherapy status

Statistical analysis

- Matching :Patients with breast cancer who underwent fertility preservation (FP) were matched in a 1:2 ratio with those without FP, according to age, diagnosis period, and region.
- Left-Truncated Cox Proportional Hazards Model ：Time scale set as 10 months after diagnosis (for live birth analysis) or 5 months after diagnosis (for ART use analysis).Estimated hazard ratios for Post-cancer live births, Post-cancer ART treatments and All-cause mortality.
- Cumulative Incidence Function with Competing Risk was estimated nonparametrically, treating death as a competing event, to assess the probabilities of live births and ART use.
- Proportional Hazards Assumption was evaluated using the Schoenfeld residuals from the models

eTable 2. Characteristics of women with breast cancer (BC) in the matched coh

Characteristic	Exposed to FP (n=425)	Unexposed to FP (n=850)	P
Educational level			
Compulsory school	27 (6.4%)	84 (9.9%)	
Secondary school	151 (35.5%)	290 (34.1%)	0.217
Higher education	244 (57.4%)	470 (55.3%)	
Missing	3 (0.7%)	6 (0.7%)	
Country of birth			
Nordic	345 (81.2%)	628 (73.9%)	0.004
Non-Nordic	80 (18.8)	222 (26.1%)	
Age at diagnosis, years			
21-29	115 (27.1%)	128 (15.1%)	<0.001
30-34	179 (42.1%)	379 (44.6%)	
35-42	131 (30.8%)	343 (40.3%)	
Geographical region			
Stockholm Gotland	226 (53.2%)	452 (53.2%)	
West region	64 (15.1%)	128 (15.1%)	1.0
Other	135 (31.7%)	270 (31.7%)	
Parity at BC diagnosis			<0.001
0	302 (71.1%)	171 (20.1%)	
1	102 (24%)	183 (21.5%)	
>=2	21 (4.9%)	496 (58.5%)	
Year of diagnosis			0.100
1994-2007	72 (16.9%)	144 (16.9%)	
2008-2017	352 (83.1%)	706 (83.1%)	
Tumor size			0.036
T0	15 (3.5%)	27 (3.2%)	
T1	184 (43.3%)	352 (41.4%)	
T2	190 (44.7%)	341 (40.1%)	
T3	34 (8.0%)	119 (14.0%)	
TX (size cannot be assessed)	2 (0.5%)	11 (1.3%)	
Lymph nodes with metastasis			0.035
0	271(63.8%)	478 (56.2%)	
1-3	120 (28.2%)	271 (31.9%)	
>3	34 (8.0%)	99 (11.7%)	
Missing	0 (0%)	2 (0.2%)	
Tumor Grade			0.178
1	26 (6.1%)	51(6.0%)	
2	108 (25.4%)	177 (20.8%)	
3	180 (42.4%)	359 (42.2%)	
Missing	111 (26.1%)	263 (30.9%)	
ER-status			0.034
Positive	289 (68.0%)	515 (60.6%)	
Negative	128 (30.1%)	313 (36.8%)	
Missing	8 (1.9%)	22 (2.6%)	
PR-status			0.029
Positive	249 (58.6%)	431 (50.7%)	
Negative	167 (39.3%)	397 (46.7%)	
Missing	9 (2.1%)	22 (2.6%)	
HER-2			
Amplified	108 (25.4%)	176 (20.7%)	
Non-amplified	199 (46.8%)	429 (50.5%)	0.158
Unknown	118 (27.8%)	245 (28.8%)	

Characteristic	Exposed to FP (n=425)	Unexposed to FP (n=850)	P
Therapy			
Neoadjuvant	105 (24.7%)	249 (29.3)	0.100
Adjuvant	419 (98.6%)	823 (96.8%)	0.161
Chemotherapy			0.002
Yes	399 (93.9%)	745 (87.7%)	
No	25 (5.9%)	98 (11.5%)	
Missing	1 (0.2%)	7 (0.8%)	
Radiotherapy			
Yes	317 (74.6%)	650 (76.5%)	
No	94 (22.1%)	141 (16.6%)	0.003
Missing	14 (3.3%)	59 (6.9%)	
Endocrine therapy			0.011
Yes	281 (66.1%)	498 (58.6%)	
No	121 (28.5%)	314 (36.9%)	
Missing	23 (5.4%)	38 (4.5%)	
Her2- therapy			0.040
Yes	111 (26.1%)	169 (19.9%)	
No	253 (59.5%)	549 (64.6%)	
Missing	61 (14.4%)	132 (15.5%)	

NOTE: Data are presented as No (%) unless noted otherwise.
Abbreviations: ER, estrogen receptor; FP, fertility preservation; PR, progesterone receptor.

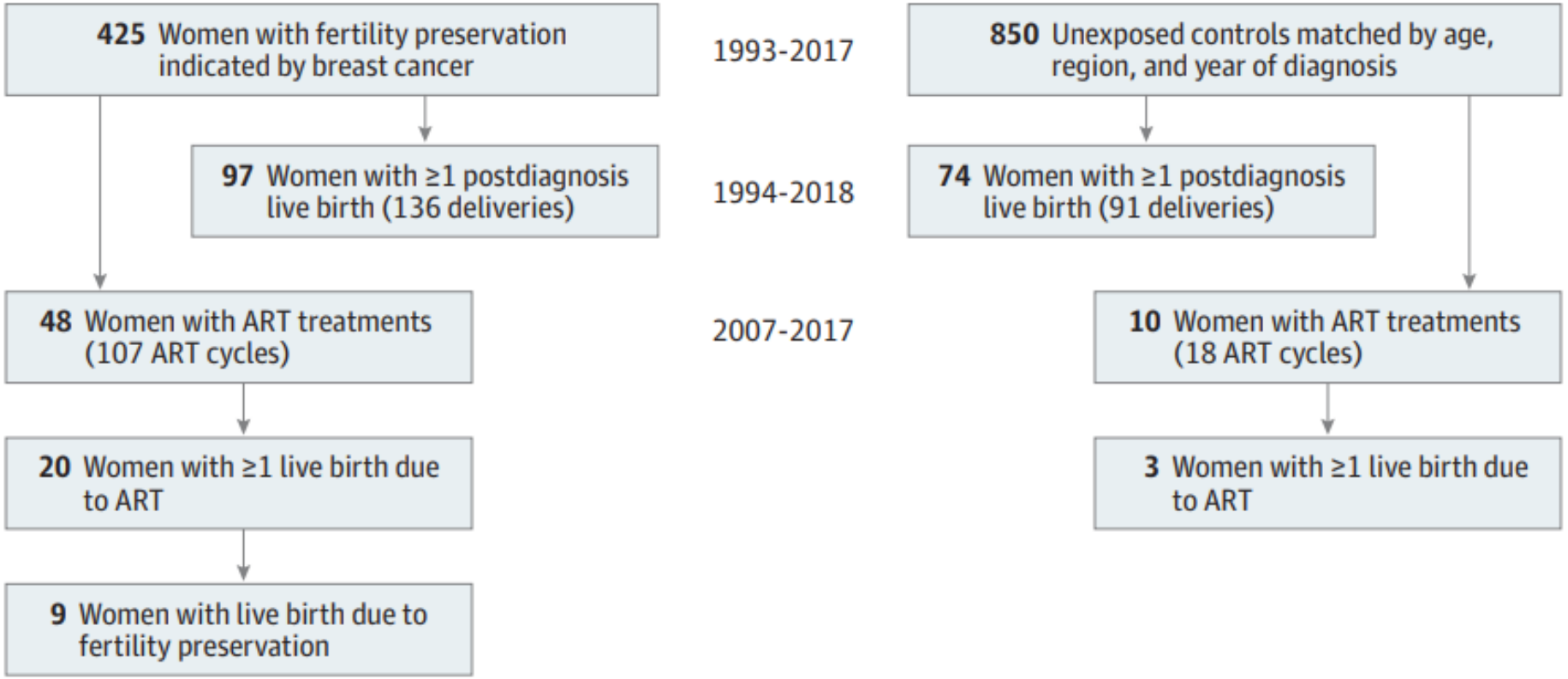
Mean age: 32.1 years (exposed) vs 33.3 years (unexposed)

Nulliparous: 71.1% (exposed) vs 20.1% (unexposed)

ER-positive tumors: 68.0% (exposed) vs 60.6% (unexposed)

Chemotherapy: 93.9% (exposed) vs 87.7% (unexposed)

Figure 1. Study Diagram



ART indicates assisted reproductive technologies.

Table. Long-term Reproductive Outcomes and All-Cause Mortality

Outcome	No. of events	Person-years	HR (95% CI) Model 1[a]	HR (95% CI) Model 2[b]
Post-BC live birth[c]				
Unexposed to FP	74	3753	1 [Reference]	1 [Reference]
Exposed to FP	97	1865	2.6 (1.9-3.5)	2.3 (1.6-3.3)
Post-BC ART treatment[d]				
Unexposed to FP	10	4028	1 [Reference]	1 [Reference]
Exposed to FP	48	2096	9.5 (4.8-18.7)	4.8 (2.2-10.7)
All-cause mortality[c]				
Unexposed to FP	110	4437	1 [Reference]	1 [Reference]
Exposed to FP	27	2477	0.4 (0.3-0.7)	0.4 (0.3-0.7)

Abbreviations: ART, assisted reproductive technology; BC, breast cancer; FP, fertility preservation; HR, hazard ratio.

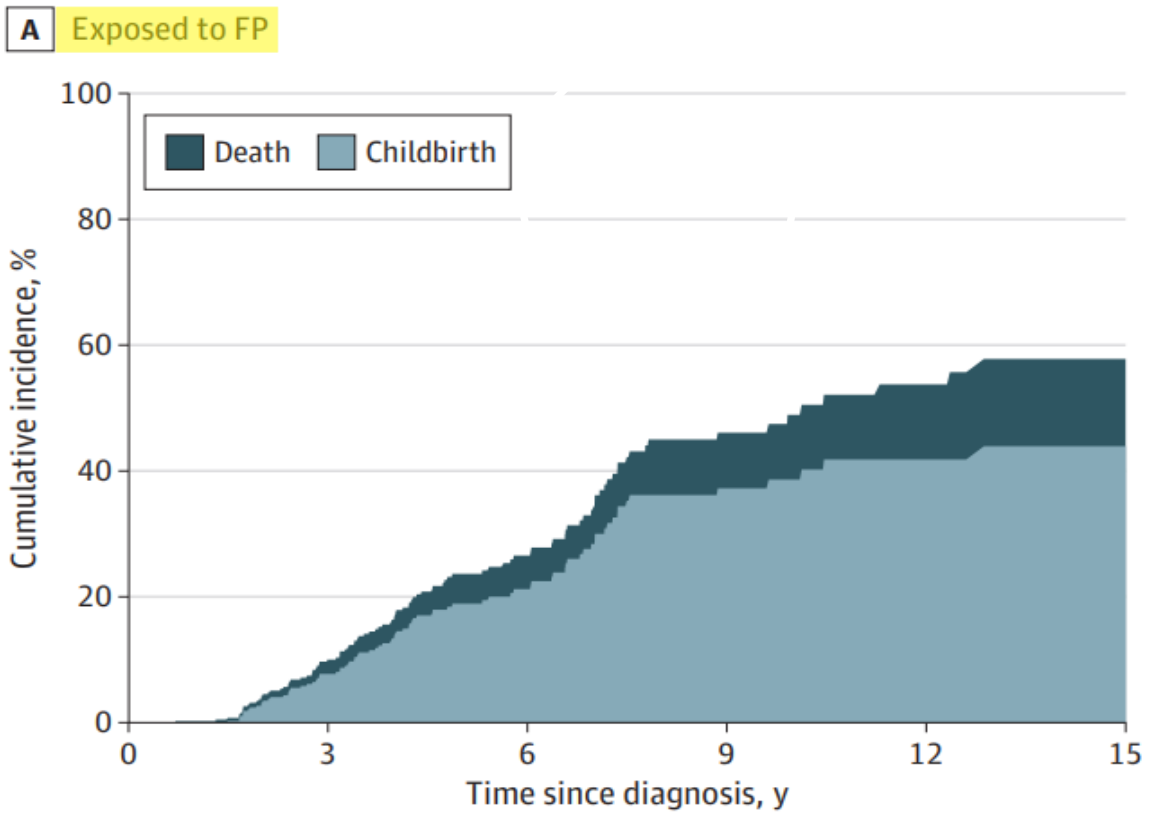
[a] Adjusted for time since diagnosis.

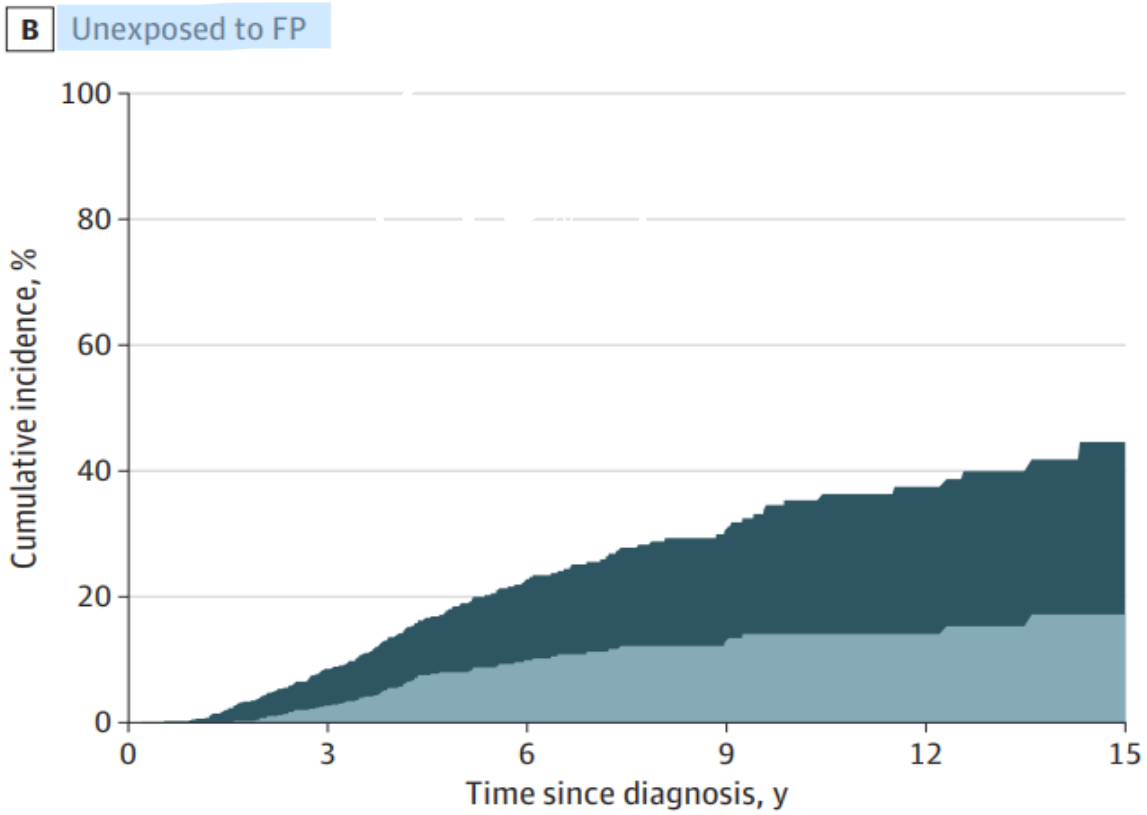
[b] Adjusted for time since diagnosis, age, country of birth, education, parity at diagnosis, calendar period, tumor size, lymph node metastases, estrogen receptor status, and chemotherapy.

[c] Until December 31, 2018.

[d] From 2007 to 2017.

Figure 2. Cumulative Incidence of Childbirth After Breast Cancer by Years Since Diagnosis, With Death as a Competing Risk





Exposed to FP

	5-y CIF (95% CI)	10-y CIF (95% CI)
Death	5.3 (3.1-9.0)	13.8 (8.0-23.4)
Childbirth	19.4 (15.2-24.6)	40.7 (33.0-49.5)

Unexposed to FP

	5-y CIF (95% CI)	10-y CIF (95% CI)
Death	11.1 (8.7-14.1)	23.2 (18.3-29.2)
Childbirth	8.6 (6.4-11.4)	15.8 (12.0-20.7)

CIF indicates cumulative incidence function; FP, fertility preservation.

eTable 4. Characteristics and reproductive outcome of women with ART-treatments after diagnosis of BC (data for treatments available for years 2007-2017).

Characteristic or outcome	Women with FP (n= 48, ART-treatments, n= 107)	Women without FP (n= 10, ART-treatments, n= 18)	*P*
Time between cancer diagnosis and first post-diagnosis ART-treatment			
<2 years	10 (20.8%)	2 (20%)	
2-5 years	23 (47.9%)	4 (40%)	0.857
>5 years	15 (31.3%)	4 (40%)	
Type of ART-treatment			
IVF (for fresh cycles)	10	3	0.347
ICSI (for fresh cycles)	30	8	0.161
Interrupted	17	5	0.220
FET	62	4	0.005
Use of frozen eggs	20 cycles/15 women	1 cycle	0.080
Donated oocytes	1	0	0.680
Number of ART-treatments/cycles per woman			
1	21 (43.7%)	6 (60%)	
2	10 (20.8%)	2 (20%)	0.36
≥3	17 (35.5%)	2 (20%)	
Outcome per cycle			
ET	90	13	0.220
Biochemical pregnancies	4 (2 women, 4 cycles)	0	0.404
Miscarriage	3 (2 women)	0	0.472
Livebirths	21 (20 women) 42%	3 (3 women) 30%	0.768

NOTE: Data are presented as No (%) unless noted otherwise.
Abbreviations: ART, assisted reproductive technologies; ET, embryo transfer; FET, frozen embryo transfer; FP, fertility preservation; IVF, in vitro fertilization; ICSI intraplasmatic sperm injection.

Main Findings

- Fertility preservation was associated with significantly higher rates of post-BC live births and ART use. FP was not associated with higher all-cause mortality.
- Results emphasize the importance of early FP counseling at BC diagnosis.

Limitation

- The study could not adjust for patients' initial desire for future childbearing, leading to potential confounding by indication.
- Data were only available for live births and ART treatments; miscarriages and early pregnancy losses were not systematically recorded.
- Despite adjustment for disease-related variables, other unmeasured factors influencing survival and fertility outcomes might still exist.

Paper 2

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

Journal of Cancer
Published: 15 January 2023
Volume 129, pages 307–319

Clare Meernik, PhD

CATEGORY
ONCOLOGY

49/322

JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
2023	49/322	Q1	84.9

She is an Assistant Investigator at The Cooper Institute and an adjunct Assistant Professor at Duke University School of Medicine.Her research focuses on tobacco control, cancer epidemiology, and cancer survivorship.

Knowledge gap

Most prior studies on fertility preservation (FP) among adolescent and young adult (AYA) women with cancer were limited to single institutions, focused mainly on breast cancer, and lacked adjustment for key confounders. Large, population-based evidence on FP-related treatment delays and post-treatment reproductive outcomes across different cancer types remains scarce. Additionally, the impact of gestational carrier use on reproductive success in this population is poorly understood.

- **Aim**：To evaluate whether FP delays cancer treatment among adolescent and young adult (AYA) women, and to compare reproductive outcomes based on the timing of ART initiation.

- **Hypothesis**：FP may cause a small delay in cancer treatment but does not significantly impact prognosis, and FP users may have higher live birth rates after ART compared to non-FP users.

Study Design

- Retrospective cohort study: Data from the North Carolina Central Cancer Registry (CCR) and the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS. to obtain fertility service data from 2004 to 2018.
- Inclusion:

1. Adolescent and young adult (AYA) women aged 15 to 39 years diagnosed with a first primary invasive cancer between 2004 and 2015.

- Exclusion：

1. Diagnosed with cancer during pregnancy
2. Did not receive gonadotoxic treatment
3. Used ART before cancer diagnosis

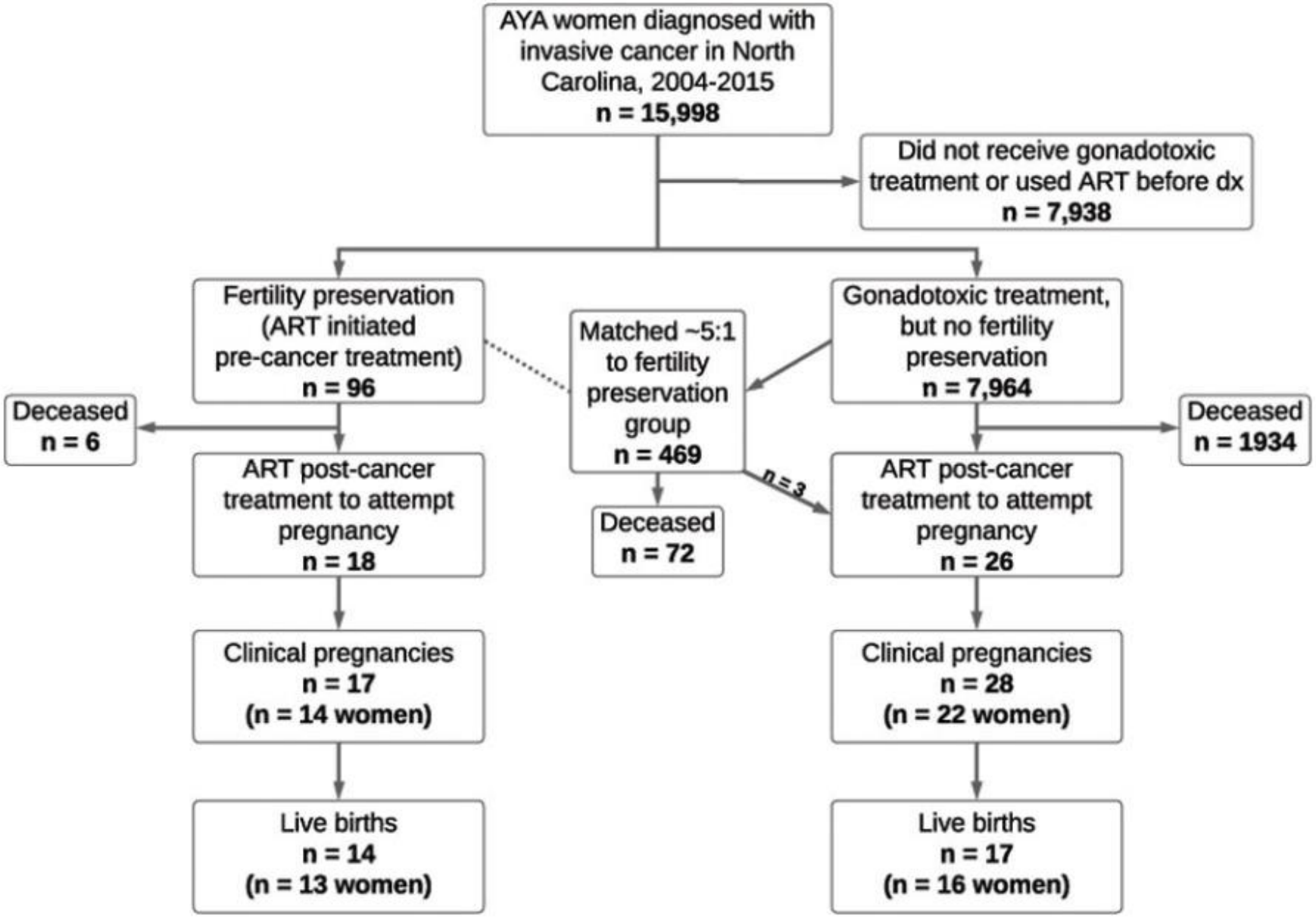


Figure 1.

Study sample flow diagram, One woman who used FP was excluded in time to cancer treatment analysis because she was diagnosed with cancer during pregnancy.

- Covariates of interest：

1. Cancer-related factors：Age at diagnosis, year of diagnosis, cancer type, cancer stage (summary stage), type of first gonadotoxic treatment.
2. Demographic and socioeconomic factors：race/ethnicity, marital status, insurance, urban/rural residence, socioeconomic status.
3. Reproductive treatment factors：timing of ART initiation, use of autologous vs. donor oocytes, gestational carrier use.

Statistical analysis

- Matching ： Patients who used FP were matched 1:5 with those who did not, based on year of diagnosis, cancer type, stage, and first gonadotoxic treatment. For breast and other non-gynecologic cancers, chemotherapy timing (neoadjuvant vs. adjuvant) was also matched.
- Linear regression models were used to compare the time from cancer diagnosis to first gonadotoxic treatment between women who underwent FP and matched controls without FP.
- Modified Poisson regression estimated RRs and 95% CIs for clinical pregnancy and live birth, comparing ART before vs. after cancer treatment.

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, years	3.9	(3.6)	4.7	(4.1)
Median (IQR) age at diagnosis, years	30.0	(7.0)	34.0	(8.0)
Age at diagnosis, years				
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

Age at diagnosis

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]
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

Race and ethnicity

Marital status at diagnosis

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]
Parity at diagnosis				
Nulliparous[e]	80	84.2	232	49.5
Parous	15	15.8	237	50.5
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

Parity at diagnosis

Insurance status at diagnosis

Rurality at diagnosis

Yost SES index at diagnosis

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, 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 2–4 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. All sample sizes are not reported because the North Carolina Central Cancer Registry requires cell sizes <11 to be suppressed.

FP users had a longer median time to cancer treatment across all cancer types.

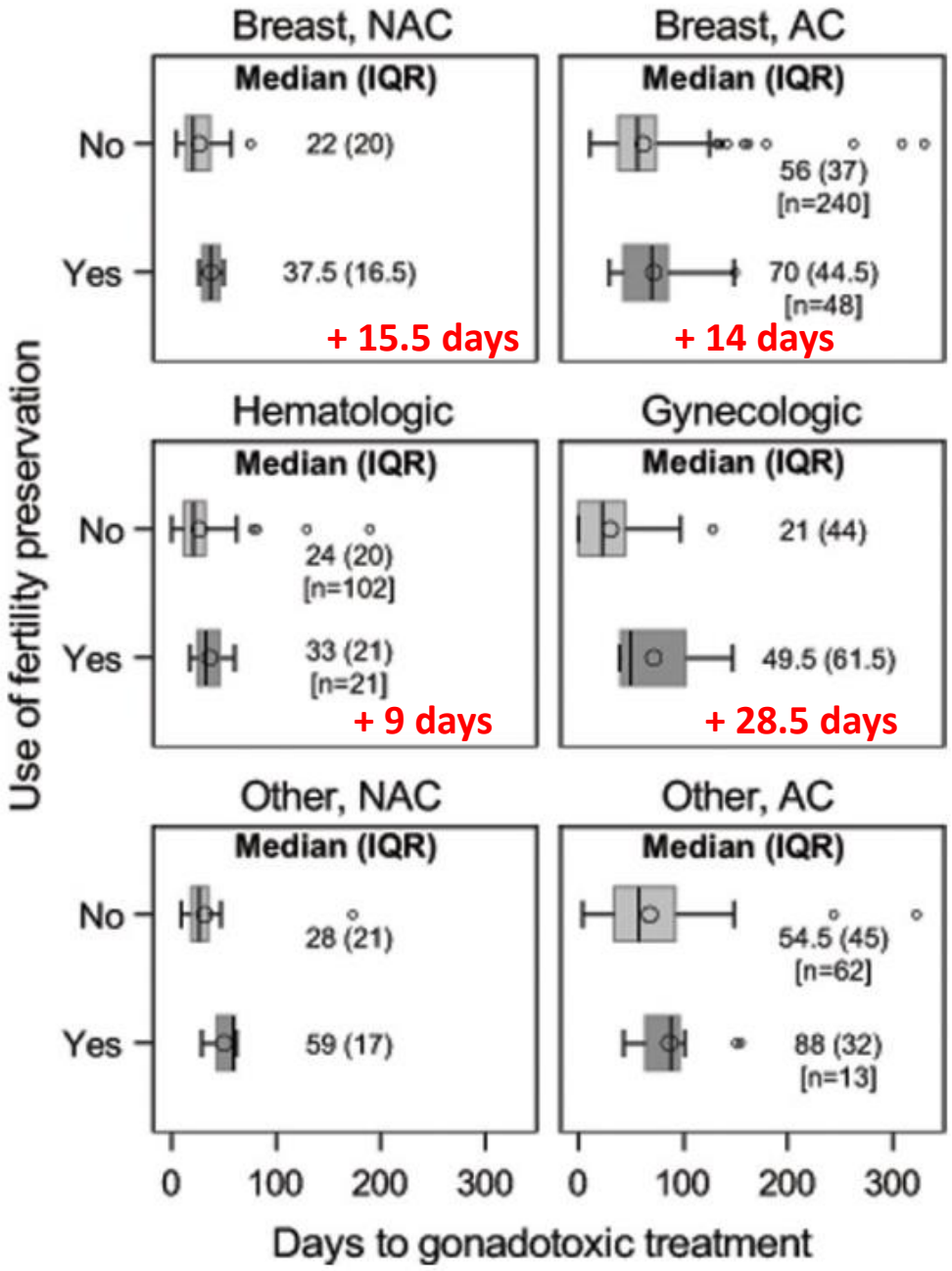


Table 2.

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

Linear regression model	n, FP	n, no FP (matched)[a]	Fertility preservation		
			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, 0.346	0.092
Adjusted for matching variables only	45	220	0.165	-0.013, 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

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

Linear regression model	n, FP	n, no FP (matched)[a]	Fertility preservation β	95% CI	SE
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

Table 3.

Cancer, sociodemographic, and assisted reproductive technology (ART) use characteristics among adolescent and young adult women with cancer in North Carolina, 2004–2015, who used ART after cancer diagnosis

	Fertility preservation but no transfer, n=78	ART with fertility preservation, n=18	ART without fertility preservation, n=26
Cancer & sociodemographic characteristics	**No. (%)**	**No. (%)**	**No. (%)**
Median (IQR) age at diagnosis, years	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 in 2004–2016[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, years	--	7.1 (4.8) [range: 3.4 – 12.5]	6.1 (7.4) [range: 1.8 – 12.8]
ART transfer cycle characteristics		**n (%)**	**n (%)**
Total thaw cycles with no transfer	1	0	1
Total transfer cycles	--	30	55

Table 3.

Cancer, sociodemographic, and assisted reproductive technology (ART) use characteristics among adolescent and young adult women with cancer in North Carolina, 2004–2015, who used ART after cancer diagnosis

Cancer & sociodemographic characteristics	Fertility preservation but no transfer, n=78 No. (%)	ART with fertility preservation, n=18 No. (%)	ART without fertility preservation, n=26 No. (%)
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 1st 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)
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)

Table 4.

Clinical pregnancy, live birth, and pregnancy loss with the use of assisted reproductive technology (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 1st 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)	n/a	n/a
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 1st 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)	n/a	n/a
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)

47%

Table 4.

Clinical pregnancy, live birth, and pregnancy loss with the use of assisted reproductive technology (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]
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)	n/a	n/a
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)

59%

Main Finding

- Fertility preservation was associated with a delay in the initiation of cancer treatment by up to 4.5 weeks, with the adjusted delay reaching 15.5 days (95% CI: 6.5–24.5) among breast cancer patients receiving adjuvant chemotherapy.
- Among women who achieved pregnancy, those who underwent fertility preservation prior to treatment had a potentially higher likelihood of live birth, with an age-adjusted risk ratio of 1.47 (95% CI: 0.98–2.23), compared to those who initiated ART after treatment.
- The use of gestational carriers was substantially more common in the fertility preservation group (47% vs. 20% of transfer cycles), which may have contributed to differences in reproductive outcomes and warrants further investigation.

Limitation

- Only 18 women with FP and 26 without underwent embryo transfer, limiting statistical power and generalizability.
- The study lacked detailed clinical data such as tumor subtype, treatment regimen, and radiation dose, which may have led to residual confounding.
- ART cycles outside North Carolina or at non-SART clinics were not included, possibly underestimating ART use and outcomes.
- Cancer outcomes were only followed through mid-2017, and shorter follow-up in the FP group made it difficult to assess the impact of treatment delay.
- Data on ART protocols, including stimulation method and oocyte source, were unavailable, limiting evaluation of factors affecting reproductive outcomes.

Comparison of the two papers

	Paper 1	Paper 2
Study question	How does fertility preservation affect long-term reproductive outcomes after breast cancer?	Does FP delay cancer treatment in AYA women? Does ART timing affect pregnancy and live birth outcomes?
Study design	Retrospective cohort study	
Study setting	Sweden's nationwide population-based health and cancer registers(2004-2017)	NC CCR and SART CORS(2004-2018)
Participants	Women aged 21 to 42 with invasive breast cancer	AYA women aged 15–39 diagnosed with a first primary invasive cancer
Sample size	A total of **1,275 women with invasive breast cancer** were included. 425 had fertility preservation (FP) 850 were matched controls without FP	A total of **564 AYA women with invasive cancer** were included. 95 had fertility preservation (FP) 469 were matched controls without FP
Outcomes measure	1.Post-treatment live births 2.ART use rate 3.All-cause mortality	1.Time to first gonadotoxic cancer treatment 2.ART outcomes: clinical pregnancy and live birth, by timing of ART initiation

Comparison of the two papers

	Paper 1	Paper 2
Statistical analyses	Left-truncated Cox proportional hazards model was used to estimate hazard ratios for post-cancer live births, ART treatments, and all-cause mortality.	Modified Poisson regression with robust error variance was used to estimate risk ratios for pregnancy and live birth after ART, comparing ART initiation before vs. after cancer treatment.
Selection bias	**Low**, the study used nationwide Swedish population and health registers, with minimal loss to follow-up unless individuals emigrated.	**Low**, Captured 96–100% of ART cycles in North Carolina during the study period; only 10.4–10.7% of AYAs moved out, indicating a stable population.
Information bias	**Likely,** Lack of data on miscarriages or abortions may underestimate the pregnancy rate.	**Likely,** Time to treatment was defined using NC CCR data, which has a sensitivity of **74–86%** and date agreement of **63–93%.**
confounding	**Fertility intention** may be a key confounding variable, as women who want children are more likely to choose FP and to try for pregnancy in the future.	**Gestational carrier** use may be a key confounder, as it is more common among FP users and associated with higher live birth rates.

Comparison of the two papers

	Paper 1	Paper 2
advantages	1. Large nationwide sample with extended follow-up. 2. The left-truncated Cox model helped define a realistic risk period based on actual treatment timelines.	1. Included **multiple cancer types**, extending beyond breast cancer and single-institution studies. 2. Included both **clinical pregnancy and live birth**, offering a more comprehensive view of reproductive outcomes.
disadvantages	The study lacked data **on fertility intentions** and **natural pregnancies** that didn't result in live birth, used only **all-cause mortality**, and may still be affected by a **healthy FP effect** even after adjusting for disease factors.	**1. Small sample size**, especially in the ART group, limited the ability to adjust for confounders and analyze subgroups. **2. Only summary stage** was matched; tumor details were not included, which may have affected treatment timing and FP decisions. 3. Treatment categories were too broad and **lacked** details like **chemo type** and **radiation dose**.

Thank you.