Hum. Reprod. Advance Access published November 17, 2015
Human Reproduction, Vol.0, No.0 pp. 1–7, 2015
doi:10.1093/humrep/dev288

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Assisted reproductive technology use and outcomes among women with a history of cancer†

Barbara Luke[1,*], Morton B. Brown[2], Stacey A. Missmer[3,4,5], Logan G. Spector[6], Richard E. Leach[1], Melanie Williams[7], Lori Koch[8], Yolanda R. Smith[9], Judy E. Stern[10], G. David Ball[11], and Maria J. Schymura[12]

[1]Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine, Michigan State University, East Lansing, MI, USA [2]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA [3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA [4]Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [6]Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA [7]Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, USA [8]Illinois State Cancer Registry, Illinois Department of Public Health, Springfield, IL, USA [9]Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA [10]Department of Obstetrics and Gynecology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA [11]Seattle Reproductive Medicine, Seattle, WA, USA [12]Bureau of Cancer Epidemiology, New York State Cancer Registry, New York State Department of Health, Albany, NY, USA

*Correspondence address. Tel: +1-517-353-1678; Fax: +1-517-353-1663; E-mail: lukeb@msu.edu

Submitted on August 15, 2015; resubmitted on October 15, 2015; accepted on October 23, 2015

STUDY QUESTION: How do the assisted reproductive technology (ART) outcomes of women presenting for ART after cancer diagnosis compare to women without cancer?

SUMMARY ANSWER: The likelihood of a live birth after ART among women with prior cancer using autologous oocytes is reduced and varies by cancer diagnosis but is similar to women without cancer when donor oocytes are used.

WHAT IS KNOWN ALREADY: Premenopausal patients faced with a cancer diagnosis frequently present for fertility preservation.

STUDY DESIGN, SIZE, DURATION: Population-based cohort study of women treated with ART in NY, TX and IL, USA.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with their first ART treatment between 2004 and 2009 were identified from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database and linked to their respective State Cancer Registries based on name, date of birth and social security number. Years were rounded, i.e. year 1 = 6–18 months before treatment. This study used reports of cancer from 5 years, 6 months prior to treatment until 6 months after first ART treatment. Women who only presented for embryo banking were omitted from the analysis. The likelihood of pregnancy and of live birth with ART using autologous oocytes was modeled using logistic regression, with women without prior cancer as the reference group, adjusted for woman's age, parity, cumulative FSH dosage, infertility diagnosis, number of diagnoses, number of ART cycles, State of residency and year of ART treatment. Results of the modeling are reported as adjusted odds ratios (AORs) and (95% confidence intervals).

MAIN RESULTS AND THE ROLE OF CHANCE: The study population included 53 426 women; 441 women were diagnosed with cancer within 5 years prior to ART cycle start. Mean (± SD) age at cancer diagnosis was 33.4 ± 5.7 years; age at start of ART treatment was 34.9 ± 5.8 for women with cancer compared with 35.3 ± 5.3 years for women without cancer ($P = 0.03$). Live birth rates among women using autologous oocytes differed substantially by cancer status (47.7% without cancer versus 24.7% with cancer, $P < 0.0001$), and cancer diagnosis (ranging from 53.5% for melanoma to 14.3% for breast cancer, $P < 0.0001$. The live birth rates among women using donor oocytes did not vary significantly by cancer status (60.4% for women with any cancer versus 64.5% for women without cancer), or by cancer diagnosis (ranging from 57.9% for breast cancer to 63.6% for endocrine cancer). Women with breast cancer make up about one-third of all cancers in this cohort. Among women with breast cancer, 2.8% of the 106 women who underwent ART within 6 months of being diagnosed with cancer used donor oocytes compared

†Presented in part at the 70th Annual Meeting of the American Society for Reproductive Medicine, Honolulu, Hawaii, 18–22 October 2014

with 34.8% of the 46 women who received ART treatment a longer time after being diagnosed with cancer ($P < 0.0001$). We conjecture that the former group were either unaware that they had cancer or decided to undergo ART therapy prior to cancer treatment. However, their live birth rate was only 11.7% compared with 28.8%, the overall live birth rate for all women with cancer using autologous oocytes ($P < 0.0001$). The live birth rate for women diagnosed with breast cancer more than 6 months before ART (23.3%) did not differ significantly from the overall live birth rate for cancer ($P = 0.49$). If this difference is substantiated by a larger study, it would indicate a negative effect of severe recent illness itself on ART success, rather than the poor outcome being only related to the destructive effects of chemotherapies on ovarian follicles. Alternatively, because of the short time difference between cancer diagnosis and ART treatment, these pre-existing cancers may have been detected due to the increased medical surveillance during ART therapy. In women who only used autologous oocytes, women with prior cancers were significantly less likely to become pregnant and to have a live birth than those without cancer (adjusted odds ratio (AOR): 0.34, [95% confidence interval (CI): 0.27, 0.42] and 0.36 [0.28, 0.46], respectively). This was also evident with specific cancer diagnoses: breast cancer (0.20 [0.13, 0.32] and 0.19 [0.11, 0.30], respectively), cervical cancer (0.36 [0.15, 0.87] and 0.33 [0.13, 0.84], respectively) and all female genital cancers (0.49 [0.27, 0.87] and 0.47 [0.25, 0.86], respectively). Of note, among women with cancer who became pregnant, their likelihood of having a live birth did not differ significantly from women without cancer (85.8 versus 86.7% for women using autologous oocytes, and 85.3 versus 86.9% for women using donor oocytes).

LIMITATIONS, REASONS FOR CAUTION: Women may not have been residents of the individual States for the entire 5-year pre-ART period, and therefore some cancers may not have been identified through this linkage. As a result, the actual observed number of cancers may be an underestimate. In addition, the overall prevalence is low due to the age distributions. Also, because we restricted the pre-ART period to 5 years prior, we would not have identified women who were survivors of early childhood cancers (younger than age 13 years at cancer diagnosis), or who had ART more than 5 years after being diagnosed with cancer. Additional analyses are currently underway evaluating live birth outcomes after embryo banking among women with cancer prior to ART, cycles which were excluded from the analyses in this paper. Future studies are planned which will include more States, as well as linkages to vital records to obtain information on spontaneous conceptions and births, to further clarify some of the issues raised in this analysis.

WIDER IMPLICATIONS OF THE FINDINGS: Since the live birth rates using donor oocytes were not reduced in women with a prior cancer, but were reduced with autologous cycles, this suggests that factors acting in the pre- or peri-conceptional periods may be responsible for the decline.

STUDY FUNDING/COMPETING INTERESTS: The study was funded by grant R01 CA151973 from the National Cancer Institute, National Institutes of Health, USA. B.L. is a research consultant for the Society for Assisted Reproductive Technology. All other authors report no conflict of interest.

Key words: oncofertility / assisted reproduction / cohort study / cancer among women / live births / breast cancer

Introduction

It is estimated that there are 13.6 million cancer survivors in the USA, including over 1 million women of reproductive age (de Moor *et al.*, 2013). The number of women diagnosed with cancer during their lifetime has been steadily increasing, due to advances in early detection and the aging of the population. For women in their reproductive years, an important concern is how the disease and its treatment will affect their future fertility. Several studies (Ives *et al.*, 2007; Kroman *et al.*, 2008) and recent meta-analyses and reviews (Azim *et al.*, 2011; Levine *et al.*, 2015; Raphael *et al.*, 2015) have addressed the safety of pregnancy after cancer, including endocrine-sensitive disease (Azim *et al.*, 2013; Goldrat *et al.*, 2015). The objective of this study was to evaluate the cancer history among women of childbearing age presenting for ART in three US States, and compare the assisted reproductive technology (ART) outcomes in women with prior cancer compared with those without.

Materials and Methods

Data sources

The Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database contains comprehensive data from more than 90% of all clinics providing ART in the USA (http://www.sart.org). Data for IVF treatment cycles were collected and verified by SART and reported to the Center for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). In 2004, after a contract change with the CDC, SART gained access to the SART CORS data system for the purposes of conducting research. The SART CORS database is left-censored at 2004, that is, ART treatment details for women prior to 2004 are not available. SART makes clinical data available for research purposes to persons or entities who have agreed to comply with SART research guidelines. Patients undergoing ART at SART-associated clinics sign clinical consent forms that include permission to use their data for research. The data are submitted by individual clinics and vouched for by the Practice Director of each clinic. Approximately 10% of the clinics are audited each year by the CDC and SART to validate the accuracy of the reported data (CDC, ASRM, SART, 2014).

Cycles that began between 1 January 2004 and 31 December 2009 and were reported to the SART CORS were included, linked by the woman's birth date, first and last names, and social security number (when present). Linkages across clinics also included partner's name and the sequence of ART outcomes. Identifying variables (including names, dates, and social security numbers) were removed and a de-identified analytic file generated. Cycles were numbered sequentially, regardless of cycle type (fresh or thawed, autologous or donor). Excluded were cycles that were designated as research and women who used gestational carriers or for whom all cycles were designated as embryo banking. Cycles of treatment have been linked to individual women (Stern *et al.*, 2010, 2011; Luke *et al.*, 2012, 2013, 2014), allowing calculation of total exposures.

Cancer registry data from NY, IL and TX were chosen for this study, because they are large, ethnically diverse States that ranked #1, 4 and 5 in number of ART cycles performed, respectively, in 2012 (CDC, ASRM, SART, 2014). These three States maintain population-based cancer registries that consistently received Gold certification by the North American Association of Central Cancer Registries during 2004–2009 (http://www.naaccr.org/Certification/USCert2011.aspx). Data available from the cancer registries included the International Classification of Disease for Oncology codes for cancer site, morphology and age at diagnosis. The study was approved by the SART Research Committee, and by the institutional review boards at Michigan State University, the University of Minnesota, the New York State Department of Health, the Texas Department of State Health Services and the Illinois Department of Public Health, and data were analyzed using the SAS 9.3 software (SAS, Cary, NC, USA).

Linkage procedures

The SART CORS database is maintained by Redshift Technologies, Inc. for SART. Cycles in the database for women who were residents of NY, TX or IL treated between 1 January 2004 and 31 December 2009 were linked by Redshift Technologies, Inc. Cycles for the same woman which occurred within one clinic were linked using the woman's birth date, first and last names and social security number (when present). Cycles across clinics for the same woman were linked with the additional factors of partner's name and the sequence of ART outcomes. Redshift Technologies, Inc. also generated study-specific unique identifiers (for each woman and each cycle).

To maintain data quality and to ensure the anonymity of the final linked file provided to the investigators, the minimum SART CORS data sufficient to achieve linkage was transferred directly from Redshift Technologies to each State. The final linked SART/cancer files were stripped of any data elements that could identify an individual. For instance, the final file did not contain any geographic unit smaller than the State itself. The investigators received a file from Redshift Technologies containing ART treatment data, reproductive history, age and the unique identifier, but no personal identifiers, in order to link treatment data to the SART/cancer files. The data records for each woman from SART were ordered by date of treatment initiation. Each woman was then screened for prior ART treatment, either a report of prior ART cycles or the use of frozen embryos on the initial cycle; women with prior ART treatment were eliminated. The data from each woman were then summarized into a single record that included data from the initial ART treatment, such as patient age, as well as the total number of cycles and total FSH dosage over all the ART cycles reported. Using the data from each State, the earliest malignancy and its organ system were identified for each woman; three malignancies that were classified as 'unknown' with respect to system were deleted. The two files were then merged so that the final file included both women with and without malignancies.

Statistical analysis

We restricted the before-treatment period to 5 years prior to initiation of ART. Since women may have the same age at treatment and cancer onset, which is equivalent to saying that with 75% probability the ages do not differ by more than 6 months in either direction, when months of diagnosis and treatment were available, we defined a year to be ± 6 months. Diagnoses within 6 months of the start of ART treatment or an age difference of zero was included in the period before ART (zero years difference); we viewed diagnoses within a period up to 6 months post-initial treatment to be most likely due to enhanced surveillance that resulted in the identification of a pre-existing condition. Live birth rates and pregnancy rates were computed for women. The univariate analyses of women's characteristics and ART treatment parameters by cancer status were compared using χ^2 for categorical variables and *t*-tests for continuous variables, with significance at $P < 0.05$. The multivariate analyses of ART outcomes were modeled into three ways: the likelihood of pregnancy, live birth and live birth for those women who became pregnant using logistic regression, with women without cancer as the reference group. Models were both unadjusted, and adjusted for woman's age, parity, cumulative FSH dosage, infertility diagnosis, number of diagnoses, number of ART cycles, State of residency and year of ART treatment.

Independent variables included State (NY, IL or TX), year of ART treatment (2004, 2005, 2006, 2007, 2008 and 2009), age at start of the first cycle of ART treatment in years (as 18–29, 30–34, 35–37, 38–40, 41–43 and 44–64), parity (0, 1 and $\geq$2), infertility diagnosis (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal factors, other factors and unexplained), number of diagnoses (1 or $>$1), number of ART cycles (1, 2, 3, 4 or $\geq$5), cumulative FSH dosage over all initiated cycles during the study period (none, $<$2000 IU, 2000–3999 IU, 4000–6999 IU and $\geq$7000 IU), oocyte source (autologous versus donor), cancer diagnosis (all cancers, endocrine, melanoma, breast, ovarian, cervical, uterine, and all female genital [cervix, uterus, other female genitalia, ovary, vagina and vulva]). The dependent variables were live birth, pregnancy and live birth for those women who became pregnant.

Infertility diagnoses were defined for data entry to SART CORS as follows: male factor is the presence of abnormal semen parameters or function; endometriosis is the presence of any stage of endometriosis whether treated or untreated; ovulation disorders can have several differing definitions including multiple cysts affecting fertility, oligo-ovulation or anovulation; diminished ovarian reserve is currently defined as high FSH or estradiol in the early follicular stage as measured on a clomiphene citrate challenge test, or reduced ovarian volume, but could also have been defined by advanced maternal age for some earlier cycles in our cohort; tubal factor is any condition affecting the patency of the Fallopian tubes; uterine factor includes any uterine abnormality. The category of other factors could have included immunological, chromosomal, cancer and any other conditions not listed in the previously defined categories. Unexplained is intended to be an absence of any defined male and female diagnoses.

Results

The study population included 53 426 women; 441 women were diagnosed with cancer within 5 years prior to ART start. Mean ($\pm$SD) age at cancer diagnosis was 33.4 $\pm$ 5.7 years; age at start of ART treatment was 34.9 $\pm$ 5.8 for women with cancer compared with 35.3 $\pm$ 5.3 years for women without cancer (Table I). Women with cancer were more likely to seek ART treatment at a younger age than those without cancer, and were more likely to be nulliparous. As expected many of the women with prior cancers were designated to have the cancer diagnosis 'Other factors'; this resulted in many other diagnoses having lower frequencies (by 1/3 to 1/2) in women with prior cancer compared with women without cancer. Women with prior cancers were less likely to become pregnant and have a live birth; among women with cancer who became pregnant, the likelihood of having a live birth did not differ significantly from women without cancer (85.8 versus 86.7% for women using autologous oocytes, and 85.3 versus 86.9% for women using donor oocytes).

Live birth rates among women using autologous oocytes differed substantially by cancer status (47.7% without cancer versus 24.7% with cancer, $P < 0.0001$), and cancer diagnosis (ranging from 53.5% for melanoma to 14.3% for breast cancer, $P < 0.0001$) (Table II). Among women with breast cancer, which represented about one-third of all cancers in this cohort, only 2.8% of those using autologous oocytes who underwent ART within 6 months of being diagnosed with cancer

Table I Description of the study population: women starting assisted reproductive technology (ART) in 2004–2009 in NY, IL and TX, USA, by cancer history.

Factor	Categories (*n*)	All study women 53 426	Women without cancer prior to ART 52 985	Women with cancer prior to ART 441	*P*-values for difference between groups
Woman's age (mean years, SD)	At cancer diagnosis			33.4 ± 5.7	
	At start of ART treatment	35.3 ± 5.3	35.3 ± 5.3	34.9 ± 5.8	0.03
Woman's age (years)	At start of ART treatment	%	%	%	
	<30	14.5	14.5	20.6	0.0002
	31–34	30.1	30.1	22.4	
	35–37	20.4	20.4	19.3	
	38–40	17.7	17.7	21.3	
	41–42	11.8	11.8	10.2	
	≥43	5.6	5.6	6.1	
Parity	0	77.6	77.6	83.4	0.009
	1	14.0	14.1	11.3	
	≥2	8.3	8.4	5.2	
Diagnosis	Male factor	33.1	33.2	19.7	<0.0001
	Endometriosis	9.2	9.2	3.9	<0.0001
	Ovulation disorders	12.8	12.8	9.3	0.03
	Diminished ovarian reserve	22.1	22.1	21.3	0.73
	Tubal factors	20.3	20.4	10.0	<0.0001
	Uterine factors	5.0	5.0	5.4	0.66
	Other factors	14.6	14.3	47.8	<0.0001
	Unexplained	12.5	12.5	9.5	0.07
Number of diagnoses	1	75.3	75.3	77.1	0.38
	>1	24.7	24.7	22.9	
Number of ART cycles	1	50.8	50.7	59.6	0.003
	2	26.2	26.2	21.1	
	3	12.5	12.5	10.0	
	4	5.6	5.6	5.9	
	≥5	5.0	5.0	3.4	
Cumulative	None	7.2	7.2	10.0	0.14
FSH dosage	<2000 IU	19.1	19.1	17.5	
	2000–3999 IU	30.0	29.9	31.1	
	4000–6999 IU	21.8	21.8	22.2	
	≥7000 IU	22.0	22.0	19.3	

Student's *t*-test was used to compare age between groups; Fisher's exact test was used to compare diagnoses and number of diagnoses (dichotomous characteristics) and the χ^2 test of independence was used to compare the remaining characteristics between groups.

used donor oocytes compared with 34.8% of their counterparts who received ART treatment a longer time after diagnosis ($P < 0.0001$). However, their live birth rate was only 11.7% compared with 28.8%, the overall live birth rate for women with cancer using autologous oocytes ($P < 0.0001$). The live birth rate for women diagnosed with breast cancer more than 6 months before ART using autologous oocytes (23.3%) did not differ significantly from the overall live birth rate for cancer ($P = 0.49$). The live birth rates among women using donor oocytes did not vary substantially by cancer status (60.4% for women with any cancer versus 64.5% for women without cancer), or by cancer diagnosis (ranging from 57.9% for breast cancer to 63.6% for endocrine cancer).

Among women using only autologous oocytes, women with cancer overall were significantly less likely to become pregnant and to have a live birth (Table III): women with the diagnoses of breast cancer (AOR: 0.20 [95% CI: 0.13, 0.32] and 0.19 [0.11, 0.30], respectively),

Table II Probability of conception and live birth rates for women, by oocyte source and cancer diagnosis.

Cancer status and diagnosis	% Using donor oocytes	Women using only autologous oocytes		Women who ever used donor oocytes	
		n, women	%	*n*	%
		Probability of conception			
No cancer	9.1	48 138	55.0	4847	74.2
All cancers	10.9	393	28.8	48	70.8
			$P < 0.0001$		$P = 0.62$
		Probability of a live birth given conception			
No cancer	12.0	26 492	86.7	3598	86.9
All cancers	23.1	113	85.8	34	85.3
			$P = 0.78$		$P = 0.80$
		Probability of a live birth			
No cancer	9.1	48 138	47.7	4847	64.5
All cancers	10.9	393	24.7	48	60.4
			$P < 0.0001$		$P = 0.55$
Endocrine	15.1	62	32.3	11	63.6
Melanoma	8.5	43	53.5	4	–
All female Genital	5.4	53	30.2	3	–
Breast	12.5	133	14.3	19	57.9
			$P < 0.0001$		
Breast-1[a]	2.8	103	11.7	3	–
Breast-2[b]	34.8	30	23.3	16	62.5

Fisher's exact test was used for dichotomous outcomes and the χ^2 test of independence was used to compare the four types of cancer.
[a]Women who were diagnosed with breast cancer and received ART treatment within 6 months.
[b]Women who received ART treatment after they were diagnosed with breast cancer (>6 months).

cervical cancer (AOR: 0.36 [0.15, 0.87] and 0.33 [0.13, 0.84], respectively), and all female genital cancers (AOR: 0.49 [0.27, 0.87] and 0.47 [0.25, 0.86], respectively). This resulted in an overall difference between women with prior cancer and those without (AOR: 0.34 [0.27, 0.42] and 0.36 [0.28, 0.46], respectively). Among women who became pregnant, the likelihood of having a live birth did not differ significantly between women with a prior cancer and women without cancer (all AORs and 95% CIs included 1, indicating non-significance).

Discussion

This is one of the first studies to evaluate the characteristics and outcomes of women with cancer who were subsequently treated with ART (Knopman *et al.*, 2009; Barton *et al.*, 2012; Das *et al.*, 2012). The main finding in this large, population-based study linking State cancer registries to the US national ART database, which included more than 53 000 women treated with ART, was that women with cancer are more likely to seek ART treatment at a younger ages than those without cancer and to be nulliparous. Specific cancer diagnoses were associated with a decreased likelihood of pregnancy and live birth, including breast cancer, cervical cancer and all female genital cancers. This may reflect an altered hormonal milieu resulting from the cancer process itself, the cancer therapy, or a combination of both factors. With the use of donor oocytes live birth rates in women with prior cancer were comparable to those of women without cancer. The likelihood of live birth for those women who became pregnant did not differ by cancer status or cancer diagnosis, suggesting that the critical issue involves factors acting in the pre- and peri-conceptional periods. Further research is needed to clarify these issues.

Women with breast cancer make up about one-third of all cancers in this cohort. Among women with breast cancer only 2.8% of the 106 women who underwent ART within 6 months of being diagnosed with cancer used donor oocytes compared with 34.8% of the 46 women who received ART treatment a longer time after their cancer diagnosis ($P < 0.0001$). We conjecture that the former group were either unaware that they had cancer or decided to undergo ART therapy prior to cancer treatment. However, their live birth rate was only 11.7% compared with 28.8%, the overall live birth rate among women with cancer who used autologous oocytes ($P < 0.0001$). The live birth rate for women diagnosed with breast cancer more than 6 months before ART (23.3%) did not differ significantly from the overall live birth rate for cancer ($P = 0.49$). If this difference is substantiated by a larger study, it would indicate a negative effect of severe recent illness itself on ART success, rather than the poor outcome being only related to the destructive effects of chemotherapies on ovarian follicles. Alternatively, because of the short time difference between cancer diagnosis and ART treatment, these pre-existing cancers may have been detected due to the increased medical surveillance during ART therapy.

The main strength of this study is its large sample size and the use of high-quality, population-based cancer registries and the national SART

Table III Likelihood of conception and live birth for women after ART by cancer diagnosis, limited to women who only used autologous oocytes.

Cancer diagnosis	*n*, women	Model	Live birth		Conception		Live birth given conception	
			OR/AOR	95% CI	OR/AOR	95% CI	OR/AOR	95% CI
No cancer	48 138		1.00	Reference	1.00	Reference	1.00	Reference
All cancers	393	Unadjusted	**0.36**	**0.29, 0.45**	**0.33**	**0.27, 0.41**	0.93	0.55, 1.58
		Adjusted[a]	**0.36**	**0.28, 0.46**	**0.34**	**0.27, 0.42**	1.21	0.69, 2.11
Endocrine	62	Unadjusted	**0.53**	**0.31, 0.90**	**0.52**	**0.31, 0.87**	0.77	0.26, 2.25
		Adjusted[a]	0.67	0.37, 1.18	0.65	0.38, 1.14	0.84	0.28, 2.56
Melanoma	43	Unadjusted	1.27	0.70, 2.32	1.14	0.62, 2.10	1.76	0.42, 7.45
		Adjusted[a]	1.59	0.83, 3.06	1.33	0.69, 2.56	3.07	0.69, 13.60
Breast	133	Unadjusted	**0.18**	**0.11, 0.30**	**0.19**	**0.12, 0.29**	0.49	0.19, 1.22
		Adjusted[a]	**0.19**	**0.11, 0.30**	**0.20**	**0.13, 0.32**	0.63	0.24, 1.64
Ovarian	12	Unadjusted	1.54	0.49, 4.86	1.15	0.37, 3.63	–	–
		Adjusted[a]	1.28	0.39, 4.16	0.98	0.30, 3.22	–	–
Cervical	24	Unadjusted	**0.37**	**0.15, 0.93**	**0.41**	**0.18, 0.96**	0.46	0.09, 2.29
		Adjusted[a]	**0.33**	**0.13, 0.84**	**0.36**	**0.15, 0.87**	0.70	0.11, 4.49
Uterine	15	Unadjusted	**0.28**	**0.08, 0.98**	**0.30**	**0.10, 0.94**	0.46	0.05, 4.43
		Adjusted[a]	0.30	0.08, 1.11	0.33	0.10, 1.05	0.38	0.04, 3.77
All female genital	53	Unadjusted	**0.48**	**0.27, 0.86**	**0.50**	**0.29, 0.87**	0.61	0.21, 1.83
		Adjusted[a]	**0.47**	**0.25, 0.86**	**0.49**	**0.27, 0.87**	0.79	0.23, 2.78

[a]Models adjusted for woman's age, parity, cumulative FSH dosage, infertility diagnosis and number of infertility diagnoses, number of ART cycles, State of residency and year of ART treatment. Bolded values are OR/AORs and 95% CIs which are significant.

database. A limitation is that women may not have been residents of the study States for the entire 5-year pre-ART period, and therefore some cancers may not have been identified through this linkage. As a result, the actual observed number of cancers may be an underestimate. In addition, the overall prevalence is low due to the age distributions. Also, because we restricted the pre-ART period to 5 years prior, we would not have identified women who were survivors of early childhood cancers (younger than age 13 years at cancer diagnosis), or who had ART more than 5 years after being diagnosed with cancer. Additional analyses are currently underway evaluating live birth outcomes after embryo banking among women with cancer prior to ART, cycles which were excluded from the analyses in this paper. Future studies are planned which will include more States, as well as linkages to vital records to obtain information on spontaneous conceptions and births, to further clarify some of the issues raised in this analysis.

In conclusion, this large US study of cancer in women prior to ART treatment, using State cancer registries and the national SART CORS database, found the likelihood of a live birth after ART among women with prior cancer using autologous oocytes is reduced and varies by cancer diagnosis, but is similar to women without cancer when donor oocytes are used.

Acknowledgements

SART wishes to thank all of its members for providing clinical information to the SART CORS database for use by patients and researchers. Without the efforts of our members, this research would not have been possible.

Authors' roles

B.L., M.B.B. and L.G.S. contributed to the conception and design of the study. B.L., L.G.S., M.W., L.K. and M.J.S. collected data from the State Cancer Registries. M.B.B. performed the statistical analyses. B.L., M.B.B. and S.A.M. contributed to the analysis of the data. B.L., M.B.B., S.A.M., J.E.S., Y.R.S. and M.J.S. drafted the manuscript and revised it. All authors contributed to the interpretation of the data, and approved the final version.

Funding

The study was supported by a grant from the National Cancer Institute, National Institutes of Health, USA. The study was also supported by the National Cancer Institute, National Institutes of Health (grant R01 CA151973). The views expressed in this paper are those of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Conflict of interest

B.L. is a research consultant for the Society for Assisted Reproductive Technology. All other authors report no conflict of interest.

References

Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer* 2011;**47**:74–83.

Azim HA Jr, Kroman N, Paesmans M, Gelber S, Rotmensz N, Ameye L, De Mattos-Arruda L, Pistilli B, Pinto A, Jensen M-B *et al*. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013;**31**:73–79.

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**:381–386.

Center for Disease Control and Prevention, American Society for Reproductive Medicine, and Society for Assisted Reproductive Technology. 2012 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. Washington, DC: US Dept. of Health and Human Services, 2014.

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**:2509–2514.

de Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, Forsythe L, Scoppa S, Hachey M, Rowland JH. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers Prev* 2013;**22**:561–570.

Goldrat O, Kroman N, Peccatori FA, Cordoba O, Pistilli B, Lidegaard O, Demeestere I, Azim HA Jr. Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome. *Eur J Cancer* 2015;**51**:1490–1496.

Ives A, Saunders C, Bulsara M, Semmens J. Pregnancy after breast cancer: population based study. *Br Med J* 2007;**334**:194.

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**: 1476–1478.

Kroman N, Jensen MB, Wohlfahrt J, Ejlertsen B. Pregnancy after treatment of breast cancer—A population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol* 2008;**47**:545–549.

Levine JM, Kelvin JF, Quinn GP, Gracia CR. Infertility in reproductive-age female cancer survivors. *Cancer* 2015;**121**:1532–1539.

Luke B, Brown MB, Wantman E, Lederman A, Gibbons W, Schattman GL, Lobo RA, Leach RE, Stern JE. Cumulative birth rates with linked assisted reproductive technology cycles. *N Engl J Med* 2012;**366**:2483–2491.

Luke B, Brown MB, Wantman E, Baker VL, Grow DR, Stern JE. Second try: who returns for additional ART treatment and the effect of a prior ART birth. *Fertil Steril* 2013;**100**:1580–1584.

Luke B, Brown MB, Wantman E, Stern JE. Factors associated with monozygosity in assisted reproductive technology (ART) pregnancies and the risk of recurrence using linked cycles. *Fertil Steril* 2014; **101**:683–689.

Raphael J, Trudeau ME, Chan K. Outcome of patients with pregnancy during or after breast cancer: a review of the recent literature. *Curr Oncol* 2015; **22**(Suppl 1):S8–18.

Stern JE, Brown MB, Luke B, Wantman E, Lederman A, Missmer SA, Hornstein MD. Calculating cumulative live-birth rates from linked cycles of assisted reproductive technology (ART): data from the Massachusetts SART CORS. *Fertil Steril* 2010;**94**:1334–1340.

Stern JE, Brown MB, Luke B, Wantman E, Lederman A, Hornstein MD. Cycle 1 as predictor of ART treatment outcome over multiple cycles: analysis of linked cycles from the SART CORS online database. *Fertil Steril* 2011; **95**:600–605.