Outcomes after assisted reproductive technology in women with cancer: a systematic review and meta-analysis

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STUDY QUESTION: What are the associations between a history of cancer and outcomes after ART?

SUMMARY ANSWER: Compared to women without cancer, on average, women with cancer had a lower return for embryo transfer and a lower likelihood of clinical pregnancy and live birth after ART.

WHAT IS KNOWN ALREADY: Small, single-institution studies have suggested that cancer and its treatment may negatively affect ART outcomes.

STUDY DESIGN, SIZE, DURATION: We conducted a systematic review with meta-analysis of studies comparing ART outcomes between women with and without cancer. PubMed, Embase and Scopus were searched for original, English-language studies published up to June 2021.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Inclusion criteria required reporting of ART outcomes after controlled ovarian stimulation (COS) among women with a history of cancer compared to women without cancer who used ART for any indication. Outcomes of interest ranged from duration of COS to likelihood of live birth after embryo transfer. Random-effects meta-analysis was used to calculate mean differences and odds ratios (ORs) with 95% CIs and 95% prediction intervals (PIs). We assessed heterogeneity by age-adjustment, referent group indication for ART, study location and among women with breast cancer and women who initiated ART before cancer treatment. We used visual inspection, Egger's test and the trim-and-fill method to assess funnel plot asymmetry.

MAIN RESULTS AND THE ROLE OF CHANCE: Of 6094 unique records identified, 42 studies met inclusion criteria, representing a median per study of 58 women with cancer (interquartile range (IQR) = 159) and 114 women without cancer (IQR = 348). Compared to women without cancer, on average, women with cancer had a lower return for embryo transfer (OR: 0.22; 95% CI: 0.07, 0.74; 95% PI: 0.00, 64.98); lower likelihood of clinical pregnancy (OR: 0.51; 95% CI: 0.35, 0.73; 95% PI: 0.19, 1.35); and lower likelihood of live birth (OR: 0.56; 95% CI: 0.38, 0.83; 95% PI: 0.19, 1.69). Substantial among-study heterogeneity was observed for COS duration, gonadotropin dose, cycle cancellation, total oocytes and mature oocytes. Fertilization percentage showed less heterogeneity, but study-specific estimates were imprecise. Similarly, number of embryos showed less heterogeneity, and most studies estimated minimal differences by cancer history. Funnel plot asymmetry was observed for estradiol peak and oocyte maturation percentage.

LIMITATIONS, REASONS FOR CAUTION: Appreciable confounding is possible in 11 studies that lacked adequate control for group differences in age, and among-study heterogeneity was observed for most outcomes. Lack of data limited our ability to assess how cancer clinical factors (e.g. cancers other than breast, cancer stage and treatment) and ART cycle characteristics (e.g. fresh versus frozen embryo transfers and use of gestational carriers) may affect outcomes.

WIDER IMPLICATIONS OF THE FINDINGS: Women with cancer may be less likely to achieve pregnancy and live birth after embryo transfer. Further examination of reproductive outcomes and sources of heterogeneity among studies is warranted to improve evidence of the expected success of ART after a cancer diagnosis.

Introduction

Cancer treatment can increase the risk of infertility for many of the roughly 1.3 million reproductive-age women diagnosed with cancer each year (Lee et al., 2006; Levine et al., 2015; Poorvu et al., 2019; International Agency for Research on Cancer, 2020), which can lead to increased psychosocial distress, poorer mental health and lower quality of life (Lee et al., 2006; Deshpande et al., 2015; Anazodo et al., 2019; Logan et al., 2019). ART is clinically recommended for women with cancer who want to preserve their fertility before cancer treatment, or who are not able to naturally conceive after treatment (Ethics Committee of the American Society for Reproductive Medicine, 2018; Oktay et al., 2018; Practice Committee of the American Society for Reproductive Medicine, 2019; Lambertini et al., 2020). ART procedures include oocyte or embryo cryopreservation for fertility preservation, and embryo transfer to attempt pregnancy using fresh (non-cryopreserved) embryos or previously cryopreserved embryos that have been thawed (Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, 2017). However, evidence of reproductive success after ART in cancer populations has been limited (Dolmans et al., 2019; Lambertini et al., 2020). Women with cancer are often counseled using ART data from the general population, though it is unclear how prior exposure to cancer or its treatments may affect outcomes (Levine et al., 2015; Lambertini et al., 2016; Practice Committee of the American Society for Reproductive Medicine, 2019; Mulder et al., 2021).

Two meta-analyses comparing ART outcomes by cancer history have been previously published (Friedler et al., 2012; Turan et al., 2018). However, neither assessed study characteristics contributing to among-study heterogeneity, outcomes among women who initiated ART after cancer treatment, nor pregnancy or birth outcomes. Our systematic review and meta-analysis sought to fill these evidence gaps and contribute novel data to the comparison of ART outcomes between women with and without cancer.

Methods

Search strategy

The guidelines recommended by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) were followed (Page et al., 2021). A literature search in PubMed, Embase and Scopus was conducted in August 2020; a second search was conducted in June 2021. Additional studies were identified by other methods (e.g. reviewing references cited in included articles). Only studies that could be obtained in English language were eligible for inclusion. There were no restrictions on study years. The search string for each database is provided in Supplementary Table SI. The review protocol was not registered.

Study selection

Inclusion criteria required reporting of ART outcomes after controlled ovarian stimulation (COS) among women with a history of any type of cancer compared to women without cancer who used ART for any indication. Outcomes of interest included: duration of COS; total gonadotropin stimulation dose; peak estradiol level on the day of triggering oocyte maturation; cycle cancellation; total and mature oocytes retrieved; oocyte maturation percentage; fertilization percentage; embryos obtained; return for embryo transfer; oocyte/embryo survival after freeze and thaw; implantation percentage; clinical pregnancy after embryo transfer; and live birth after embryo transfer. Studies were excluded if they did not report any outcomes of interest for an exclusive cancer group and a non-cancer referent group. Non-original research and abstracts only were excluded. One reviewer (C.M.) screened titles, abstracts, and full-text articles for final inclusion.

Data extraction

Study characteristics

One author (C.M.) extracted data from the included articles, including study setting and years, inclusion and exclusion criteria, sample size, cancer types, referent group indications for ART, analytic methods and outcomes. Table I details the main characteristics of included studies and Supplementary Table SII details study-specific inclusion and exclusion criteria.

Outcome measures

For continuous outcomes, the mean and SD per group were extracted; standard errors were converted into SDs (Higgins et al., 2021), and the median and interquartile range (IQR) was used to approximate the mean and SD when necessary (Wan et al., 2014). For binary outcomes, the number of events and the total sample size per group were extracted. Adjusted odds ratios (ORs) were directly extracted when available. Oocyte maturation percentage and fertilization percentage were analyzed as continuous because the mean or median percentage was reported across studies (rather than data on the number of mature oocytes among all oocytes retrieved in order to analyze as binary). For all outcomes, multiple groups among either the cancer or referent group were combined (e.g. outcomes reported separately by cancer type were combined into one cancer group) (Higgins et al., 2021).

Table I Characteristics of studies comparing ART outcomes among women with versus without a history of cancer.

First author (year)	Study period; country	Sample size		Cancer types[a]	ART timing relative to cancer treatment	Referent indication for ART	Age at ART initiation mean (SD)		Comments regarding internal validity concerns
		Cancer	Referent				Cancer	Referent	
Pal et al. (1998)	1995–1997; USA	5	12	gyn (3), other (2)	Prior	Tubal	31 (4.5)[b]	31 (3.5)	None
Oktay et al. (2006)	2003–2005; USA	47	56	breast (47)	Prior	Tubal	36.4 (3.6)[b]	36.9 (3.9)	None
Knopman et al. (2009)	2001–2006; USA	28	135	breast (10), gyn (9), heme (6), other (3)	Prior	Male	34 (5.1)[b]	35.4 (3.5)	None
Klock et al. (2010)	2005–2008; USA	28	57	breast (11), gyn (1), heme (7), other (9)	Prior	Multiple	31.0 (5.3)[b]	31.2 (4.6)	None
Michaan et al. (2010)	2002–2007; Israel	22	22	breast (12), heme (2), other (7) *n = 1 non-cancer	Prior	Tubal	32.8 (5.7)[b]	34 (4.2)	Groups additionally matched on period of treatment and COS protocol.
Noyes et al. (2010)	2004–2009; USA	50	32	breast (12), gyn (22), heme (8), other (8)	Prior	Other	31 (7.1)	32 (5.7)	No age adjustment but groups were comparable.
Quintero et al. (2010)	1999–2007; USA	50	50	breast (28), heme (11), other (11)	Prior	Multiple	32.3 (5.0)[b]	32.3 (5.0)	None
Werner et al. (2010)	2006–2010; USA	49	81	breast (10), gyn (21), heme (9), other (9)	Prior	Elective	30 (7.0)	36 (3.2)	Cancer group younger and no age adjustment.
Das et al. (2011)	2003–2010; Canada	39	48	gyn (7), heme (19), other (13)	Prior	Male	28.4 (5.5)[b]	30.7 (2.1)	None
Robertson et al. (2011)	2001–2007; USA	26	921	breast (16), gyn (5), other (5)	Prior	Male	34.8 (5)	35 (4)	No age matching, but groups were comparable and total oocyte and embryo analysis adjusted for age, gonadotropin dose, peak estradiol, ICSI use and length of COS—no covariates were statistically significant, so only unadjusted summary statistics were presented.
Sabatini et al. (2011)	1997–2007; USA	28	393	breast (17), gyn (6), other (5)	Prior	Multiple	33.9 (3.4)	36.1 (3.9)	Cancer group younger, and no age adjustment reported except for birth analysis (report conducting age-adjusted analysis for pregnancy, but outcomes not reported). Birth analysis additionally adjusted for infertility diagnosis, prior IVF, and fertilization method.
Almog et al. (2012)	2000–2011; Israel	81	81	breast (42), heme (12), other (27)	Prior	Male	31.8 (4.8)[b]	31.7 (4.7)	Groups additionally matched on date of COS.
Barton et al. (2012)	1998–2009; USA	53	7030	breast (17), gyn (8), heme (22), other (6)	After	Multiple	34.2 (19.3–43.9)[b,c]	35.8 (19.3–43.9)[c]	Additional adjustment for COS protocol and fertilization method, but did not change effect estimates by >10% so were not included in final models.
Das et al. (2012)	2003–2010; Canada	14	42	breast (1), gyn (3), heme (7), other (3)	After	Male	28.4 (4.5)[b]	30.2 (2.6)	None

(continued)

Table I Continued

First author (year)	Study period; country	Sample size		Cancer types[a]	ART timing relative to cancer treatment	Referent indication for ART	Age at ART initiation mean (SD)		Comments regarding internal validity concerns
		Cancer	Referent				Cancer	Referent	
Domingo et al. (2012)	2007–2011; Spain	208	97	breast (143), heme (37), other (28)	Prior	Male	32.4 (4.9)[b]	31.9 (5.3)	None
Garcia-Velasco et al. (2013)	2007–2012; Spain	340	560	breast, heme, other	Prior	Multiple	31.9 (5.1)	36.7 (4.2)	Cancer group younger and no age adjustment.
Fujimoto et al. (2014)	1999–2012; Japan	21	42	gyn (21)	After	Multiple	34 (30–39)[b,c]	34 (29–41)[c]	Groups additionally matched on date of ART.
Cardozo et al. (2015)	1997–2014; USA	63	122	breast (41), gyn (8), heme (5), other (9)	Prior	Tubal	33.7 (4.1)[b]	34.5 (3.5)	Groups additionally matched on date of ART.
Goldrat et al. (2015)	2012–2014; Belgium	21	21	breast (21)	Prior	Multiple	31.7 (6.4)	32.3 (4.8)	No age adjustment but groups were comparable.
Lekovich et al. (2016)	2010–2013; USA	192	365	breast (99), gyn (15), heme (69), other (9)	Prior	Elective	31.8 (4.8)	36.5 (3.2)	Cancer group younger and no outcomes are reported after age adjustment (only P-values after age-adjustment reported).
Luke et al. (2016a)	2004–2009; USA	441	52985	breast (152), gyn (56), other (233)	Unknown	Multiple	34.9 (5.8)[b]	35.3 (5.3)	Analysis of reproductive outcomes adjusted for age, parity, cumulative gonadotropin dose, infertility diagnosis and number of diagnoses, number of ART cycles, state of residency, and year of ART.
Luke et al. (2016b)	2004–2009; USA	270	68	breast (131), gyn (37), heme (64), other (37)	Unknown	Male	32.5 (5.5)	32.2 (4.2)	No age adjustment but groups were comparable.
Nurudeen et al. (2016)	2005–2012; USA	49	49	breast (35), gyn (1), heme (4), other (9)	Prior	Multiple	33.6 (4.8)[b]	34.3 (4.6)	None
Pereira et al. (2016)	2005–2014; USA	220	439	breast (220)	Prior	Elective	35.7 (3.7)	36.7 (3.7)	No age adjustment but groups were comparable.
Quinn et al. (2017)	2009–2015; USA	191	398	breast (191)	Prior	Elective	34.9 (4.6)[b]	36.4 (3.0)	COS length and peak estradiol adjusted for age and BMI; total oocytes, mature oocytes and maturation percentage analysis additionally adjusted for total gonadotropin dose and letrozole use.
Cobo et al. (2018)	2007–2018; Spain	1073	5289	breast (694), gyn (44), heme (191), other (144)	Prior	Elective	32.3 (3.5)	37.2 (4.9)	Cancer group younger and no age adjustment, though pregnancy and live birth outcomes were stratified by broad age categories; age-adjusted ORs were calculated, though residual confounding may be present.
Decanter et al. (2018)	2011–2014; France	90	180	breast (49), heme (25), other (16)	Prior	Male	29 (5)[b]	29 (5)	Groups additionally matched on date of COS.
Dolinko et al. (2018)	2007–2014; USA	147	664	breast (79), gyn (8), heme (38), other (22)	Both	Male	31.7 (6.0)	34.6 (4.2)	No age matching but age-adjusted outcomes are reported.

(continued)

Table I Continued

First author (year)	Study period; country	Sample size		Cancer types[a]	ART timing relative to cancer treatment	Referent indication for ART	Age at ART initiation mean (SD)		Comments regarding internal validity concerns
		Cancer	Referent				Cancer	Referent	
Tsampras et al. (2018)	2009–2016; UK	157	2128	breast (80), gyn (8), other (69)	Prior	Male	30.3 (6.0)[b]	32.0 (4.5)	None
Ben-Haroush et al. (2019)	2007–2017; Israel	313	105	breast (145), other (168)	Prior	Elective	29.8 (7.2)	36.0 (3.5)	Cancer group younger and no age adjustment.
de Moraes et al. (2019)	2010–2017; Brazil	23	164	breast (13), gyn, heme, other	Prior	Elective	31.0 (5.1)	35.7 (3.1)	Cancer group younger and no age adjustment.
Goldrat et al. (2019)	2012–2017; Belgium	23	24	breast (23)	Prior	Multiple	30.4 (3.8)	30.8 (3.9)	No age adjustment but groups were comparable.
Gunnala et al. (2019)	2010–2015; USA	176	600	breast (91), gyn (7), heme (42), other (36)	Prior	Elective	31.4 (5.5)	36.6 (3.0)	Cancer group younger and no age adjustment comparing cancer group vs. non-cancer group.
Rodriguez-Wallberg et al. (2019)	1998–2018; Sweden	382	180	breast, gyn, heme, other	Both	Multiple	30.9 (5.5)	27.1 (7.2)	Cancer group older; only outcome adjusted for age was return for embryo transfer.
Bercaire et al. (2020)	2015–2016; Brazil	69	92	breast (69)	Prior	Male	31.5 (4.1)[b]	33.1 (7.1)	None
Kawwass et al. (2020)	2012–2016; USA	2715	26916	breast, heme, other	Unknown	Multiple	<35: 63%[b]	<35: 25%	Cancer group younger; age-adjusted outcomes are reported though residual confounding may result from broad age categorization.
Nordan et al. (2020)	2007–2018; USA	10	30	other (10)	Prior	Male	30.4 (4.5)[b]	30.5 (3.9)	Groups additionally matched on COS protocol.
Porcu et al. (2020)	2014–2019; Italy	46	181	breast (46)	Prior	Male	32.4 (4.1)	32.4 (2.8)	No age adjustment but groups were comparable.
Huang et al. (2021)	2010–2018; China	64	320	other (64)	After	Other	33.8 (4.3)[b]	33.6 (3.9)	Groups additionally matched on BMI, infertility diagnosis, date of ART, COS protocol and type of embryo transfer. Reproductive outcomes further adjusted for free T4, TSH and fertilization method. Pregnancy outcomes were self-reported.
Hussein et al. (2021)	2009–2018; USA	96	75	breast (30), gyn (20), heme (24), other (22)	Prior	Elective	28.1 (7.0)	34.9 (5.5)	Cancer group younger and no age adjustment.
Tamauchi et al. (2021)	2009–2020; Japan	14	30	gyn (14)	After	Multiple	34.8 (29.0–40.4)[c]	36.5 (22.9–42.8)[c]	No age adjustment but groups were comparable.
Fabiani et al. (2022)	2016–2019; Italy	82	180	breast (52), gyn (9), heme (15), other (6)	Prior	Multiple	32.2 (4.3)[b]	33.2 (5.1)	Groups additionally matched on date of ART.

[a]Cancer types without a sample size indicates that this data were not reported in the study.
[b]Cancer and non-cancer referent groups were age-matched or the study reported age-adjusted outcomes.
[c]Median (range) reported.
COS, controlled ovarian stimulation; gyn, gynecologic cancer; heme, hematologic malignancy; TSH, thyroid-stimulating hormone.

Most studies included a woman's first or only cycle of COS and reported outcomes per woman. Some studies included all cycles of COS per woman and reported certain outcomes per cycle; in those instances, number of cycles was used as the sample size. Reproductive outcomes are reported as the cumulative proportion of clinical pregnancy or live birth per woman, except for two studies that reported outcomes as per vitrification and warming cycle (Cobo et al., 2018), or per frozen embryo transfer cycle (Cardozo et al., 2015). Study authors were contacted for additional data when needed for inclusion in meta-analysis (e.g. reporting of only a median and range for a continuous outcome).

Risk of bias assessment

Risk of bias was assessed by one author (C.M.) using the U.S. Preventive Services Task Force criteria for assessing internal validity (U.S. Preventive Services Task Force, 2021). All studies included in the review were cohort studies and were assessed based on comparability of groups, loss to follow-up, measurement of variables and appropriate adjustment for confounders.

Statistical analysis

Stata 16.1 was used to calculate summary mean differences (MDs) for continuous outcomes and ORs for binary outcomes using random-effects meta-analysis. ORs rather than risk ratios were calculated because of the availability of adjusted ORs and 95% CIs in some studies that could be directly extracted rather than unadjusted summary statistics. Among-populations variance (τ^2) was estimated by restricted maximum likelihood. Both 95% CIs and 95% prediction intervals (PIs) are presented. The CI conveys probable values for the average treatment effect, but this range may not apply to all settings given among-study heterogeneity (Riley et al., 2011; IntHout et al., 2016). The PI accounts for this heterogeneity and presents the variation in effect on the same scale as the outcome, enhancing its interpretability relative to other measures of heterogeneity commonly presented such as I^2 (IntHout et al., 2016). The PI can be interpreted as the expected range of possible effects in similar future study populations (Riley et al., 2011; IntHout et al., 2016). Summary effect estimates with 95% CIs and 95% PIs were calculated for outcomes that were reported in at least three studies. R 3.5.1 was used to create forest plots.

Heterogeneity assessment

Heterogeneity was assessed using Cochran's Q statistic and PIs. Other measures of heterogeneity (I^2 and τ^2) are also presented within forest plots or summary tables. Subgroup analysis was used to investigate a priori covariates as possible sources of heterogeneity, including: age-matching or age-adjustment, referent group indication for ART, and study location (USA or non-USA). Study characteristics with at least three studies per stratum were eligible for inclusion in subgroup analysis. Most outcomes were also examined comparing women with breast cancer to a non-cancer referent group. Analyses across other cancer types were not possible due to lack of data.

Funnel plot asymmetry

Funnel plots were visually examined for asymmetry for outcomes with at least 10 studies; a scatter plot of the MD or OR (log scale) versus inverse-variance was examined (Sterne et al., 2011). The regression-based test of Egger was used to test the null hypothesis of funnel plot symmetry (Egger et al., 1997; Sterne et al., 2000, 2011). The trim-and fill-method to adjust for publication bias was used as a sensitivity analysis only, given that it tends to under-impute in cases of substantial among-study heterogeneity and is therefore anti-conservative (Peters et al., 2007). In cases of substantial visual funnel plot asymmetry, overall summary aggregation is not presented. R 3.5.1 was used to create funnel plots.

Sensitivity analyses

Continuous outcomes included data from some studies for which the mean and SD were approximated from the median and IQR. Given the potential limitations in this approach in the presence of highly skewed data (Wan et al., 2014), studies for which this approximation was done were excluded. We also had an a priori interest in assessing heterogeneity of effects by timing of ART initiation among women with cancer (i.e. ART initiated for cryopreservation of oocytes or embryos before cancer treatment or ART initiated after cancer treatment). However, only five studies exclusively included women who initiated ART after cancer treatment (Barton et al., 2012; Das et al., 2012; Fujimoto et al., 2014; Huang et al., 2021; Tamauchi et al., 2021). Instead, as a sensitivity analysis, we excluded studies which included women who initiated ART after cancer treatment, or which timing of ART initiation relative to cancer treatment was unknown. To make comparable to the two previous meta-analyses on this topic (Friedler et al., 2012; Turan et al., 2018), we present results restricted to studies which used age-matching or age-adjustment and only included women who initiated ART prior to cancer treatment.

Results

Study selection

Records were identified from two database searches (n = 8985) and PubMed search alerts (n = 3), which yielded a total of 6094 unique records for screening. After title and abstract screening, 133 full-text articles were assessed for eligibility and 42 studies met inclusion criteria. A PRISMA flow diagram of study identification and selection is presented in Fig. 1. Studies that examined outcomes after ovarian tissue cryopreservation (Dolmans et al., 2014) or in vitro maturation (Moria et al., 2011) were not included, nor were studies that included non-malignancies in the case group (Johnson et al., 2013). Three studies that initially met inclusion criteria were subsequently excluded because additional data were needed in order to be included in meta-analysis and study authors did not respond to data requests (Pavone et al., 2014; Kim et al., 2015; Brun et al., 2021).

Study characteristics

Table I details the main characteristics of the 42 included studies, including concerns regarding internal validity. Studies had a median of 58 women with cancer (IQR = 159) and 114 women without cancer (IQR = 348). Roughly half of studies (k = 22) were conducted in the USA; the other studies were conducted in Canada, Europe, Asia or South America. Study periods spanned from 1995 to 2020, with a median study duration of 8 years (IQR = 5). Among studies that reported sample sizes by cancer type (k = 39), studies were a majority women
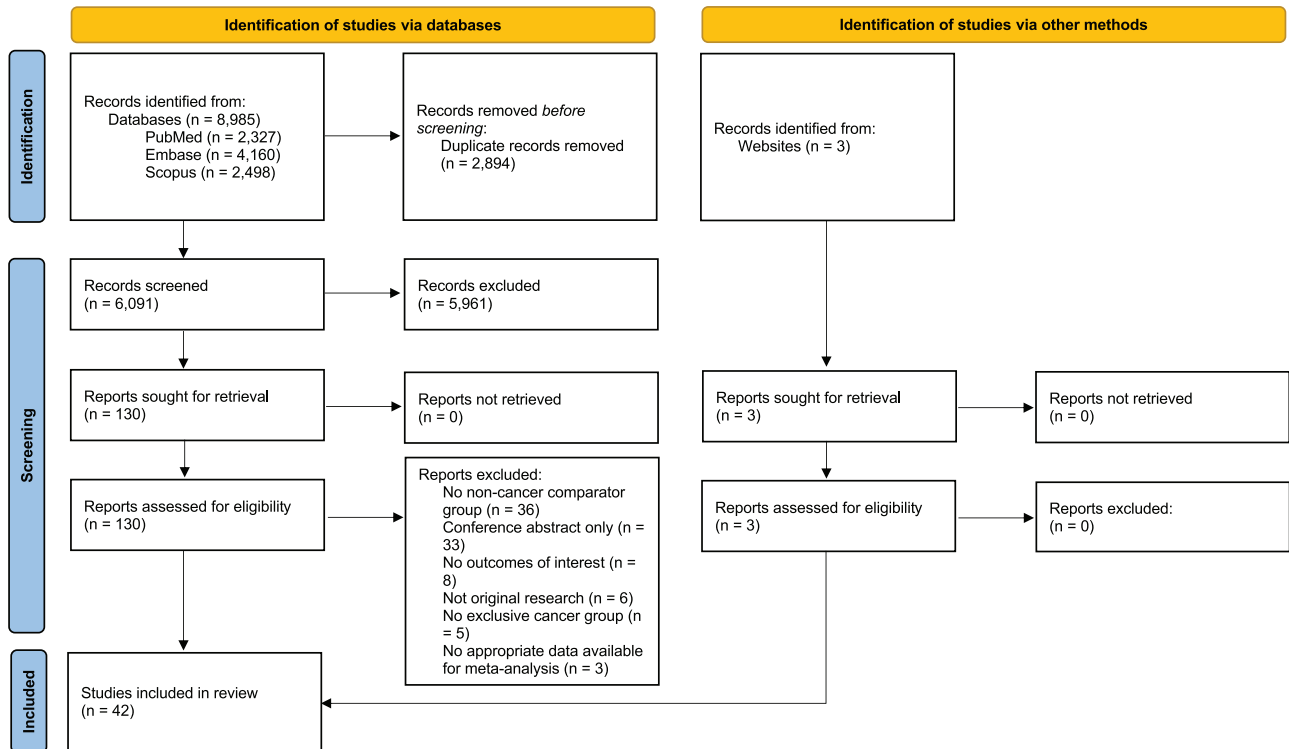
Figure 1. PRISMA flow diagram of study identification and selection.

with breast cancer (median = 42 women, IQR = 74), followed by hematologic malignancies (median = 15 women, IQR = 30), gynecologic cancers (median = 8 women, IQR = 14) and other cancers (median = 10 women, IQR = 2). Most studies included a mix of cancer types, though 10 were limited to one cancer type (k = 7 breast, k = 2 gynecologic and k = 1 glioma). The large majority of studies (k = 32) examined women with cancer who initiated ART prior to cancer treatment; five studies included women who initiated ART after cancer treatment; two studies included women who initiated ART before or after cancer treatment; and three studies reported unknown timing of ART initiation relative to cancer treatment. Many studies (k = 16) included women with multiple indications for ART in the non-cancer referent group, followed by women with male factor infertility (k = 13), elective cryopreservation (k = 9) or tubal factor infertility (k = 4). Three studies excluded women with ovarian insufficiency based on levels of FSH or anti-Müllerian hormone (AMH) among the cancer group only (Quintero et al., 2010) or among both the cancer and non-cancer groups (Goldrat et al., 2015, 2019).

Duration of COS

Twenty-five studies reported duration of COS (Table II and Supplementary Fig. S1; MD: 0.05; 95% CI: −0.21, 0.31; 95% PI: −1.16, 1.26). Twelve studies controlled for age, with one study additionally adjusting for BMI (Quinn et al., 2017). Among-study heterogeneity was high, but women with cancer can expect COS duration to

be within roughly 1 day of the duration among women without cancer. Studies conducted in the USA tended to observe a longer COS duration among women with cancer relative to studies outside the USA (Cochran's Q: 18.4, P < 0.0001), though the magnitude of difference was small (difference in MDs of <1 day) (Supplementary Table SIII). No large differences in summary estimates were observed for other study characteristics. The estimate among age-adjusted studies limited to women with cancer who initiated ART before cancer treatment (k = 11) was similar to the overall summary estimate (MD: 0.03; 95% CI: −0.38, 0.45; 95% PI: −1.45, 1.52). No funnel plot asymmetry was observed (Supplementary Fig. S2).

Total gonadotropin stimulation dose

Twenty-nine studies reported total gonadotropin dose administered during COS (Table II and Supplementary Fig. S3; MD: 228.20; 95% CI: −11.36, 467.77; 95% PI: −1059.38, 1515.79). Among-study heterogeneity was high and study-specific estimates were imprecise. Variability was most evident by referent indication for ART: in most settings, women with cancer received a higher gonadotropin dose than women with male factor infertility or multiple/other indications, while women with cancer received a lower dose than women who used ART for elective or donor indications (Cochran's Q: 19.9, P < 0.0001) (Supplementary Table SIII). Studies in the USA showed a more positive association between cancer history and gonadotropin dose (higher gonadotropin among women with cancer), while analysis among women

Table II Summary of ART outcomes comparing women with versus without a history of cancer.[a]

Outcome	# of studies	Sample size[b] median (IQR)		Cochran's Q (P-value)	Random-effects variance (τ^2)	MD (95% CI)[c]	(95% prediction interval)
		Cancer	Non-cancer				
Stimulation duration (days)	25	81 (158)	105 (375)	130.3 (<0.0001)	0.33	0.05 (−0.21, 0.31)	(−1.16, 1.26)
Total gonadotropin dose (IU)	29	50 (121)	97 (133)	369.7 (<0.0001)	378856.04	228.20 (−11.36, 467.77)	(−1059.38, 1515.79)
Peak estradiol (pg/ml)	17	40 (55)	97 (132)	n/a	n/a	n/a	n/a
Total oocytes	36	50 (135)	105 (291)	190.6 (<0.0001)	4.44	0.47 (−0.34, 1.29)	(−3.89, 4.84)
Mature oocytes	22	86 (141)	172 (288)	163.1 (<0.0001)	3.61	0.27 (−0.64, 1.18)	(−3.81, 4.35)
Maturation percentage	14	93 (1612)	89 (130)	n/a	n/a	n/a	n/a
Fertilization percentage	9	39 (37)	55 (74)	13.3 (0.10)	13.30	−1.81 (−5.73, 2.11)	(−11.65, 8.02)
Total embryos	10	46 (38)	151 (319)	11.3 (0.25)	0.09	−0.30 (−0.68, 0.08)	(−1.11, 0.51)

Outcome	# of studies	Sample size[a] median (IQR)		Cochran's Q (P-value)	Random-effects variance (τ^2)	OR (95% CI)[c]	(95% prediction interval)
		Cancer	Non-cancer				
Cycle cancellation	11	76 (181)	664 (3924)	77.9 (<0.0001)	0.83	1.85 (0.93, 3.67)	(0.20, 16.93)
Return for embryo transfer	4	466 (390)	423 (1512)	55.2 (<0.0001)	1.37	0.22 (0.07, 0.74)	(0.00, 64.98)
Clinical pregnancy	9	53 (54)	53 (645)	20.4 (0.009)	0.14	0.51 (0.35, 0.73)	(0.19, 1.35)
Live birth	10	42 (48)	50 (401)	23.7 (0.005)	0.19	0.56 (0.38, 0.83)	(0.19, 1.69)

[a]Summary aggregation is not reported for outcomes demonstrating funnel plot asymmetry.
[b]In most studies, sample size represents the number of women, but in studies that reported outcomes at the cycle level, sample size represents the number of cycles.
[c]Referent is women without a history of cancer.
IQR, interquartile range; OR, odds ratio.

with breast cancer only showed a less positive association compared to the overall summary estimate, though these subgroup estimates were imprecise. The estimate among age-adjusted studies limited to women with cancer who initiated ART before cancer treatment ($k = 12$) was similar to the overall summary estimate, though less precise (MD: 221.64; 95% CI: −188.77, 632.06; 95% PI: −1356.19, 1799.48). No funnel plot asymmetry was observed (Supplementary Fig. S4).

Peak estradiol level on day of triggering oocyte maturation

Seventeen studies reported peak estradiol levels during COS (Table II and Supplementary Fig. S5). Eleven studies controlled for age, with one study additionally adjusting for BMI (Quinn et al., 2017). Studies or subgroups within studies in which aromatase inhibitors (e.g. letrozole) or tamoxifen were used during COS to suppress estradiol were excluded from analysis (Bonardi et al., 2020).

Visual funnel plot asymmetry was observed and detected via Egger's test, and trim-and-fill imputed five hypothetically missing estimates on the left side (estimates showing lower peak estradiol among women with cancer) (Supplementary Fig. S6). An overall summary estimate is thus not provided, though study characteristics were examined as potential sources of asymmetry due to true heterogeneity or methodologic quality—as such characteristics, in addition to publication bias,

can contribute to funnel plot asymmetry (Sterne et al., 2011). The association varied by age-adjustment (lower estradiol among women with cancer in studies not age-adjusted); referent indication for ART (lower estradiol among women with cancer when compared with women who used ART for elective or donor indications); study location (lower estradiol among women with cancer in studies outside of the USA); and among women with breast cancer only (lower estradiol) (Supplementary Table SIII). Studies conducted outside the USA produced estimates that were generally more negative (lower estradiol among women with cancer) and less precise than estimates produced in the USA, and this heterogeneity appears to have driven the observed asymmetry (Supplementary Fig. S6).

Cycle cancellation

Eleven studies reported cycle cancellation (Table II and Supplementary Fig. S7; OR: 1.85; 95% CI: 0.93, 3.67; 95% PI: 0.20, 16.93). Among-study heterogeneity was high; studies tended to report point estimates on the right side of the null (positive association between a history of cancer and cycle cancellation), though study-specific estimates were imprecise. No funnel plot asymmetry was evident through visual assessment or Egger's test, but trim-and-fill imputed one hypothetically missing estimate, which moved the summary estimate downward and slightly closer to the null (OR from 1.85 to 1.73) (Supplementary Fig. S8). Higher cancellation among women with cancer was observed

in studies that were age-adjusted; when compared with women with male factor infertility (versus multiple/other indications); and in non-USA studies (Supplementary Table SIV). The estimate among age-adjusted studies limited to women with cancer who initiated ART before cancer treatment ($k = 5$) was similar to the overall summary estimate, though less precise (OR: 2.12; 95% CI: 0.57, 7.90; 95% PI: 0.03, 150.80).

Number of oocytes

Thirty-six studies reported the total number of oocytes retrieved after COS (Table II and Supplementary Fig. S9; MD: 0.47; 95% CI: −0.34, 1.29; 95% PI: −3.89, 4.84). Nineteen studies controlled for age, with one study additionally adjusting for BMI, total gonadotropin dose and letrozole use (Quinn et al., 2017). Among-study heterogeneity was high and showed variability by study characteristics. More oocytes were retrieved in women with cancer in studies that were not age-matched or when compared with women who used ART for elective/donor or tubal factor indications—though only one of the elective/donor studies controlled for age (Quinn et al., 2017), and the referent group was, on average, 1–7 years older than women with cancer across those studies (Supplementary Table SIII). Retrieval of more oocytes in women with cancer were also reported in studies conducted in the USA; when ART was initiated before cancer treatment; or when excluding studies which reported a median and IQR. The estimate among age-adjusted studies limited to women with cancer who initiated ART before cancer treatment ($k = 17$) was similar to the overall summary estimate (MD: 0.73; 95% CI: −0.44, 1.90; 95% PI: −3.79, 5.25).

No funnel plot asymmetry was evident through visual assessment or Egger's test, though trim-and-fill imputed six hypothetically missing estimates, which moved the summary estimate upward and further from the null (MD from 0.47 to 1.03) (Supplementary Fig. S10).

Number of mature oocytes

Twenty-two studies reported the total number of mature oocytes retrieved after COS (Table II and Supplementary Fig. S11; MD: 0.27; 95% CI: −0.64, 1.18; 95% PI: −3.81, 4.35). Eight studies controlled for age, with one study additionally adjusting for BMI, total gonadotropin dose, and letrozole use (Quinn et al., 2017). Among-study heterogeneity was high and showed variability by study characteristics. More mature oocytes were retrieved in women with cancer when compared to women who used ART for elective/donor indications (though similar to the total oocytes analysis, only one study controlled for age (Quinn et al., 2017)); and in studies conducted in the USA (Supplementary Table SIII). The estimate among age-adjusted studies limited to women with cancer who initiated ART before cancer treatment ($k = 8$) was similar to the overall summary estimate (MD: 0.08; 95% CI: −1.40, 1.55; 95% PI: −5.01, 5.16).

No funnel plot asymmetry was evident through visual assessment or Egger's test, though trim-and-fill imputed one hypothetically missing estimate, which moved the summary estimate upward and slightly further from the null (MD from 0.27 to 0.44) (Supplementary Fig. S12).

Oocyte maturation percentage

Fourteen studies reported oocyte maturation percentage after COS (Table II and Supplementary Fig. S13). Nine studies controlled for age, with one study additionally adjusting for BMI, total gonadotropin dose and letrozole use (Quinn et al., 2017). Visual funnel plot asymmetry was observed, and trim-and-fill imputed three hypothetically missing estimates on the left side (estimates showing lower oocyte maturation among women with cancer) (Supplementary Fig. S14). An overall summary estimate is thus not provided, though study characteristics were examined as potential sources of asymmetry. The association between cancer history and oocyte maturation percentage varied by age-adjustment (lower maturation among women with cancer in studies that were age-adjusted); study location (lower maturation among women with cancer in US studies); among women with breast cancer only (lower maturation); and in studies that were age-adjusted and only included women who initiated ART before cancer treatment (lower maturation) (Supplementary Table SIII). Studies conducted outside the USA produced estimates that were generally more positive (higher maturation among women with cancer) and slightly less precise than estimates produced in the USA, and this heterogeneity appears to have driven the observed asymmetry (Supplementary Fig. S14).

Fertilization percentage

Nine studies reported oocyte fertilization percentage (Table II and Supplementary Fig. S15; MD: −1.81; 95% CI: −5.73, 2.11; 95% PI: −11.65, 8.02). Study-specific estimates showed less heterogeneity, though they were imprecise. No clear patterns of association were observed by study characteristics in subgroup analysis (Supplementary Table SIII). The estimate among age-adjusted studies limited to women with cancer who initiated ART before cancer treatment ($k = 5$) was similar to the overall summary estimate (MD: −1.48; 95% CI: −5.62, 2.67; 95% PI: −8.21, 5.25).

Number of embryos

Ten studies reported the number of embryos obtained (Table II and Supplementary Fig. S16; MD: −0.30; 95% CI: −0.68, 0.08; 95% PI: −1.11, 0.51). Study-specific estimates showed less heterogeneity, with most studies estimating minimal differences by cancer history. Variability was observed by age-adjustment and cancer type: fewer embryos were obtained among women with cancer in studies that were age-adjusted (Cochran's Q: 6.6, $P = 0.01$), and in studies that included women with breast cancer only (Supplementary Table SIII). The estimate among age-adjusted studies limited to women with cancer who initiated ART before cancer treatment ($k = 5$) was similar to the overall summary estimate (MD: −0.50; 95% CI: −0.66, −0.34; 95% PI: −0.75, −0.25).

No funnel plot asymmetry was evident through visual assessment or Egger's test, though trim-and-fill imputed two hypothetically missing estimates, which moved the summary estimate downward and slightly further from the null (MD from −0.30 to −0.44) (Supplementary Fig. S17).

Proportion of return for embryo transfer

Four studies reported return for embryo transfer (Table II and Supplementary Fig. S18; OR: 0.22; 95% CI: 0.07, 0.74; 95% PI: 0.00,

64.98), of which one reported an age-adjusted estimate (Rodriguez-Wallberg et al., 2019). All studies observed a lower likelihood of return among women with cancer compared to women without cancer (summary OR: 0.22; 95% CI: 0.07, 0.74; 95% PI: 0.00, 64.98) (Table II), though follow-up times between groups were not necessarily comparable (e.g. Rodriguez-Wallberg et al., 2019 reported a mean follow-up time of 6.2 years in women with cancer compared to 7.8 years in women without cancer). Given the small number of studies, no subgroup analyses were conducted. Referent groups in these studies included male factor ($k = 1$), elective or donor indications ($k = 1$), and multiple/other indications ($k = 2$); three of the studies were conducted outside the USA; and two studies only included women who initiated ART before cancer treatment.

Oocyte or embryo survival percentage after freeze and thaw

Two studies reported oocyte or embryo survival after freeze and thaw. In one study that used vitrification, 81.8% of oocytes survived among women with cancer versus 83.9% among women undergoing elective fertility preservation, though among women who were aged ≤35 years at cryopreservation, women with cancer had lower oocyte survival (81.2% versus 91.4%) (Cobo et al., 2018). A second study that used slow-freezing reported that 62.8% of embryos survived over all transfer cycles among women with cancer versus 72.0% among women who froze embryos to reduce the risk of ovarian hyperstimulation syndrome (Sabatini et al., 2011).

Implantation percentage

Four studies reported data on implantation, though none reported the denominator of number of embryos transferred and thus could not be meta-analyzed. Over all transfer cycles, implantation ranged from 12.9% to 32.5% among women with cancer and 29.9–43.8% among women without cancer (Sabatini et al., 2011; Cardozo et al., 2015; Cobo et al., 2018). Per embryo transferred, women with cancer had 4.9% of embryos implant versus 21.0% among women without cancer (Fujimoto et al., 2014).

Clinical pregnancy after embryo transfer

Nine studies reported clinical pregnancy after embryo transfer (Table II and Supplementary Fig. S19; OR: 0.51; 95% CI: 0.35, 0.73; 95% PI: 0.19, 1.35). Six studies controlled for age, including one study that additionally adjusted for parity, cumulative gonadotropin dose, infertility diagnosis and number of diagnoses, number of ART cycles, state of residency and year of ART treatment (Luke et al., 2016a); and one study among women with thyroid cancer that additionally adjusted for free T4, thyroid-stimulating hormone and fertilization method (Huang et al., 2021). On average, women with cancer had a lower likelihood of clinical pregnancy compared to women without cancer. Subgroup differences were observed by study location, with studies conducted in the USA observing a stronger negative association of cancer on pregnancy (Cochran's Q: 17.0, $P < 0.0001$) (Supplementary Table SIV). Only two studies were age-adjusted and limited to women with cancer who initiated ART before cancer treatment (OR: 0.63; 95% CI: 0.41, 0.98).

The use of gestational carriers is an additional clinically relevant factor to consider in these studies, but could not be assessed given the lack of data. Two studies reported that 48–67% of women with cancer used a gestational carrier (ART initiated before cancer treatment in both studies), while no gestational carriers were reported in the non-cancer group, though pregnancy rates by gestational carrier use were not reported (Sabatini et al., 2011; Cardozo et al., 2015). All other studies either excluded outcomes using gestational carriers, or were conducted in countries where surrogacy is not legal or regulated.

Live birth after embryo transfer

Ten studies reported live birth after embryo transfer (Table II and Supplementary Fig. S20; OR: 0.56; 95% CI: 0.38, 0.83; 95% PI: 0.19, 1.69). Seven studies controlled for age, including one study that additionally adjusted for parity, cumulative gonadotropin dose, infertility diagnosis and number of diagnoses, number of ART cycles, state of residency and year of ART treatment (Luke et al., 2016a); one study that additionally adjusted for infertility diagnosis, prior IVF and fertilization method (Sabatini et al., 2011); and one study among women with thyroid cancer that additionally adjusted for free T4, thyroid stimulating hormone, and fertilization method (Huang et al., 2021). On average, women with cancer had a lower likelihood of live birth compared to women without cancer. No meaningful differences in the summary estimate were observed by study characteristics (Supplementary Table SIV). The estimate among age-adjusted studies limited to women with cancer who initiated ART before cancer treatment ($k = 3$) was similar to the overall summary estimate (OR: 0.58; 95% CI: 0.36, 0.94; 95% PI: 0.03, 13.15). Adverse birth outcomes (e.g. preterm birth or low birth weight) were only reported in two studies (Garcia-Velasco et al., 2013; Huang et al., 2021) and could not be examined.

No funnel plot asymmetry was evident through visual assessment or Egger's test, though trim-and-fill imputed one hypothetically missing estimate, which did not substantively change the summary estimate (Supplementary Fig. S21).

Risk of bias assessment

Eleven of 42 studies (26%) had no or inadequate control for age differences between cancer and non-cancer groups for some or all outcomes (Table I). In 10 of those studies, the cancer group was, on average, 2.2–6.8 years younger than the non-cancer group at ART initiation.

Discussion

This systematic review and meta-analysis of 42 studies provides an updated summary of ART outcomes comparing women with and without a history of cancer, including the first synthesis, to our knowledge, of reproductive outcomes after embryo transfer. Substantial among-study heterogeneity was observed for COS duration, total gonadotropin dose, cycle cancellation, total oocytes and mature oocytes; and evidence of appreciable funnel plot asymmetry was observed for peak estradiol and oocyte maturation percentage. However, our meta-analysis found that, on average, women with cancer had lower odds of return for embryo transfer, clinical pregnancy, and live birth, suggesting potentially adverse effects of cancer and its treatment on reproductive success using ART.

Two systematic reviews with meta-analyses on this topic have been previously published (Friedler et al., 2012; Turan et al., 2018). In a 2012 review of 7 studies, the authors concluded that, compared to women without cancer who used ART, women with cancer received a lower total gonadotropin dose, had lower peak estradiol levels, and had fewer total and mature oocytes retrieved (Friedler et al., 2012). In contrast, in a 2018 review of 10 studies (including the same seven studies as the 2012 review), the authors concluded that cancer was not associated with a differential response to ART for any outcome examined (Turan et al., 2018). However, neither previous review assessed study characteristics contributing to among-study heterogeneity nor examined likelihood of pregnancy or live birth. Importantly, our review used broader search criteria (including the search of two additional databases) and included three additional years of data, capturing 14 studies published after the end date of the 2018 review.

Notably, we found, on average, a lower likelihood of clinical pregnancy and live birth after ART among women with cancer, even among women who had initiated ART before cancer treatment for fertility preservation. It is well-documented that cancer treatments including chemotherapy and abdominal-pelvic radiation can rapidly accelerate the decline of a woman's primordial follicles, or ovarian reserve, and result in immediate or premature ovarian failure (Lee et al., 2006; Knopman et al., 2010; Levine et al., 2015; Poorvu et al., 2019; Spears et al., 2019). But even among women who cryopreserve oocytes or embryos before cancer treatment, reproductive outcomes after ART may still be affected by radiation or surgical treatments that damage reproductive organs, impair cardiovascular or pulmonary function, or cause dysfunction of the hypothalamic-pituitary-gonadal axis (Critchley and Wallace, 2005; Lee et al., 2006; Wo and Viswanathan, 2009; Knopman et al., 2010; Poorvu et al., 2019; Griffiths et al., 2020). Given our findings, further exploration of how specific cancer treatments may affect these associations is warranted.

Though we observed lower reproductive success among women with cancer, evidence was not conclusive regarding differences in the number of total oocytes, mature oocytes or embryos obtained—all of which are clinically significant predictors of ART success (van Loendersloot et al., 2010; McLernon et al., 2016; Practice Committee of the American Society for Reproductive Medicine, 2019; Lambertini et al., 2020). Heterogeneity across these outcomes was observed by age-adjustment, referent indication for ART, study location and among women with breast cancer. Further examination of heterogeneity related to these study characteristics and other cancer- and ART-related factors is needed within larger studies that control for age, including the influence of institutional- or country-level variation in COS protocols and differential response by cancer type.

We additionally found that women with cancer, on average, were less likely to return after oocyte or embryo cryopreservation to attempt pregnancy, an outcome that had not been synthesized in prior meta-analyses. However, this result should be interpreted in the context of the small number of studies analyzed (four), the duration of follow-up after ART initiation across studies, and the potential for selection bias. Regarding follow-up, one study reported shorter follow-up among women with cancer compared to the referent group (6.2 versus 7.8 years) (Rodriguez-Wallberg et al., 2019); one pilot study reported a mean follow-up of all women of 2 years (Luke et al., 2016b); and two studies reported 5–11.5 years of ART data but did not report average follow-up per woman (Garcia-Velasco et al., 2013;

Cobo et al., 2018). Additional studies with longer follow-up (at least 10 years) are needed to assess whether lower return among women with cancer persists, and to identify the barriers to return. If and when women return after cryopreservation may be influenced by recommendations to wait to attempt pregnancy for at least 1 year after completion of cancer treatment to decrease the likelihood of pregnancy complications (Hartnett et al., 2018; ESHRE Guideline Group on Female Fertility Preservation et al., 2020); return may also be influenced by physician beliefs that pregnancy after cancer (particularly for hormone-sensitive cancers) may increase the risk of recurrence (Lambertini et al., 2018), though the safety of both fertility preservation and pregnancy for these patients has been demonstrated (Lambertini et al., 2021; Arecco et al., 2022). Additionally, women with hormone-sensitive cancers may receive up to 10 years of endocrine therapy and may choose to attempt pregnancy after (rather than interrupting) such treatment (Lambertini et al., 2020).

Regarding potential selection bias, returning for transfer after cryopreservation is conditional on being alive and also on not being able to conceive naturally. Though cancer survival among reproductive-age women is high, 10–20% will die within 5 years (Close et al., 2019), higher than would be expected in the general infertile population without cancer. Additionally, women with a history of cancer could be more likely to conceive naturally compared to the general infertile population because the infertile population, by definition, has been unsuccessful in conceiving for at least 12 months; in contrast, in certain circumstances, women with cancer may maintain some fertility after cancer treatment and may not require use of their previously frozen oocytes or embryos. Thus, cancer history is associated with two factors that are being selected on for inclusion into the sample for this analysis (i.e. women with cancer are more likely to die and may be more likely to naturally conceive), which may contribute to the lower likelihood of return among women with cancer.

Appreciable funnel plot asymmetry was observed for estradiol peak and oocyte maturation percentage, which could result from publication bias, poor methodological quality, true heterogeneity or chance (Sterne et al., 2011). In this literature, we hypothesized that publication bias would result in the lower likelihood of publishing small studies that find more favorable ART outcomes among women with cancer. What we observed were gaps in the funnel plots for small studies that showed lower estradiol among women with cancer (unclear clinical favorability (Kosmas et al., 2004; Karatasiou et al., 2020)) and lower oocyte maturation percentage among women with cancer (less favorable). Given this, publication bias is not likely to be appreciable in this literature. The observed asymmetry may have been produced, instead, by true heterogeneity. For both estradiol peak and oocyte maturation percentage, we observed heterogeneity by study location that appears to have produced the asymmetry (generally less precise estimates produced in studies conducted outside the USA that drove estimates a certain direction).

Our results are limited by the potential for confounding by age; age at ART initiation is one of the strongest predictors of reproductive success (van Loendersloot et al., 2010; McLernon et al., 2016), but more than one in four studies reported baseline differences in age between cancer and non-cancer groups and lacked adequate control for these differences in study design or analysis. Results should also be interpreted in the context of substantial among-study heterogeneity, which did not appear to be fully explained by age-adjustment, referent group indication for ART, or study location.

Further, we lacked sufficient data to explore other relevant cancer- and ART-related factors that could influence our results. Such factors need further examination in larger studies, including outcomes by cancer type (particularly cancers other than breast), cancer treatments received, and other prognostic factors (e.g. BRCA mutation status); COS protocol and oocyte maturation trigger; type of embryo transfer (fresh versus frozen/thawed); and use of gestational carriers. We were also not able to examine differences by race and ethnicity, as most studies did not report such distributions, even though prior research demonstrates that racial and ethnic groups who are minoritized, particularly Black women, experience lower pregnancy and birth rates after ART (Huddleston et al., 2010; Seifer et al., 2020; Makhijani et al., 2021). The lack of reporting of race and ethnicity within this field precludes documentation of disparities in fertility treatment and outcomes (Krieger, 2021) and should be a focus for future research. Outcomes after ovarian tissue transplantation and in vitro maturation are also important to assess as these procedures become more common in clinical practice, particularly among prepubertal patients or those who need to start cancer treatment urgently (Practice Committee of the American Society for Reproductive Medicine, 2019).

Nevertheless, our review contributes new perspectives to this growing field of research, including the first synthesis, to our knowledge, of reproductive outcomes after ART. We were able to assess heterogeneity in observed associations across multiple a priori factors, including referent group indication for ART and study location, and examined outcomes subset to women with breast cancer and women who initiated ART before cancer treatment. Unfortunately, women with cancer continue to face a multitude of barriers in accessing ART for fertility preservation at the time of diagnosis (Jones et al., 2017; Logan et al., 2018; Covelli et al., 2019) and may not access fertility services until after cancer treatment, indicating a need for further study of how previous exposure to gonadotoxic therapies (e.g. chemotherapy) affects predictors of ART success (i.e. quantity and quality of oocytes and embryos) and subsequent pregnancy and birth rates (Practice Committee of the American Society for Reproductive Medicine, 2019).

In summary, we observed substantial among-study heterogeneity or funnel plot asymmetry that was not fully explained by the examined study characteristics for most outcomes. However, women with cancer, on average, were less likely to return for embryo transfer and less likely to have a clinical pregnancy or live birth after embryo transfer. Larger-scale studies with longer follow-up (from cancer diagnosis, to ART initiation, to pregnancy attempt and live birth) and comprehensive assessment of potentially influential patient-, cancer- and ART-related factors are needed to improve data on ART outcomes for cancer populations. Future studies should account for differences by age, BRCA status, AMH levels and COS protocol between cancer and comparator groups through study design or analysis and should consider improving data in areas with existing gaps, including: understanding the barriers to return after cryopreservation and how outcomes may differ based on time since last cancer treatment; examining the effect of specific cancer treatments (e.g. chemotherapeutic agents or pelvic radiation dosage) on ART outcomes (including pregnancy complications and adverse birth outcomes); assessing outcomes by race and ethnicity; and studying outcomes after ovarian tissue transplantation and in vitro maturation.

Though questions remain, these data add to the body of evidence available to clinicians who provide fertility counseling to women with cancer—a body of evidence acknowledged to be severely lacking by leading oncology and reproductive societies (Practice Committee of the American Society for Reproductive Medicine, 2019; Lambertini et al., 2020). Researchers, clinicians and policymakers should continue to increase access to fertility treatment at the time of cancer diagnosis and into survivorship; refine ovarian stimulation and embryo transfer protocols for individuals with cancer to maximize safety, efficiency, and effectiveness; and reduce the gonadotoxicity of cancer treatments to improve fertility-related outcomes after cancer diagnosis.

Supplementary data

Supplementary data are available at Human Reproduction online.

Data availability

The data underlying this article are available in the article and its supplementary material.

Authors' roles

C.M.: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing—original draft, writing—review & editing; C.P.: methodology, supervision, writing—review & editing; S.M.E.: writing—review & editing; J.A.R.-H.: writing—review & editing; B.L.: writing—review & editing; and H.B.N.: supervision, writing—review & editing.

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Conflict of interest

J.A.R.-H. reports receiving consulting fees from Schlesinger Group and Guidepoint. The remaining authors declare no conflicts of interest.

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