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Association of platinum-based chemotherapy with live birth and infertility in female survivors of adolescent and young adult cancer

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Objective: To estimate the effect of platinum-based chemotherapy on live birth (LB) and infertility after cancer, in order to address a lack of treatment-specific fertility risks for female survivors of adolescent and young adult cancer, which limits counseling on fertility preservation decisions.
Design: Retrospective cohort study.
Setting: US administrative database.
Patients: We identified incident breast, colorectal, and ovarian cancer cases in females aged 15–39 years who received platinum-based chemotherapy or no chemotherapy and matched them to females without cancer.
Intervention: Platinum-based chemotherapy.
Main Outcome Measures: We estimated the effect of chemotherapy on the incidence of LB and infertility after cancer, overall, and after accounting for competing events (recurrence, death, and sterilizing surgeries).
Results: There were 1,287 survivors in the chemotherapy group, 3,192 in the no chemotherapy group, and 34,147 women in the no cancer group, with a mean age of 33 years. Accounting for competing events, the overall 5-year LB incidence was lower in the chemotherapy group (3.9%) vs. the no chemotherapy group (6.4%). Adjusted relative risks vs. no chemotherapy and no cancer groups were 0.61 (95% confidence interval [CI] 0.42–0.82) and 0.70 (95% CI 0.51–0.93), respectively. The overall 5-year infertility incidence was similar in the chemotherapy group (21.8%) compared with the no chemotherapy group (20.7%). The adjusted relative risks vs. no chemotherapy and no cancer groups were 1.05 (95% CI 0.97–1.15) and 1.42 (95% CI 1.31–1.53), respectively.
Conclusions: Cancer survivors treated with platinum-based chemotherapy experienced modestly increased adverse fertility outcomes. The estimated effects of platinum-based chemotherapy were affected by competing events, suggesting the importance of this analytic approach for interpretations that ultimately inform clinical fertility preservation decisions. (Fertil Steril® 2024;121:1020–30. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Platinum chemotherapy, live birth, infertility, cancer

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Approximately 50,000 female adolescents and young adults (AYAs) aged 15–39 years are diagnosed with cancer annually in the United States (1, 2). Data suggest overall poorer fertility outcomes. Female AYA cancer survivors are more likely to experience infertility compared with siblings (15%–27% vs. 7%) and less likely to have a live birth (LB) (standardized birth ratio 0.5) (3–6). Importantly, adverse fertility risks vary by cancer type and cancer treatment (7–12). However, data are limited to a few treatments, i.e., alkylating chemotherapy (13–15), cranial and pelvic radiation (4, 15, 16), and cervical trachelectomy (17). The lack of treatment-specific risk estimates for many cancer treatments is a barrier to accurate risk counseling and fertility preservation decision-making.

Platinum agents are commonly used in AYA cancers. We demonstrated that the ovarian reserve marker antimüllerian hormone follows a similar pattern after platinum-based chemotherapy as after cyclophosphamide-based chemotherapy in breast cancer survivors, suggesting platinating agents incur harm to the finite ovarian reserve (18). These findings are consistent with ovarian primordial follicle apoptosis after exposure in rodents and 1 report of increased premature ovarian insufficiency after exposure in AYA cancer survivors (19–21). However, small cohorts of female AYA cancer survivors exposed to platinum-based chemotherapy, mostly with germ cell tumors, have reported favorable menstrual and LB outcomes (22–24). Hence, evidence-based fertility preservation counseling for patients receiving platinum agents is limited by scant and contradictory data.

Competing events—endpoints that preclude the occurrence of the primary outcome—are commonly overlooked but important to address to interpret studies accurately (25–28). This is particularly relevant when studying fertility after cancer. Whether recurrence, metastasis, or death occur, competing events such as deaths can contribute to fewer infertility diagnoses and LBs, not because of a direct effect but rather because they preclude fertility attempts from occurring. Censoring alone at the time of occurrence of competing events is commonly used but can result in bias because this approach considers risk because of exposure among those with competing events similar to when they had dropped out of the study randomly (27, 29). Separable effect analysis is a recently developed approach for data with competing risks that is well suited for assessing fertility after cancer by estimating an exposure's total effect and direct effect.

Clinically, the total effect of platinum-based chemotherapy on fertility is the overall likelihood of birth and infertility after this exposure, which can be used to counsel patients on their overall prognosis. In contrast, the direct effect isolates the effect attributable to platinum-based chemotherapy. This is important for fertility preservation decisions, which are made in large part when a treatment directly causes adverse fertility outcomes.

The objective was to evaluate fertility in female AYA cancer survivors who receive platinum-based chemotherapy overall and after accounting for competing events. We hypothesized that after accounting for competing events, platinum-based chemotherapy causes fewer births and more infertility, compared with fertility outcomes in cancer survivors with no chemotherapy and females without cancer.

MATERIALS AND METHODS

Data Source

A retrospective cohort study was conducted using administrative claims data from OptumLabs Data Warehouse, which contains over 200 million deidentified, commercially insured patients in the United States (30, 31). The data include longitudinal health information in the form of medical and pharmacy claims and enrollment records. Claims are verified and adjudicated before inclusion in the research dataset. Diagnoses, treatments, and outcomes were obtained using the International Statistical Classification of Diseases (ICD9/ICD10), Current Procedural Terminology, Diagnosis Related Group, and Healthcare Common Procedure Coding System codes (Supplemental Table 1, available online). Code combinations are sensitive and specific for identifying incident cancers, cancer treatment, fertility outcomes, and competing risks (32–40). Our study spanned July 1, 2005, until December 31, 2019. We required continuous medical and pharmacy coverage until the end of a participant's enrollment in that health plan. The study was exempt from institutional review board approval.

Study Population

Identification of incident breast, colorectal, and ovarian cancers. We identified females diagnosed with cancer by querying for ICD9/ICD10 cancer diagnosis codes, requiring ≥ 2 codes for the same cancer site within 12 months (41, 42). To identify incident cancer, we required an observed 6-month continuous enrollment period without any cancer diagnosis before the first cancer diagnosis code. We retained those aged 15–39 years at cancer diagnosis.

Because platinum-based chemotherapies are first-line treatment options for breast, ovarian, and colon cancer, we restricted our analysis to these cancers. To further identify incident cases, this cohort was restricted to those who underwent surgery related to their cancer site, e.g., lumpectomy for breast cancer (43–45). Patients who underwent an initial bilateral oophorectomy or hysterectomy were excluded. Survivors were followed until fertility outcomes, competing events, disenrollment, or the end of the study (December 2019), whichever came first.

Defining exposure groups. Chemotherapy group: we identified all chemotherapy, endocrine therapy, and biologic therapy. Platinum-based chemotherapy was classified on the basis of at least 2 administrations (to minimize low-dose exposure) of carboplatin, cisplatin, or oxaliplatin (46). Those who received alkylating chemotherapy before or during initial treatment were excluded. The index date was defined as the first date of platinum-based chemotherapy administration.

No chemotherapy group: cancer survivors who underwent cancer-related surgery within 6 months of the first cancer-related ICD code and did not receive any chemotherapy within 6 months of their cancer surgery were classified into the group. The index date was the surgery date.

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No cancer group: a cancer-free group was selected by matching (up to 10:1) females without cancer codes to cancer survivors by birth year, race, and observation time (i.e., length of continuous enrollment before and after the index cancer date and start and end date of the matched cancer survivor) (47). Assignment of index dates for all groups and matching on observation time were used to minimize the potential for mismatched time zero, immortal time bias, and balance factors related to disenrollment (48).

Outcomes

The primary fertility outcomes were LB and infertility after the index date, with the index date defined as the first day of platinum-based chemotherapy for the chemotherapy group, the cancer surgery date for the no chemotherapy group, and, for the no cancer group, the index date assigned to the matched cancer survivor.

Identification of births. Pregnancy episodes and outcomes were identified using an algorithm that was developed and validated in multiple US and United Kingdom administrative databases (49). Briefly, among pregnancies, LBs were identified. Then, the pregnancy start dates of these births were estimated using claims that included gestational age at birth and the timing of testing for pregnancy markers. Live births where the pregnancy start date was $\geq$12 months from the index date (to exclude pregnancy-associated cancer) were retained.

Identification of preexisting and incident infertility. Infertility before and after a cancer diagnosis was determined using claims for infertility diagnoses and treatments (assisted reproductive technology) (40, 50, 51). Infertility diagnoses and treatments before a cancer diagnosis were designated as preexisting infertility. After a cancer diagnosis, claims for infertility diagnoses and treatments were retained and designated incident infertility. Claims for fertility preservation counseling and fertility preservation treatment were not counted as incidents of infertility.

Competing Events and Covariates

Competing events were bilateral oophorectomy or salpingectomy, hysterectomy, and/or tubal ligation, recurrence, secondary malignancy, and death. Recurrence was defined as chemotherapy, radiation, or cancer-related surgery after a surveillance period of at least 90 days where no chemotherapy, radiation, or surgery occurred. Validation studies report sensitivities of 80%–100% and specificities of 89%–99% for identifying recurrences (52–55). Because follow-up ended with competing events, estimates of fertility outcomes are unaffected by treatments related to recurrence occurring after observation time ended.

Covariates included radiation, obesity, smoking, race and ethnicity, year of birth, household income, as well as education.

Statistical Analysis

Participant characteristics, competing events, and outcomes were compared among the platinum-based chemotherapy, no chemotherapy and cancer groups. A schematic illustrates the relationships among exposure, outcomes, competing events, and confounders (Supplemental Fig. 1, available online).

We used an extension of the parametric g-formula for the estimation of separable effects on posttreatment LB and infertility risks as an approach to estimate counterfactual risks and address competing events (25, 56). Counterfactual risks refer to the hypothetical likelihood of LB and infertility when an exposed group (i.e., a platinum-based chemotherapy group) did not have as many competing events (e.g., hysterectomy or cancer recurrence) that precluded pregnancy attempts as an unexposed group (i.e., no chemotherapy and no cancer groups). Under the separable effects approach, we used pairwise comparisons of exposure groups to decompose a total causal effect into an indirect effect on outcomes because of the influence of competing events and a direct effect on outcomes through other mechanisms, allowing for causal inference in data affected by competing events (56). Accordingly, direct effects represent counterfactual comparisons between groups (e.g., platinum-based chemotherapy vs. no chemotherapy) when competing events in both groups were equal.

To control for confounding, models for LB were adjusted for time-to-event (outcome or competing event), age at index date, education, income, race, obesity, smoking, radiation, and infertility before cancer. Models of infertility included age at index date, education, income, race, obesity, ever smoking, and radiation as covariates. We estimated counterfactual outcomes to determine 5-year risks for each group overall and survival curves for up to 10 years after the index date under varying competing event probabilities. Pairwise comparisons of these counterfactual 5-year risks were used to determine adjusted relative risks (aRR), and 95% confidence intervals (CI) were determined using the 2.5th and 97.5th percentiles from a nonparametric bootstrap. Subgroup analyses were performed by cancer type, age, and restricting the study period from 2010–2019 to consider temporal advances in cancer therapy. Sensitivity analysis was performed by restricting infertility outcomes to infertility and assisted reproductive technology treatments >12 months after the index date. Statistical analyses were performed in R.

RESULTS

Among 46,064 AYA female cancer survivors, there were 6,684 breast, 982 colon, and 1,031 ovarian cancer survivors (Supplemental Fig. 2, available online). There were 576 breast, 363 colon, and 348 ovarian cancer survivors in the chemotherapy group, 2,351 breast, 277 colorectal, and 564 ovarian cancer survivors in the no chemotherapy group, and 34,147 females in the no cancer group. Participant characteristics, competing events, and outcomes by group are in Table 1. In the chemotherapy group, the median time between the chemotherapy start and the date of cancer-related surgery was 31 days. No meaningful differences were observed among the groups regarding mean age (years) at index date (33.9, 33.5, and 33.2) and median

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TABLE 1

Participant characteristics by group.[a]

Characteristics	Platinum-based chemotherapy N = 1,287	No chemotherapy N = 3,192	No cancer N = 34,147	*P* value
Cancer type (No. %)				<.001
Breast	576 (44.8)	2,351 (73.7)	NA	
Colorectal	363 (28.2)	277 (8.7)	NA	
Ovarian	348 (27.0)	564 (17.7)	NA	
Age (y) at index date (mean, ±SD)	33.9 (5.0)	33.5 (5.6)	33.2 (5.0)	<.001
Year of index date (No. %)				
2000–2004	74 (5.7)	230 (7.2)	2,301 (6.7)	<.001
2005–2009	327 (25.4)	1,298 (40.7)	12,062 (35.3)	
2010–2014	435 (33.8)	1,076 (33.7)	11,961 (35.0)	
2015–2019	451 (35.0)	588 (18.4)	7,823 (22.9)	
Length of continuous enrollment in days (median, interquartile range)	1,768 (1,064–2,739)	1,672 (943–2,737)	1,765 (1,825–3,864)	.07
Length of continuous enrollment after the index date in days (median, interquartile range)	595 (309–1,158)	627 (239–1,376)	634 (277–1,272)	<.001
Race/ethnicity (No. %)				<.001
Asian	81 (6.3)	236 (7.4)	2,015 (5.9)	
Black	204 (15.9)	514 (16.1)	5,177 (15.2)	
Hispanic	155 (12.0)	429 (13.4)	3,781 (11.1)	
White	579 (45.0)	1,486 (46.6)	15,247 (44.7)	
Unknown	268 (20.8)	527 (16.5)	7,927 (23.2)	
Income (No. %)				
<$40,000	302 (23.5)	676 (21.2)	6,457 (18.9)	<.001
$40,000–74,999	346 (26.9)	719 (22.5)	7,550 (22.1)	
$75,000–124,999	287 (22.3)	555 (17.4)	7,951 (23.3)	
$125,000–199,999	98 (7.6)	365 (11.4)	3,422 (10.0)	
$200,000+	59 (4.6)	193 (6.0)	1,760 (5.2)	
Unknown	195 (15.2)	555 (17.4)	7,951 (23.3)	
Education (No. %)				<.001
<12th grade	25 (1.9)	84 (2.6)	829 (2.4)	
High school diploma	554 (43.0)	1,296 (40.6)	13,075 (38.3)	
<Bachelor degree	567 (44.1)	1,418 (44.4)	14,381 (42.1)	
Bachelor degree +	117 (9.1)	335 (10.5)	3,245 (9.5)	
Unknown	24 (1.9)	59 (1.8)	2,617 (7.7)	
Obesity (No. %)	392 (30.5)	775 (24.3)	8,962 (11.3)	<.001
Smoking (No. %)	226 (17.6)	602 (18.9)	6,362 (18.6)	<.001
Infertility before the index date (No. %)	365 (28.4)	795 (24.9)	5,331 (15.6)	<.001
Systemic therapy (No. %)				
Biologic therapy	595 (46.2)	<11 (<0.3)	NA	<.001
Endocrine therapy	223 (17.3)	571 (17.9)	NA	.65
Radiation therapy	242 (18.8)	479 (15.0)	NA	.001
Competing events[b]				
Recurrence (No. %)	153 (11.9)	221 (6.9)	0 (0)	<.001
End-of-life services (No. %)	44 (3.4)	34 (1.1)	75 (0.2)	<.001
Secondary malignancy (No. %)	496 (38.5)	339 (10.6)	0 (0)	<.001
Death (No. %)	251 (19.5)	159 (5.0)	569 (1.7)	<.001
Sterilizing surgery (No. %)	140 (10.8)	577 (18.0)	2,064 (6.0)	<.001
Outcomes after cancer				
Infertility (No. %)	345 (26.8)	799 (25.0)	6,544 (19.2)	<.001
Live birth (No. %)	36 (2.8)	196 (6.1)	1,778 (5.2)	<.001

Note: CMS = Centers for Medicare and Medicaid Services; NA = not applicable; No. = number; SD = standard deviation.

[a] To maintain the deidentified nature of the OptumLabs Data Warehouse and in line with CMS's policy to minimize the risk. of reidentifying an individual, all summary tables may not display cells on identifiable patient attributes with <11 patients.

[b] An individual can experience multiple competing events over follow-up. In analysis, the earliest competition was used.

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follow-up (years) after index date (1.6, 1.7, and 1.7). Compared with the no chemotherapy group, the chemotherapy group was more likely to have colorectal or ovarian cancer and undergo biologic therapy, e.g., immunotherapy. The chemotherapy group had a higher incidence of competing events than the other 2 groups.

Live Birth—No Chemotherapy group vs. No Cancer Group

The overall 5-year cumulative LB incidence was 6.4% in the no chemotherapy group compared with 6.9% in the no cancer group (aRR 0.94, 95% CI 0.82–1.08) (total effect, Table 2). Accounting for competing events, LBs were then modestly

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higher in the no chemotherapy group (7.9%); the aRR comparing LB probabilities when the no chemotherapy group had similar competing events as the no cancer group was 1.16 (95% CI 1.02–1.34) (direct effect, Table 2). These results suggest that the lower overall likelihood of LBs in the no chemotherapy group is largely explained by more competing events in patients with cancer. In models of estimated 10-year incidence of LB, the no cancer group (black line, Fig. 1A) was similar to that in the no chemotherapy group when accounting for competing events (dashed green line), whereas lower total incidence was observed among the no chemotherapy group in models not accounting for competing events.

Live Birth—Platinum-Based Chemotherapy Group vs. No Chemotherapy or No Cancer Group

The overall 5-year cumulative LB incidence for the chemotherapy group (2.9%) was lower than the no chemotherapy group (aRR 0.46, 95% CI 0.31–0.61) and the no cancer group (aRR 0.42, 95% CI 0.29–0.57) (total effect, Table 2). Accounting for competing events, estimated 5-year LB incidence with chemotherapy remained lower than in the no chemotherapy group (aRR 0.61, 95% CI 0.42–0.82) and no cancer group (aRR 0.70, 0.51–0.93) (direct effect, Table 2). The estimated 10-year incidence of LB for the chemotherapy group (solid red line, Fig. 1B), chemotherapy accounting for competing events (dotted red line), no chemotherapy group (green line), and no cancer group (black line) groups showed fewer LBs after chemotherapy. Estimates were increasingly divergent across the observation period.

Infertility—No Chemotherapy Group vs. No Cancer Group

The overall 5-year cumulative incidence of infertility was 20.7% in the no chemotherapy group and 18.8% in the no cancer group (aRR 1.10, 95% CI 1.03–1.17) (total effect, Table 2). Accounting for competing events, infertility in the no chemotherapy group remained higher (aRR 1.35, 95% CI 1.28–1.43) (direct effect, Table 2). In models of 10-year incidence of infertility (Fig. 2A), estimates for the no cancer group (black line) were similar to those of the no chemotherapy group without accounting for competing events (solid green line), whereas the elevated 10-year incidence of infertility was observed in the no chemotherapy group after accounting for competing events (dashed green line).

Infertility—Platinum-Based Chemotherapy Group vs. No Chemotherapy or No Cancer Group

The overall 5-year cumulative incidence of infertility was lower in the platinum-based chemotherapy group compared with the no chemotherapy group (18.6% vs. 20.7%, aRR 0.90, 95% CI 0.81–0.98) and similar compared with the no

TABLE 2

A 5-year cumulative incidence and adjusted relative risk (aRR) of live birth and infertility among no cancer, no chemotherapy, and platinum-based chemotherapy groups.

Cumulative incidence	% (95% CI)	aRR[c] (95% CI) (reference group no cancer)	aRR[c] (95% CI) (reference group no chemotherapy)
Live birth			
Total effect			
No cancer	6.9 (6.6–7.2)	1	—
No chemotherapy	6.4 (5.6–7.3)	0.94 (0.82–1.08)	1
Platinum-based chemotherapy	2.9 (2.0–3.8)	0.42 (0.29–0.57)	0.46 (0.31–0.61)
Direct effect			
No chemotherapy[a]	7.9 (7.0–9.0)	1.16 (1.02–1.34)	-
Platinum-based chemotherapy[b]	3.9 (2.8–5.1)	—	0.61 (0.42–0.82)
Platinum-based chemotherapy[a]	4.9 (3.5–6.3)	0.70 (0.51–0.93)	—
Infertility[d]			
Total effect			
No cancer	18.8 (18.4–19.3)	1	—
No chemotherapy	20.7 (19.5–21.9)	1.10 (1.03–1.17)	1
Platinum-based chemotherapy	18.6 (16.8–20.2)	0.98 (0.89–1.08)	0.90 (0.81–0.98)
Direct effect			
No chemotherapy[a]	25.5 (24.0–26.9)	1.35 (1.28–1.43)	—
Platinum-based chemotherapy[b]	21.8 (20.1–23.5)	—	1.05 (0.97–1.15)
Platinum-based chemotherapy[a]	26.8 (24.8–28.8)	1.42 (1.31–1.53)	—

Note: CI = confidence interval.
[a] Direct effect when competing events were set to be equal to the no cancer group.
[b] Direct effect when competing events were set to be equal to the no chemotherapy group.
[c] Adjusted for age, race, income, education, radiation, obesity, smoking, and preexisting infertility.
[d] Excluding preexisting infertility.

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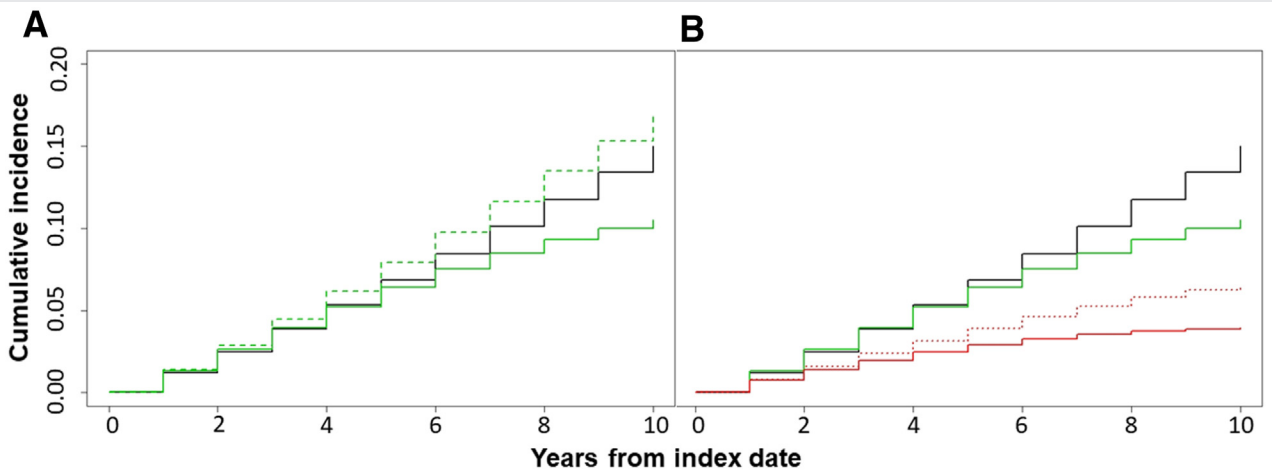
FIGURE 1



(**A**) The modeled 10-year cumulative incidence of live birth for the no cancer group (black), the no chemotherapy group (solid green), and the direct effect of no chemotherapy when competing risks were set to be equal to the no cancer group (dashed green). (**B**) The modeled 10-year cumulative incidence of live birth for the no cancer group (black), the no chemotherapy group (solid green), the platinum-based chemotherapy group (red), and the direct effect of platinum-based chemotherapy when competing risks were set to be equal to the no chemotherapy group (dashed red).

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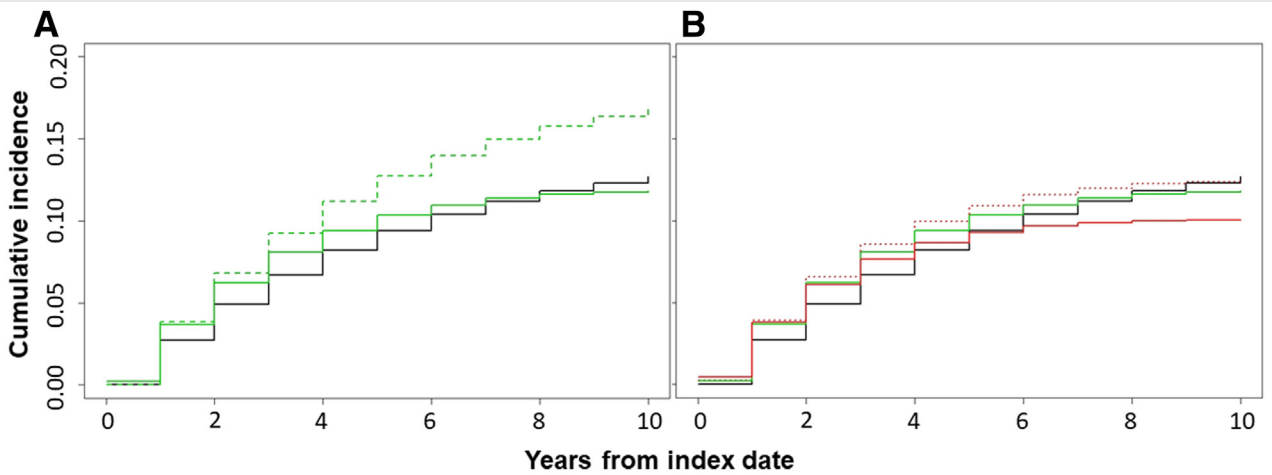
cancer group (18.6% vs. 18.8%, aRR 0.98, 95% CI 0.89–1.08) (total effect, Table 2). Accounting for competing events, the 5-year cumulative incidence of infertility for the chemotherapy group was 21.8% compared with 20.7% in the no chemotherapy group (aRR 1.05, 95% CI 0.97–1.15) (direct effect, Table 2). The 5-year cumulative incidence of infertility in the platinum-based chemotherapy group was significantly higher than that of the no cancer group (aRR 1.42, 95% CI 1.31–1.53) (direct effect, Table 2). These results suggest that the initial overall lower (compared with the no chemotherapy group) or similar (compared with the no cancer group) likelihood of infertility in the chemotherapy group is largely explained by more competing events in this group. In Figure 2B, the estimated 10-year incidence of infertility for chemotherapy after accounting for competing events (dotted red line) was higher than that observed before accounting for

FIGURE 2



(**A**) The modeled 10-year cumulative incidence of infertility for the no cancer group (black), the no chemotherapy group (solid green), and direct effect of no chemotherapy if competing risks were set to be equal to the no cancer group (dashed green). (**B**) The modeled 10-year cumulative incidence of infertility for no cancer group (black), no chemotherapy group (solid green), platinum chemotherapy (red), and direct effect of chemotherapy when competing risks were set to be equal to the no chemotherapy group (dashed red).

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competing events and the estimated incidence in the no chemotherapy group (solid green line).

In sensitivity analysis, to address the potential impact of cancer diagnosis-related fertility counseling or treatment, we restricted infertility outcomes to treatment ≥12 months after the index date. In adjusted models, the chemotherapy group was 1.20 times more likely to undergo infertility treatment than the no chemotherapy group and 1.45 times more likely to undergo infertility treatment than the no cancer group (Supplemental Fig. 3, available online). Subgroup analyses restricted by cancer (Supplemental Tables 2 and 3, available online) or age (Supplemental Table 4, available online) showed similar estimates to the whole population. Subgroup analyses restricted to cancers diagnosed between 2010 and 2019 did not materially change results (data not shown).

DISCUSSION

Characterizing the effect of platinum-based chemotherapy on female fertility is necessary to counsel AYA cancer patients about their risks and inform fertility preservation decisions. Although the total effect gives the probability that a patient will have fertility after the treatment, the direct effect derived from competing events analysis indicates whether platinum-based chemotherapy causes infertility and whether fertility preservation should be considered. Using this approach, our findings of a decrease in LBs (compared with survivors who did not receive chemotherapy and females with no cancer) and an increase in infertility (compared with females with no cancer) after platinum-based chemotherapy support our hypothesis that heavy metal agents modestly impact clinical fertility outcomes. These data significantly extend current knowledge on the fertility risks of platinating agents and provide a methodologic approach to estimating other treatment-related fertility risks. Alignment of these data with observed platinum-associated increases in primary ovarian insufficiency in AYA cancer survivors warrants consideration of adding platinum-based chemotherapy as an exposure that poses fertility risk to risk-stratification guidelines (21, 57, 58).

Births and infertility are complementary clinical fertility measures. Cohort studies consistently show overall fewer LBs among AYA cancer survivors and that risks vary by broad treatment exposures, e.g., any chemotherapy and/or radiation (59–61). Existing infertility estimates for AYA cancer survivors are scarce (62, 63). A population-based Canadian cohort reported a relative risk of 1.30 for infertility, with risks differing by cancer type (5). In uncontrolled studies, the cumulative incidence of infertility ranged from 15%–90% (62, 63). Although estimating treatment-related fertility risks is central to fertility preservation decisions, few datasets (Childhood Cancer Survivor Study, Danish National Lymphoma Registry, Ontario Cancer Registry) encompass data on specific cancer treatments and large enough populations to enable this research (21, 63–65). The current study demonstrates the feasibility of leveraging claim data for these efforts. Although there was no dose-dependent relationship between cisplatin tertiles and LBs in the Childhood Cancer Survivor Study, our findings of fertility harm in AYAs may stem from reproductive physiology and clinical pharmacology differences between AYAs and childhood cancer patients (19, 20, 61, 64, 66, 67).

Accounting for competing risks in cancer survivors is key to determining fertility risks attributable to platinum exposure. Without addressing events that preclude the possibility of experiencing LBs or infertility, studies report total effects, which may underrepresent or overrepresent the direct effect of treatments (68, 69). The recently developed separable effects approach allows the estimation of causal effects by separating the total effect of the exposure on outcomes into direct (e.g., because of the gonadotoxicity of treatment) and indirect (e.g., precluding pregnancy attempts because of recurrence) effects, under the presumption that effects occur via different known or hypothetical mechanisms. Because a significant proportion of the overall LB and infertility risk was attributable to more competing events in the cancer groups (thus precluding pregnancy attempts and infertility diagnoses), this novel approach changed both magnitude and directional estimates to show the causal effect of platinum-based chemotherapy and cancer diagnosis on fertility outcomes. Causal effects are clinically useful to inform up-front fertility preservation decisions.

Several limitations warrant discussion. Combining 3 cancers improved power but introduced heterogeneity, e.g., the number of cycles of platinum agents (70, 71); however, subgroup analysis by cancer yielded similar results. More precise dose-specific risks were not calculated because of a lack of body surface area measurements in the claims data. Infertility benefits vary among insurance plans, and thus, infertility outcomes are likely undercaptured for all groups. Whether women with cancer are more likely to be infertile and use services not covered by health insurance, underestimation would be greater in the cancer groups, resulting in a bias toward the null. Sensitivity analyses, to address misclassification of infertility status, for example, including only infertility treatments (excluding diagnoses), yielded similar results.

The potential for pregnancy intention and attempts to be influenced by factors such as cancer prognosis and concern for perinatal and offspring outcomes, among others, has been described (3, 72–77). Serial assessments of pregnancy intentions are necessary to fully classify those attempting pregnancy as the denominator for pregnancy outcomes. These data are generally unmeasured in large cohorts and claims data. Comparison of cumulative 5-year risks rather than instantaneous hazards helps to account for potentially delayed trying time, and consideration of the full observation period is necessary to avoid bias to separable effects because competing events occur throughout follow-up for all groups. Despite factors that may result in underestimation of absolute risks, so long as these are similar across groups, relative risk can be estimated in comparisons among the chemotherapy, no chemotherapy, and no cancer groups. Although a lack of data on the duration of attempts at conception remains a concern, the data suggest no association of stage and severity of disease with attempting pregnancy after cancer, minimizing the potential for confounding by cancer stage and severity (78, 79). By excluding individuals with alkylating chemotherapy, we do not expect confounding to result because of this chemotherapy class with known

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gonadotoxicity. Expected regimens for each cancer type were observed, most commonly carboplatin and taxane for ovarian and breast cancer and folinic acid, fluorouracil (FOLFOX), and oxaliplatin, as well as folinic acid, fluorouracil, and irinotecan (FOLFIRI) for colorectal cancer. In this setting, the colinearity of platinum with other nonalkylating agents prevents the separation of the effect of platinum-based chemotherapy from other molecules. In future work, we will consider an additional comparison group of females receiving other types of systemic therapy. Finally, observation time is limited with these data. This results in low overall estimates of incidence; however, matching on observation days minimizes potential bias in group comparisons and estimates of relative incidence.

CONCLUSION

Because oncofertility research aligns with precision medicine to improve risk estimates, estimating treatment-specific fertility risks is clinically important. By leveraging a national health claims dataset, we showed decreased cumulative incidences of LB and infertility after platinum-based chemotherapy in AYA breast, colorectal, and ovarian cancer survivors to inform fertility preservation decisions. We also demonstrated the potential contribution of models that account for competing events to the interpretation of findings and clinical practice. Additional research on understudied cancer treatment exposures and analytical approaches that match study goals is needed to expand the knowledge base that informs fertility counseling.

CRediT Authorship Contribution Statement

Beth Zhou: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Brian Kwan:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Milli J. Desai:** Writing – review & editing, Methodology, Formal analysis. **Vinit Nalawade:** Writing – review & editing, Methodology, Formal analysis. **Joe Henk:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Nina Viravalli:** Writing – review & editing, Methodology, Formal analysis. **James D. Murphy:** Writing – review & editing, Methodology, Conceptualization. **Paul C. Nathan:** Writing – review & editing, Methodology. **Kathryn J. Ruddy:** Writing – review & editing, Methodology. **H.Irene Su:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Brian W. Whitcomb:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization.

Declaration of Interests

B.Z. reports funding from NIH T32 ES007059 for the submitted work. B.K. has nothing to disclose. M.J.D. has nothing to disclose. V.N. has nothing to disclose. J.H. was an employee of Optum labs until 0/2021. N.V. has nothing to disclose. J.D.M. has nothing to disclose, P.C.N. has nothing to disclose. K.J.R. has nothing to disclose. K.S. has nothing to disclose. H.I.S. has nothing to disclose. B.W.W. has nothing to disclose.

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Asociación de la quimioterapia con platino con nacimientos vivos e infertilidad en mujeres sobrevivientes de cáncer adolescentes y adultas jóvenes.

Objetivo: Estimar el efecto de la quimioterapia basada en platino en el nacimiento de hijos vivos y la infertilidad después del cáncer, con el fin de abordar una falta de riesgos de fertilidad específicos del tratamiento para las sobrevivientes femeninas de cáncer en adolescentes y adultos jóvenes, lo cual limita el asesoramiento sobre decisiones de preservación de la fertilidad.

Diseño: Estudio de cohorte retrospectivo.

Contexto: Base de datos administrativa de EE. UU.

Pacientes: Identificamos casos de cáncer de mama, colorrectal y ovárico en mujeres de 15 a 39 años que recibieron quimioterapia basada en platino o ninguna quimioterapia, y se emparejaron con mujeres sin cáncer.

Intervención: Quimioterapia basada en platino.

Medidas de Resultado Principal: Estimamos el efecto de la quimioterapia en la incidencia de nacidos vivos e infertilidad después del cáncer, en general, y después de tener en cuenta los eventos competidores (recurrencia, muerte y cirugías de esterilización).

Resultados: Hubo 1,287 sobrevivientes en el grupo de quimioterapia, 3,192 en el grupo sin quimioterapia y 34,147 mujeres en el grupo sin cáncer, con una edad media de 33 años. Teniendo en cuenta los eventos competitivos, la incidencia de nacimientos de nacidos vivos a los 5 años en general fue menor en el grupo de quimioterapia (3.9%) en comparación con el grupo sin quimioterapia (6.4%). Los riesgos relativos ajustados en comparación con los grupos sin quimioterapia y sin cáncer fueron de 0.61 (intervalo de confianza [IC] del 95%: 0.42–0.82) y 0.70 (IC del 95%: 0.51–0.93), respectivamente. La incidencia de infertilidad a los 5 años en general fue similar en el grupo de quimioterapia (21.8%) en comparación con el grupo sin quimioterapia (20.7%). Los riesgos relativos ajustados en comparación con los grupos sin quimioterapia y sin cáncer fueron de 1.05 (IC del 95%: 0.97–1.15) y 1.42 (IC del 95%: 1.31–1.53), respectivamente.

Conclusiones: Los sobrevivientes de cáncer tratados con quimioterapia basada en platino experimentaron resultados adversos ligeramente aumentados en la fertilidad. Los efectos estimados de la quimioterapia basada en platino se vieron afectados por eventos competitivos, lo que sugiere la importancia de este enfoque analítico para interpretaciones que finalmente informen decisiones clínicas sobre la preservación de la fertilidad.

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