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Fertility counseling before cancer treatment and subsequent reproductive concerns among female adolescent and young adult cancer survivors

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Conflicts of Interest

No conflict of interest to disclose from any authors. Dr. Dietz works for Bluebird Bio, Inc. which did not sponsor, support, or have oversight with this research.

These authors contributed equally to this work.

Abstract

Background: Fertility counseling prior to cancer treatment has been advocated by clinical guidelines, with little known about its long-term impact on the unique reproductive concerns of female adolescent and young adult (AYA) cancer survivors. The objective was to measure the association between fertility counseling by fertility specialists prior to cancer treatment and subsequent reproductive concerns.

Methods: The current cross-sectional analysis was performed among 747 AYA survivors ages 18–40, recruited from cancer registries, physician and advocacy group referrals between 2015–2017. Participants self-reported information on past fertility counseling at cancer diagnosis, cancer type and treatment, and current reproductive concerns, measured by the multi-dimensional Reproductive Concerns After Cancer (RCAC) scale. Multivariable log-binomial regression models tested associations between fertility counseling and reproductive concerns.

Results: Mean age was 33.0 (SD 5.1). Mean years since diagnosis was 7.7 (SD 5.0). Seventy-three percent of participants were white, 24% were Hispanic. Fertility counseling was reported by 19% of survivors; moderate to high overall reproductive concerns were reported by 44% of participants. In adjusted analysis, fertility counseling was significantly associated with moderate to high reproductive concerns (RR 1.22, 95% CI 1.02–1.45) and not modified by exposure to fertility-threatening treatments ($p_{\text{interaction}}=0.23$).

Conclusions: A large proportion of AYA cancer survivors, across cancer types and treatment exposures, reported moderate to high reproductive concerns, evoking the need to address these cancer-specific reproductive health concerns post-treatment. Higher concerns, even with counseling, suggests the need to improve the quality of fertility counseling throughout the cancer continuum.

Precis

In reproductive-aged, AYA cancer survivors, fertility counseling prior to cancer treatment was associated with higher subsequent reproductive concerns. Improved counseling to address reproductive concerns unique to this population is needed.

Protection of Human Subjects

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Keywords

cancer; fertility counseling; fertility preservation; young adult; female; reproductive concerns

Introduction

Following advances in cancer therapy, the majority of women diagnosed with cancer as adolescents or young adults will become long-term survivors (AYA survivors).¹ Currently, there are nearly 370,000 reproductive-aged female AYA survivors in the United States.¹ Young cancer survivors experience higher overall risk of infertility than sibling or general population controls, but individual risk is highly variable depending on type and dose of cancer treatment.^{2–5} For example, while the overall proportion of infertile female childhood cancer survivors is 13%, those who underwent total body irradiation have a 28% risk.² Fertility loss can be a devastating consequence of cancer treatments for AYA survivors, resulting in poorer quality of life.^{6–8} Prior studies have shown that potential loss of fertility can be as painful as the cancer diagnosis itself,⁹ and for some, the possibility of preserving fertility is instrumental to coping with the burden of cancer treatment.¹⁰ In addition to the adverse impact of infertility itself, unmet informational needs on fertility are also associated with distress.¹¹ Considering infertility risks, informational needs, and the existence of effective fertility preservation strategies, professional societies such as the American Society of Reproductive Medicine and the American Society of Clinical Oncology have had clinical guidelines for over a decade advocating for counseling on infertility risk and fertility preservation options at cancer diagnosis (fertility counseling).^{12–14} AYA cancer patients desire fertility counseling, regardless of infertility risk.^{15, 16}

Fertility counseling prior to cancer treatment is intended to inform patients and families on future fertility potential and facilitate fertility preservation needs.^{12–14} Fertility counseling of individuals at increased risk of infertility could inform them of this risk and drive consideration of fertility preservation options; conversely, counseling of individuals at low risk of infertility could provide reassurance. Importantly, fertility counseling needs in the cancer population are distinct from the general infertility population because the informational needs of cancer survivors encompasses additional considerations. These needs range from medical risks such as cancer treatment-specific risk of infertility, offspring health and pregnancy health risks, to psychosocial support such as disclosing their cancer history to partners. If responsive to the informational needs of AYA survivors, fertility counseling is anticipated to have long-term impact on reproductive concerns in survivorship. However, there is evidence that fertility counseling does not consistently address specific oncofertility needs.^{17–19}

There are limited studies on the long-term impact of fertility counseling prior to cancer treatment.^{18, 19} Fertility counseling is consistently associated with improved decision-making on fertility preservation, specifically less regret and conflict about the fertility preservation decision and better coping with the burden of cancer treatment.^{9, 18, 20, 21} Fertility counseling has been positively associated with social well-being.²² With regard to provider, fertility counseling by oncology providers does not appear to be related to general measures of quality of life, but counseling by fertility specialists may result in improvement in satisfaction with life over counseling by oncology providers alone.⁹ Other data suggest that fertility concerns may not be adequately addressed during counseling at cancer diagnosis, rendering unmet informational needs after fertility counseling and a desire for more fertility care in survivorship.^{23, 24}

Beyond impact on the quality of decision-making on fertility preservation and general quality of life, there are very few studies on whether fertility counseling impacts the reproductive concerns unique to AYA survivors.^{25, 26} Hence, the objective of this study was to measure the association between fertility counseling prior to cancer treatment and subsequent reproductive concerns in female AYA survivors who have completed cancer treatment. Reproductive concerns were measured by the multi-dimensional Reproductive Concerns After Cancer (RCAC) scale, developed in AYA survivors, which extends beyond concerns about infertility and are inclusive of partner disclosure of fertility status, offspring health, personal health, becoming pregnant, and acceptance of the inability to have biologic children.¹¹ As fertility counseling, particularly by fertility specialists, is intended to meet the informational needs of newly diagnosed cancer patients, the a priori hypothesis was that AYA survivors who received fertility counseling prior to cancer treatment would have fewer overall reproductive concerns than AYA survivors who did not receive fertility counseling. Because infertility risk differs by cancer treatment and AYA survivors at higher risk of infertility may have correspondingly higher concerns, we additionally tested if the association between fertility counseling and reproductive concerns differed by exposure to cancer treatments that increase infertility risk. Anticipating that fertility is the focus of counseling and data offspring health is largely reassuring, we secondarily tested the hypothesis that among the dimensions of reproductive concerns, fertility counseling would be associated with less fertility and offspring health concerns.

Materials and Methods

Cross-sectional analyses were performed of data from baseline questionnaires completed by participants in the Reproductive Window Study, a prospective study of ovarian function in cancer survivors. Despite the contemporaneous collection of information at baseline, participants reported on fertility counseling received prior to cancer treatments and cancer history (e.g., cancer type, age at diagnosis, treatment), which precede reproductive concerns as experienced at the time of baseline questionnaires. Eligibility criteria for the Reproductive Window Study included: females with cancer diagnoses between ages 15–35, ages 18–40 at study enrollment, completion of primary cancer treatment, and presence of at least one ovary. The following cancer types were included: breast, leukemia, lymphoma, gynecologic (cervix, uterus, ovary), intestines, gall bladder, pancreas, bone, soft tissue tumor of bone/fat, skin, and thyroid. Window Study participants enrolled in the study through a secure web-based study portal and completed serial online questionnaires over 18 months.

For the current analysis on fertility counseling and reproductive concerns, we included Reproductive Window Study participants enrolled between March, 2015 and May, 2017 and used their baseline questionnaire data. AYA survivors were recruited from the California and Texas Cancer Registries (36.0%), University of California, San Diego Health System (29.6%), cancer advocacy organizations (10.8%), physician referrals (3.9%), and other sources (19.7%). The State of California Committee for the Protection of Human Subjects and the institutional review boards at the University of California, San Diego and the Texas Department of State Health Services approved this study.

Participants provided self-reported information on demographics, cancer history (including cancer type, years since cancer diagnosis, age at cancer diagnosis and cancer treatments), reproductive history (including lifetime history of pregnancy and live birth, pregnancy and live birth after cancer diagnosis, infertility, and adoption), fertility counseling prior to cancer treatment, and reproductive concerns. To assess fertility counseling from a fertility specialist, participants were asked if they saw a fertility specialist after cancer diagnosis and before treatment, during treatment, or after cancer treatment. They were also asked if they underwent fertility preservation procedures, including embryo or oocyte banking, ovarian tissue banking, ovarian suppression, ovarian shielding, ovarian transposition or other procedures.

Reproductive concerns at study baseline were assessed with the RCAC scale.¹¹ AYA survivors who report higher reproductive concern as measured by the RCAC scale are more likely to experience depression¹⁹ and lower quality of life.⁸ The 18-item RCAC scale assesses 6 constructs via specific subscales: fertility potential (e.g., “I am afraid I won’t be able to have any (more) children”), offspring health (e.g., “I am worried about passing on a genetic risk for cancer to my children”), personal health (e.g., “I am scared of not being around to take care of my children someday”), acceptance (e.g., “I can accept it if I’m unable to have (more) children”), becoming pregnant (e.g., “I worry that getting pregnant (again) would take too much time and effort”), and partner disclosure (e.g., “I worry about telling my (potential) spouse/partner that I may be unable to have children”).¹¹ The response scale is a five-point Likert scale ranging from 1 “Strongly disagree” to 3 “Neither agree nor disagree” to 5 “Strongly agree.” Each subscale encompasses 3 questions. Scores are derived from averaging responses (range 1–5) across questions for the entire RCAC scale or for individual subscales, with higher scores indicating a greater level of concern. The internal consistency of the total RCAC scale ($\alpha = 0.82$) and each subscale (α range 0.78 to 0.88) were good, and the scale has undergone translation and cross-cultural adaptation into Chinese.²⁷

Statistical Methods

We calculated descriptive statistics as frequencies and percentages or means and standard deviations, as applicable. The exposure of interest was fertility counseling at cancer diagnosis. The primary outcome of interest was the overall RCAC score; secondary outcomes were RCAC fertility potential and offspring health subscale scores. To facilitate interpretation, we categorized participants as having moderate to high reproductive concerns if their overall RCAC score was >3 , because this categorization was previously associated with higher risk of depression measured by the PHQ-8 in a prior cohort.¹⁹ Accordingly, participants had higher fertility or offspring health concerns if the respective subscale scores were >3 . We performed bivariable analysis using Fisher’s Exact test or Chi-square test of proportions to compare proportions with moderate to high reproductive concerns by participant characteristics and fertility counseling. We used multivariable log-binomial regression models to test associations between fertility counseling and reproductive concerns, while controlling for confounding.^{28, 29} We evaluated effect modification of fertility counseling by exposure to cancer treatments that increase infertility risk using a Wald test of a cross-product interaction term added to the regression model. In multivariable

models we included variables associated with reproductive concerns at $p = 0.10$ in bivariable analyses or were postulated to be related to reproductive concerns. We set statistical significance for multivariable analysis at $p < 0.05$. All analyses were conducted using SPSS statistical software v24 (IBM Corporation).

Results

Seven hundred forty-seven female AYA survivors were included in this analysis (Table 1). Mean age (standard deviation [SD]) was 33.0 (5.1) years. Seventy-three percent of participants were white, 24% were Hispanic, and 72% completed college. Mean time since cancer diagnosis (SD) was 7.7 (5) years (Table 2). The most common cancer types were thyroid cancer (25%), breast cancer (21%), and Hodgkin's lymphoma (18%). High proportions of participants underwent chemotherapy (61%) and radiation not including radioiodine for thyroid cancer (31%). Eighteen percent underwent only surgery.

Nineteen percent of participants received fertility counseling from a fertility specialist prior to cancer treatment, and 12% underwent a fertility preservation procedure. Several participant characteristics at cancer diagnosis were associated with undergoing fertility counseling, including older age ($p < 0.001$), cancer type ($p < 0.001$) and chemotherapy as part of cancer treatment ($p < 0.001$) (Table 3). Breast cancer survivors were most likely to receive fertility counseling, while thyroid cancer survivors were least likely (47% v. 2.7%, $p < 0.001$).

Forty-four percent of participants reported moderate to high overall reproductive concerns. In bivariable analyses, survivors who underwent fertility counseling were more likely to have moderate to high overall reproductive concerns compared to those who did not undergo counseling (56% v. 41%, $p = 0.001$) (Figure 1). When assessed as a continuous variable, the RCAC score for survivors who underwent fertility counseling was significantly higher than that of AYA survivors who did not undergo counseling (3.06 [SD 0.66] versus 2.85 [SD 0.68], $p = 0.001$). Among RCAC subscales, those who underwent fertility counseling were more likely to report moderate to high concerns about fertility potential ($p < 0.001$), becoming pregnant ($p = 0.02$), impact of personal health on having children ($p = 0.02$), and being able to accept infertility ($p = 0.01$). Survivors who underwent fertility counseling were less likely to have moderate to high reproductive concerns about offspring health compared to survivors who did not (53% vs. 62%, $p = 0.06$). We further categorized the fertility counseling group into those who only received fertility counseling and those who underwent both fertility counseling and a fertility preservation procedure. The associations with reproductive concerns were similar between these two groups.

Several demographic and cancer variables were also associated with reproductive concerns. Survivors who were younger ($p < 0.001$), had lower income ($p = 0.03$) and were not in a partnered relationship ($p < 0.001$) were more likely to have moderate to high reproductive concerns than those who were older, had higher income and were in a partnered relationship, respectively (Table 1). Survivors without prior pregnancy or live birth, either before or after cancer, were also more likely to have moderate to high reproductive concerns ($p < 0.001$) than those with prior pregnancy or live birth. Among cancer characteristics, shorter time since cancer diagnosis ($p = 0.01$), prior chemotherapy ($p = 0.03$) and prior radiation (not including

radioiodine for thyroid cancer treatment) ($p=0.05$) were related to more reproductive concerns (Table 2). Cancer type, age at diagnosis, radioiodine therapy and surgery were not associated with reproductive concerns. The test for interaction between fertility counseling and receipt of therapies that increase infertility risk (chemotherapy, bone marrow transplant or radiation to the abdomen) on reproductive concerns was not significant ($p=0.24$).

In a multivariable analysis, those who underwent fertility counseling prior to cancer treatment remained 1.2 times more likely to have moderate to high subsequent reproductive concerns, compared with those who did not receive fertility counseling prior to cancer treatment (adjusted RR 1.22, 95% CI 1.02–1.45) (Table 4). Years since cancer diagnosis was not included because of co-linearity with current age, cancer type was not included because of co-linearity with radiation, and additional pregnancy variables were also not included due to co-linearity with prior live birth. In addition, survivors who had a prior live birth (adjusted RR 0.65, 95% CI 0.52–0.81) were less likely to report moderate to high reproductive concerns.

Discussion

Counseling to discuss infertility risk and fertility preservation options prior to starting cancer treatment has been advocated by professional oncology and reproduction societies for over a decade, with limited information on the long-term impact of this counseling on quality of life, including the specific reproductive concerns of AYA survivors.^{18, 19, 25, 30} In this cohort of reproductive-aged, female AYA cancer survivors, a large proportion across all cancer types and treatment exposures reported reproductive concerns, as measured by the RCAC scale,¹⁰ highlighting the need to address these cancer-specific reproductive health concerns post-treatment. Survivors who underwent fertility counseling by fertility specialists prior to cancer treatment subsequently reported higher reproductive concerns compared to survivors who did not receive fertility counseling. Moreover, increased concerns spanned multiple domains, including worry about fertility potential, becoming pregnant and personal health, as well as less acceptance of not having more children. While the findings may reflect appropriately increased concerns experienced by AYA survivors who are at increased risk, the association did not differ by exposures to cancer treatments that increase infertility risk. These results show that fertility counseling prior to cancer treatment for this AYA population did not adequately address their reproductive concerns into the survivorship period. The study suggests that fertility counseling at cancer diagnosis and in survivorship can be improved to address AYA survivors' reproductive concerns.

The RCAC scale has been used in four other published studies and one abstract on four separate populations of female young adult cancer survivors, one of which was conducted by our group.^{19, 26, 27, 31} Summary RCAC scores in 3 of these populations were not reported for comparison to scores in the current study. In our prior study, 204 female young adult cancer survivors between ages 18 and 35 recruited primarily through social media outlets and local community outreach, participants had a mean RCAC score of 58.3 (SD 10.9) with 65% reporting a moderate to high RCAC score.¹⁹ This is higher than the mean RCAC summary score of 52.0 (SD 12.2) with 44% in the moderate to high category of the current study. We

attribute the difference to disparate recruitment strategies, with the current study undertaking more population-based approaches aiming to decrease selection bias.

The finding of higher post-treatment reproductive concerns following fertility counseling at cancer diagnosis was in the opposite direction of our original hypothesis. There are several possible explanations. First, higher concern may be appropriate, because some cancer treatments do increase risk of infertility and pregnancy-related complications. For example, high doses of alkylating chemotherapy and radiation treatment directed toward reproductive organs are associated with higher risk of infertility;^{4, 5, 32} pelvic radiation also increases the risk of spontaneous abortion and premature birth.^{33, 34} Patients who have been adequately counseled would have an accurate understanding of these adverse cancer treatment effects on reproductive potential, and accordingly, report more reproductive concerns. This explanation is supported by our unadjusted finding that prior chemotherapy and radiation was associated with more reproductive concerns, but this was attenuated in adjusted analyses. We suggest that there are clinical and research implications for this finding. Clinically, not all chemotherapy or radiation significantly increase infertility risk,^{35, 36} and improved dissemination of this information, which would be optimized by collaboration between oncology and fertility healthcare providers, is needed. In research, significantly more work in measuring infertility risk is needed to derive primary data for counseling. We also observed that participants who underwent fertility counseling had less concern about offspring health, consistent with data that overall, children of childhood cancer survivors do not have significantly higher risks of birth defects or childhood cancer.^{34, 37, 38}

A second explanation is that fertility counseling at cancer diagnosis was not adequate to alleviate the spectrum of reproductive concerns in survivorship. An older survey of young breast cancer survivors showed that among women who discussed concerns with a doctor, 51% felt that their concerns were addressed adequately.²³ Interestingly, we did not observe a significant interaction between fertility counseling and therapies that increase infertility risk on reproductive concerns, suggesting that regardless of toxicity of treatments, fertility counseling at diagnosis did not adequately address reproductive concerns for post-treatment survivors. Because the RCAC scale measures multiple dimensions beyond fertility potential, including partner disclosure of fertility status, child's health, personal health, acceptance, and becoming pregnant,¹¹ it is possible that these domains may not be adequately addressed or reviewed during a fertility counseling encounter immediately prior to cancer treatment, which may focus primarily on infertility risk and fertility preservation options. This may also occur if fertility counseling by reproductive specialists is limited to general infertility counseling and does not address the unique reproductive concerns of cancer survivors.^{17, 18} Future work to develop an effective fertility counseling intervention by reproductive specialists to address these concerns is needed to better meet AYA survivors' needs at diagnosis and after they have completed cancer treatment. Qualitative and quantitative studies support that female survivors want counseling to include written, standardized oncofertility information delivered at multiple time points across the cancer care continuum.^{17, 18, 39, 40} Optimal models of care or the effectiveness of incorporating reproductive health into survivorship care plans remain unknown, thus active dissemination and implementation work will be needed to determine how to spread effective interventions into clinical practice.

One published study reported decreased reproductive concerns with reproductive health counseling, using the Reproductive Concerns Scale (RCS).^{6, 25} In a retrospective cohort study of female non-gynecologic cancer survivors recruited from the California Cancer Registry, 356 participants completed the RCS and answered 10 questions that asked if fertility counseling covered content such as post-treatment fertility, resources to preserve fertility, early menopause and sexual function. Each content item that was addressed by fertility counseling improved the RCS score by 1 point ($p=0.001$).²⁵ The disparate findings between these two studies are not inconsistent. The RCS and RCAC scale differ in that the RCS is a unidimensional scale that predominantly focuses on negative feelings about fertility and inability to have children; examples include loss of control over reproductive future, discontent with number of children, frustration and anger about ability to have children. The RCS was developed based on literature, cognitive interviews with 9 content experts, and refined in focus interviews, yielding a 14-item measure. Similar to the RCAC scale, the increased reproductive concerns measured by RCS is associated with poorer quality of life and distress. The novelty and strength of this study is in measuring the multiple additional dimensions of reproductive concerns experienced by AYA survivors.¹¹ Because the RCAC scale used in this study measured different aspects of reproductive concerns, it is not surprising that we observed different results. However, as the content of fertility counseling was not measured in our study, we cannot exclude that the observed difference is due to poorer quality of counseling experienced by participants.

Previously, a limited number of studies examined other long-term outcomes of fertility counseling, demonstrating that counseling improved the quality of the decision on fertility preservation (less conflict, regret) and coping with the burden of cancer treatment.^{9, 10, 20} One small cross-sectional study showed no association with distress,⁴¹ while a second retrospective cohort study of 1041 female cancer survivors reported no association between counseling by an oncologic provider and either satisfaction with life or global quality of life.⁹ Among the subset counseled by oncologists, those who went onto fertility specialist counseling scored higher on physical health within the global quality of life measure, compared with those who did not have fertility specialist counseling; women who underwent fertility preservation reported higher satisfaction with life, but no difference in global quality of life. Arguably, global measures of distress and quality of life are less specific as an outcome of fertility counseling than reproductive concerns.

There are a few limitations to this study. First, we do not know the quality and content of the fertility counseling for this diverse group of participants to ascertain whether counseling addressed the many domains of reproductive concerns or how women received this information. Second, while recruitment sources were varied, there could be selection bias in a study on ovarian function after cancer treatment, limiting the generalizability of our results. Without pre-counseling measures of reproductive concerns, we cannot exclude confounding by indication, that women who are more concerned about their future fertility may be more inclined to seek fertility counseling. Another limiting factor is that this is a cross-sectional study, and we cannot infer a cause and effect relationship. However, because our exposure of pretreatment fertility counseling occurred before the outcome of current reproductive concerns, there is a temporal component to the study. Finally, misclassification

of treatment risk may occur because cancer treatments were self-reported in this analysis,⁴² limiting our ability to correlate reproductive concern with intensity of therapy.

In conclusion, we observed a significant proportion of AYA female survivors reporting moderate to high reproductive concerns. A minority of our participants received fertility counseling at cancer diagnosis, highlighting a continued gap in oncofertility care. Prior fertility counseling was not associated with improved reproductive concerns in survivorship. Further research is needed to see how these concerns can be addressed at diagnosis and in long-term survivorship.

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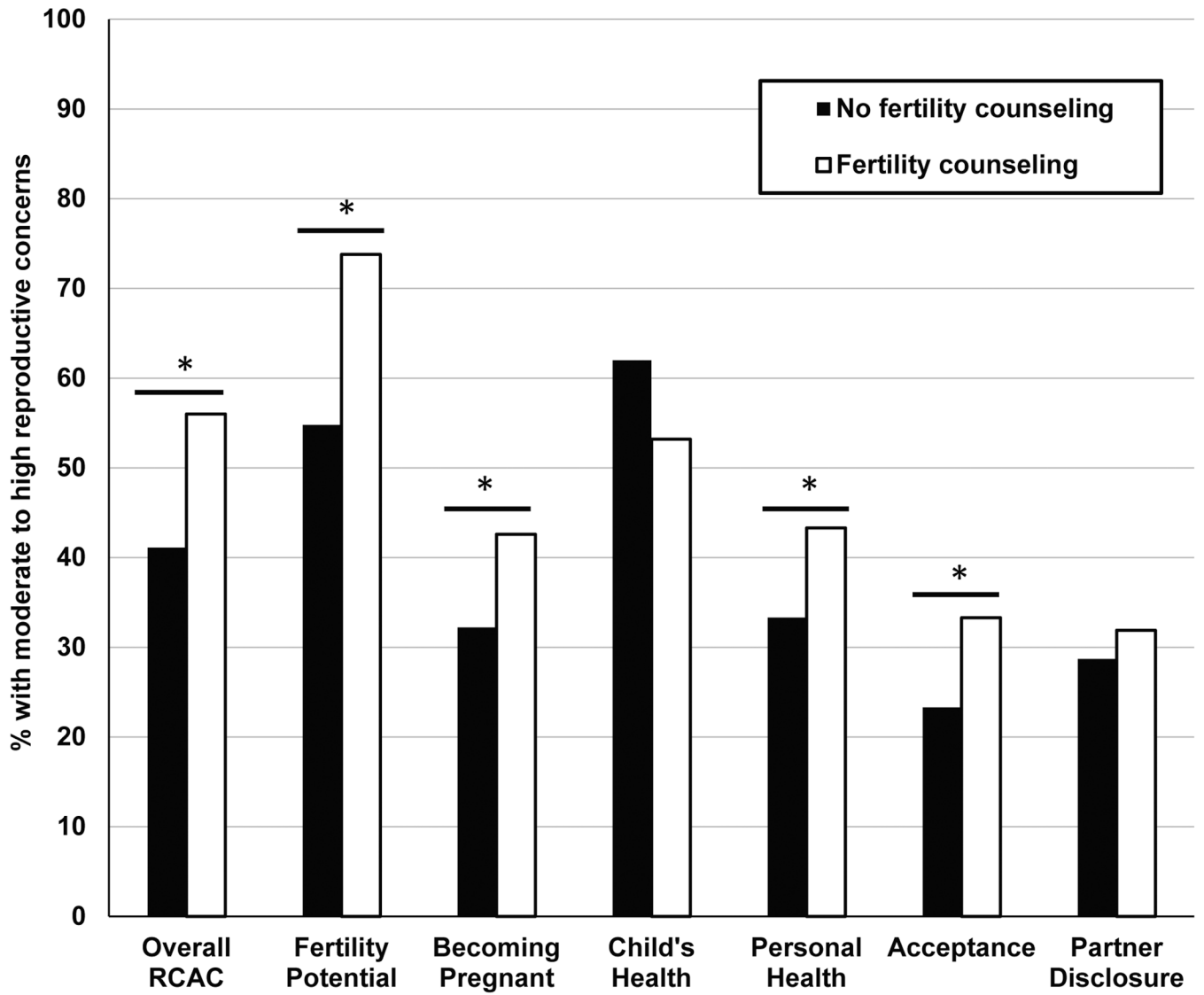


Figure 1: Receipt of fertility counseling at cancer diagnosis and reproductive concerns (overall concerns and individual subscales) in female AYA cancer survivors. Reproductive concerns measured by the Reproductive Concerns After Cancer (RCAC) scale. * $p < 0.05$

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Table 1:

Participant demographic and reproductive characteristics by reproductive concerns. RCAC score >3 indicates moderate to high reproductive concerns (N=747)

	Overall N=747 (%)	RCAC > 3 N=328 (%)	RCAC ≤ 3 N=419 (%)	p-value
Age				<0.001
18–24	61 (8.3)	32 (9.9)	29 (7.0)	
25–30	178 (24.2)	100 (31.1)	78 (18.8)	
31–35	250 (34.0)	96 (29.8)	154 (37.2)	
36–40	247 (33.6)	94 (29.2)	153 (37.0)	
Completion of college				0.87
Yes	544 (72.8)	240 (73.2)	304 (72.6)	
No	203 (27.2)	88 (26.8)	115 (27.4)	
Income				0.03
< \$51,000	200 (26.8)	104 (31.7)	96 (22.9)	
\$51,000	500 (66.9)	204 (62.2)	296 (70.6)	
Prefer not to answer	47 (6.3)	20 (6.1)	27 (6.4)	
Race				0.78
White	544 (72.8)	236 (72.0)	308 (73.5)	
Black or African American	16 (2.1)	8 (2.4)	8 (1.9)	
Asian ¹	52 (7.0)	26 (7.9)	26 (6.2)	
Mixed or other race ²	135 (18.1)	58 (17.7)	77 (18.4)	
Hispanic ethnicity				0.35
Yes	183 (24.5)	86 (26.2)	97 (23.2)	
No	564 (75.5)	242 (73.8)	322 (76.8)	
Married or living with a partner				<0.001
Yes	498 (66.7)	186 (56.7)	312 (74.5)	
No	249 (33.3)	142 (43.3)	107 (25.5)	
Prior live birth				<0.001
Yes	292 (39.1)	86 (26.2)	206 (49.2)	
No	455 (60.9)	242 (73.8)	213 (50.8)	
Live birth after cancer				<0.001
Yes	188 (25.2)	48 (14.6)	140 (33.4)	
No	559 (74.8)	280 (85.4)	279 (66.6)	
Prior infertility				0.17
Yes	108 (14.5)	54 (16.5)	54 (12.9)	
No	639 (85.5)	274 (83.5)	365 (87.1)	
Prior adoption				1.0
Yes	11 (1.5)	5 (1.5)	6 (1.4)	
No	736 (98.5)	323 (98.5)	413 (98.6)	
Fertility counseling at cancer diagnosis				0.001
Yes	141 (18.9)	79 (24.1)	62 (14.8)	

	Overall N=747 (%)	RCAC > 3 N=328 (%)	RCAC 3 N=419 (%)	p-value
No	606 (81.1)	249 (75.9)	357 (85.2)	
Fertility preservation treatment at cancer diagnosis				0.02
Yes	88 (11.8)	49 (14.9)	39 (9.3)	
No	659 (88.2)	279 (85.1)	380 (90.7)	

Note: Due to missing data, some variables do not add up to 747

¹ Asian, American Indian or Alaskan native, Native Hawaiian or other Pacific Islander

² Mixed or other race, Don't know, Prefer not to answer

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Table 2:

Participant cancer and treatment characteristics by reproductive concerns. RCAC score > 3 indicates moderate to high reproductive concerns (N=747)

	Overall N=747 (%)	RCAC > 3 N=328 (%)	RCAC ≤ 3 N=419 (%)	p-value
Cancer Type				0.87
Thyroid, Skin, Melanoma	218 (29.2)	90 (27.4)	128 (30.5)	
Breast	156 (20.9)	71 (21.7)	85 (20.3)	
Cervix, Ovary, Uterus	57 (7.6)	25 (7.6)	32 (7.6)	
Blood, Bone, Lymphoma, Sarcoma	296 (39.6)	134 (40.9)	162 (38.7)	
Gastrointestinal	20 (2.7)	8 (2.4)	12 (2.9)	
Years since cancer diagnosis				0.01
< 2	85 (11.4)	49 (14.9)	36 (8.6)	
2–5	183 (24.5)	86 (26.2)	97 (23.2)	
> 5	479 (64.1)	193 (58.8)	286 (68.3)	
Age at cancer diagnosis				0.13
15–20	157 (21.3)	79 (24.5)	78 (18.8)	
21–30	371 (50.4)	160 (49.7)	211 (51.0)	
31–35	208 (28.3)	83 (25.8)	125 (30.2)	
Cancer treatments				
Surgery				0.14
Yes	500 (66.9)	210 (64.0)	290 (69.2)	
No	247 (33.1)	118 (36.0)	129 (30.8)	
Chemotherapy				0.03
Yes	455 (60.9)	214 (65.2)	241 (57.5)	
No	292 (39.1)	114 (34.8)	178 (42.5)	
Radiation (excludes radioiodine)				0.05
Yes	229 (30.7)	113 (34.5)	116 (27.7)	
No	518 (69.3)	215 (65.5)	303 (72.3)	
Radioiodine				0.83
Yes	130 (17.4)	56 (17.1)	74 (17.7)	
No	617 (82.6)	272 (82.9)	345 (82.3)	

Note: Due to missing data, some variables do not add up to 747

Table 3:

Participant cancer and treatment characteristics by fertility counseling at cancer diagnosis (N=747)

	Fertility counseling N=141 (%)	No fertility counseling N=606 (%)	p-value
Cancer Type			<0.001
Thyroid, Skin, Melanoma	4 (2.8)	214 (35.3)	
Breast	73 (51.8)	83 (13.7)	
Cervix, Ovary, Uterus	7 (5.0)	50 (8.3)	
Blood, Bone, Lymphoma, Sarcoma	53 (37.6)	243 (40.1)	
Gastrointestinal	4 (2.8)	16 (2.6)	
Age at cancer diagnosis			<0.001
15–20	7 (5.0)	150 (20.4)	
21–30	71 (50.4)	300 (40.8)	
31–35	63 (44.7)	145 (24.4)	
Cancer treatments			
Surgery			0.77
Yes	96 (68.1)	404 (66.7)	
No	45 (31.9)	202 (33.3)	
Chemotherapy			<0.001
Yes	125 (88.7)	330 (54.5)	
No	16 (11.3)	276 (45.5)	
Radiation (excludes radioiodine)			<.0001
Yes	75 (53.2)	154 (25.4)	
No	66 (46.8)	452 (74.6)	
Radioiodine			<.0001
Yes	3 (2.1)	127 (21.0)	
No	138 (97.9)	479 (79.0)	

Note: Due to missing data, some variables do not add up to 747

Table 4:

Unadjusted and adjusted models of factors associated with moderate to high reproductive concerns (RCAC score > 3) in reproductive-aged, female AYA cancer survivors

	Unadjusted RR (95% CI)	p-value	Adjusted RR (95% CI)	p-value
Fertility counseling at cancer diagnosis	1.37 (1.15–1.64)	0.001	1.22 (1.02–1.45)	0.03
Age				
18–24	Ref		Ref	
25–30	1.07 (0.82–1.41)	0.62	1.20 (0.92–1.57)	0.17
31–35	0.73 (0.55–0.97)	0.03	0.94 (0.70–1.25)	0.66
36–40	0.73 (0.54–0.97)	0.03	1.00 (0.75–1.34)	0.98
Income				
< \$51,000	Ref		Ref	
\$51,000	0.80 (0.67–0.95)	0.01	0.93 (0.79–1.11)	0.43
Prefer not to answer	0.85 (0.59–1.21)	0.36	0.84 (0.60–1.19)	0.32
Married or living with a partner				
No	Ref		Ref	
Yes	0.67 (0.57–0.79)	<0.001	0.84 (0.70–1.00)	0.05
Prior live birth				
No	Ref		Ref	
Yes	0.55 (0.45–0.67)	<0.001	0.65 (0.52–0.81)	<0.001
Chemotherapy				
No	Ref		Ref	
Yes	1.20 (1.01–1.43)	0.03	1.04 (0.87–1.25)	0.64
Radiation				
No	Ref		Ref	
Yes	1.18 (1.00–1.40)	0.05	1.18 (0.99–1.40)	0.06

Note: Adjusted model included all variables shown in the table