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Experiencing reproductive concerns as a female cancer survivor is associated with depression

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Abstract

Background—Young adult female cancer survivors have unmet reproductive concerns and informational needs that are associated with poorer quality of life. The purpose of this study was to examine the association between current reproductive concerns and moderate to severe depression among young survivors.

Methods—This cross-sectional study includes 200 female cancer survivors between the ages of 18 and 35 years who completed a web-based survey measuring reproductive history, parenthood desires, reproductive concerns after cancer, and quality of life indicators.

Results—The mean age of participants was 28 years (SD = 4.4) and almost two-thirds were diagnosed within 5 years of completing the survey. Multivariable logistic regression analysis controlling for education, duration of survivorship, and social support revealed an association between experiencing reproductive concerns and moderate to severe depression (OR = 1.30, 95% CI = 1.06–1.60 for each 5 unit increase in RCAC score). Of those with moderate to severe depression, 23% had high RCAC scores as compared to 6% of those with minimal to mild depression ($p < 0.001$).

Conclusion—A higher level of reproductive concerns was associated with greater odds of experiencing moderate to severe depression. Almost a quarter of survivors in this sample reported moderate to severe depression, and addressing reproductive concerns represents one potential area of intervention to improve the psychosocial health of young survivors.

Keywords

Depression; Fertility; Pregnancy; Quality of Life; Reproductive Health; Survivors; Female

INTRODUCTION

In addition to coping with long-term medical concerns and the late effects of treatment, young adults who have survived cancer face considerable developmental and life plan

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interruptions. Compared to those diagnosed as older adults, younger survivors experience higher informational and support needs and an increased risk of psychological distress¹⁻⁷. New challenges after treatment can heighten anxiety, including changes in how often and from whom they receive their health care, management of side effects, interrupted life goals, and resumption of roles and responsibilities. Young survivors also face second malignancies and late effects such as gonadal toxicity that can persist for years after treatment has ended. These experiences are associated with distress beyond the completion of treatment⁸⁻¹².

Young adulthood represents the stage in life when family-building typically begins, and most young female survivors express a desire for biological children¹³. However, for those who have had cancer, having biological children may be more difficult than expected. While estimates of risk vary by treatment exposures¹⁴⁻¹⁶, biological parenthood is less likely among cancer survivors than in the general population^{15, 17-20}. The 10-year post-diagnosis pregnancy rate for women diagnosed between 15 and 44 has been observed to be half of that expected²⁰. Concerns about fertility and biological parenthood are substantial for many young adult (YA) survivors and most are not being adequately informed about their options^{4, 21-24}. These concerns persist beyond the time of diagnosis and treatment and may actually worsen in survivorship²⁵⁻²⁷. Female survivors are particularly vulnerable because they are at a greater risk of not receiving fertility information²⁸ and have greater infertility-related distress than male survivors^{29, 30}. Women express concerns and uncertainty about their fertility potential, and they are worried about disclosing their fertility status to their partner, surviving to raise their children, accepting their possible inability to have children, potential barriers to attempting pregnancy, and how their child's health might be affected by their cancer or cancer treatment^{4, 31}. Unaddressed reproductive concerns and informational needs are associated with poorer quality of life outcomes^{3, 6, 24, 32-36}.

Research has identified reproductive concerns as a risk factor for poorer psychosocial health outcomes later in survivorship^{3, 33, 34}, but this study is the first to quantitatively examine the relationship between current reproductive concerns and depression in a sample of reproductive-age female cancer survivors. A prior study by this research team with women diagnosed with breast cancer under the age of 45 provided preliminary evidence that reproductive concerns independently predict depressive symptoms later in survivorship (12 years on average)³³. However, that study's design introduced a potential bias by relying on recalled reproductive concerns at the time of diagnosis. In the present study, we test the hypothesis that current reproductive concerns reported by a younger group of female survivors, age 18-35 years, will be associated with moderate to severe depression.

MATERIALS AND METHODS

Study Design and Population

The Fertility and Pregnancy After Cancer study employed a nationwide online survey to determine the reproductive health concerns and outcomes of YA female cancer survivors. Participants completed a single 20-minute survey focused on their reproductive health experiences after cancer. The study was conducted between March and September 2012. Eligible cancer survivors were female, at least one year post-diagnosis, not currently pregnant, and English-speaking. The study enrolled 204 YA female cancer survivors

between the ages of 18 and 35 years via the Internet, primarily through social media outlets and local community outreach³⁷. Potential participants completed a web-based screening form and, if eligible, were provided electronic informed consent and asked if they would like to participate. Those agreeing were directly linked to the web-based survey. The University of California, San Diego Institutional Review Board approved the study.

Measurement

The survey collected self-report information about demographics, cancer diagnoses and treatments, parenthood desire, and reproductive history (including attempted pregnancy, births, miscarriage, and infertility), and quality of life indicators. Sources of reproductive history study measures included the National Survey for Family Growth³⁸, Time to Pregnancy³⁹, and the Penn Ovarian Aging Study Menstrual Questionnaire⁴⁰, which gathers menstrual pattern data over the past year. Social support was measured using the Medical Outcome Study (MOS) Social support survey⁴¹ ($\alpha = 0.93$).

Reproductive Concerns After Cancer—The 18-item multidimensional Reproductive Concerns After Cancer (RCAC) scale³¹ measured reproductive concerns ($\alpha = 0.82$), the primary explanatory variable. Six subscales measure different dimensions of reproductive concerns: Fertility potential ($\alpha = 0.86$) (e.g., “I am afraid I won’t be able to have any (more) children”); Partner disclosure of fertility status ($\alpha = 0.88$) (e.g., “I worry about telling my (potential) spouse/partner that I may be unable to have children”); Child’s health ($\alpha = 0.88$) (e.g., “I am worried about passing on a genetic risk for cancer to my children”); Personal health ($\alpha = 0.83$) (e.g., “I am scared of not being around to take care of my children someday”); Acceptance of possibly not having children ($\alpha = 0.82$) (e.g., “I can accept it if I’m unable to have (more) children”); and Becoming pregnant ($\alpha = 0.78$) (e.g., “I worry that getting pregnant (again) would take too much time and effort”). The response scale is a five-point Likert scale ranging from 1 = “Strongly disagree” to 5 = “Strongly agree.” A summary score results in a score ranging from 18 to 90, with higher scores indicating a greater level of concern.

Depression—The depression scale of the Patient Health Questionnaire (PHQ-9)⁴², a nine item self-administered assessment tool based on the diagnostic criteria of the Diagnostic and Statistical Manual Fourth Edition (DSM-IV), measured depression ($\alpha = 0.86$). Higher scores are indicative of more severe depression; scores of 5, 10, 15, and 20 correspond to mild, moderate, moderately severe, and severe depression, respectively. The PHQ-9 has been shown to have adequate construct validity and criterion validity^{42, 43} and has been used in studies with cancer patients and survivors^{43–46}.

Statistical Analysis

We calculated mean PHQ-9 depression scores and the association between PHQ-9 summary scores and each of the sample characteristics using ANOVA. We examined the bivariate correlation (Pearson correlation coefficient) between scores measuring depression and those measuring reproductive concerns and social support. In the multivariate logistic regression model, we categorized depression using the established PHQ-9 cut point, with a minimum score of 10 (range 0–20) indicating moderate to severe levels of depression⁴⁷. We

considered variables associated with the proportion of women with moderate to severe depression ($p < 0.10$) for inclusion in the multivariate logistic regression model. We used forward selection stepwise logistic regression to explore the relationship between overall reproductive concerns (summary score) and moderate to severe depression. We retained the primary explanatory variable (reproductive concerns) and variables with $p < 0.05$, to develop a data driven model.

For exploratory analyses, we categorized participants with mean overall RCAC and subscale scores of > 4 on a 5-point Likert scale as having high scores, those with mean scores 3 to 4 as having moderate scores, and those with mean scores below < 3 as having low scores. We used a chi-square test to calculate the bivariate association between overall reproductive concerns (High/Moderate/Low mean scores) and moderate to severe depression (Yes/No), and used ANOVA to compare mean PHQ-9 depression scores across these reproductive concerns categories. We then used a chi-square test to evaluate the relationship between each dimension of reproductive concerns represented in the RCAC scale (High/Not high mean scores) with moderate to severe depression (Yes/No). For each of these reproductive concerns dimensions, we used ANOVA to compare mean PHQ-9 depression scores across High/Not high score categories. We analyzed data in SAS Version 9.2 (SAS Institute, Inc., Cary, North Carolina) using two-tailed tests (critical alpha < 0.05).

RESULTS

Sample characteristics

Of 249 potential FAPAC participants identified through online screening, 236 (95%) were eligible, and 204 (86%) went on to complete the survey. For this study, we use data from 200 female cancer survivors who reported on both depression and reproductive concerns. Of the 26 cancer types reported, the most common were breast (17%), Hodgkin lymphoma (14%), leukemia (14%), thyroid (11%), non-Hodgkin lymphoma (9%), brain (6%) and soft tissue cancers (6%). Participants had a mean age of 28.4 years ($SD = 4.4$), were diagnosed between the ages of infancy and 34 years (Median = 23, Interquartile range = 8.0), and had an average duration of survivorship of 5.8 years ($SD = 5.5$). Most participants were White (80%) and were either married or in a committed relationship (60%). At the time of the survey, almost all participants (95%) reported having some type of health insurance coverage, 53% were employed full time, 16% were employed part time, and 17% were students. Additionally, 18% had biological children, 3% had adopted children, and 77% indicated that they had considered adoption after their cancer diagnosis (see Table 1).

Reproductive Concerns and Depression

Twenty-two percent of our sample reported moderate to severe depression, as indicated by a score of 10 or greater on the PHQ-9 assessment. The average RCAC summary score was 58.3 ($SD = 10.9$, Range 18 – 90). In bivariate analyses, PHQ-9 scores were associated with education, occupation status, life stage at diagnosis, and duration of survivorship (all with $p < 0.01$). PHQ-9 scores were also correlated with scores measuring reproductive concerns ($r = 0.37$, $p < 0.001$) and social support ($r = -0.39$, $p < 0.001$). Depression scores were not, however, associated with reproductive history or cancer characteristics. In addition to

reproductive concerns ($p < 0.001$), variables under consideration for inclusion in the multivariable model predicting moderate to severe depression included education ($p = 0.002$), occupation status ($p = 0.03$), having a biological child ($p = 0.07$), life stage at diagnosis ($p = 0.01$), duration of survivorship ($p = 0.001$), and social support ($p < 0.001$).

In the multivariate logistic regression model (see Table 2), for every 5 unit increase in the RCAC score, there was 1.3 higher odds of moderate to severe depression (95% CI = 1.06 – 1.60). College graduates (OR = 0.43, 95% CI = 0.19 – 0.96) and those with longer survivorship (OR = 0.42, 95% CI 0.21 – 0.86, units = 5 years) had lower odds of moderate to severe depression. For every 5 units increase in MOS social support score, odds of moderate to severe depression were reduced (OR = 0.65, 95% CI = 0.50 – 0.85).

Upon categorizing overall RCAC scores for unadjusted exploratory analyses, 10% of participants had high scores, 55% had moderate scores, and 35% had low scores. Mean PHQ-9 scores across these RCAC categories were 11.2 (SD = 6.1) for the high reproductive concerns category, 6.1 (SD = 5.1) for the moderate concerns category, and 4.2 (SD = 4.2) for the low concerns category ($p < 0.001$). Of those with moderate to severe depression, 23% had high RCAC scores as compared to 6% of those with minimal to mild depression ($p < 0.001$). Those with moderate to severe depression also had higher RCAC scores than those with minimal to mild depression for the following RCAC subscales: partner disclosure (42% vs. 14%); child's health (58% vs. 29%); personal health (54% vs. 19%); and becoming pregnant (26% vs. 8%) (see Table 3).

DISCUSSION

This study is the first to quantitatively examine the relationship between current, rather than recalled, reproductive concerns and depression in a sample of female cancer survivors who are in their reproductive years. In our sample, reproductive concerns after cancer were associated with moderate to severe depression, even after controlling for duration of survivorship, education, and social support. These findings are consistent with other studies exploring the association between reproductive concerns and quality of life outcomes among young cancer survivors, including our prior study with breast cancer survivors^{3, 6, 33}.

Twenty-two percent of our sample reported moderate to severe depression. By comparison, incidence rates of depression experienced by young adults in the United States are 11.1% (age 18–24 years) and 9.3% (age 25–34 years)⁴⁸. Our results indicate greater odds of depression among those earlier in survivorship, with the highest scores among those within less than five years of survivorship. Participants in this study largely represent those earlier in the transition to life after cancer. All were diagnosed one year or more prior to enrollment, with 64% between one and four years post-diagnosis. During this period, young survivors are managing their ongoing medical appointments and health concerns⁸ and often coping with significant disruptions in their life plans, all while making the developmental transition to adulthood^{49, 50}. For many young survivors, whether they are physically able to have children or not, experiencing reproductive concerns could have a considerable impact on their future plans. Although this cross-sectional study cannot determine the trajectory of individual experiences of depression over time or how that relates to reproductive concerns,

the results suggest a need to address these concerns during the transition phase from patient to survivor.

Many female YA survivors experience concerns about fertility and parenthood after cancer. In this sample, 65% had mean RCAC scores of three or greater on a five-point Likert scale, with 10% of those having mean scores greater than four. Survivors are not only concerned about their fertility potential, but express a number of related post-treatment concerns associated with their relationships, long-term health, discussing fertility issues with their partner, and the health of their potential children^{4, 31}. In this sample, about one-third of participants reported being highly concerned about their (potential) child's health and one quarter were highly concerned about being healthy enough to raise a child. Participants in both of these groups were also more likely to be experiencing moderate to severe depression. After further research establishes clinically significant RCAC cutoff scores, these scores can be used to identify vulnerable groups who could benefit from tailored information and referral for care to address their specific concerns.

A plausible mechanism for the relationship between reproductive concerns and depression is unmet informational needs⁵¹. Patient-reported outcomes data in cancer survivors indicate that failing to meet the informational needs of survivors may contribute to poorer quality of life outcomes⁵². Young survivors with significant unmet informational needs are at increased risk of psychological distress as compared to those diagnosed as older adults^{24, 51, 53–56}. Survivors may also face barriers to seeking and obtaining information to address their reproductive concerns. While there are guidelines for clinical care and long-term follow-up to monitor the reproductive health of YA survivors⁵⁷, they may not realize the importance of ongoing follow-up care or have low perceived susceptibility to late effects, such as earlier ovarian senescence^{58, 59}. There is also evidence that YA survivors are uncertain about what type of doctor to see, how and when to access specialized care, and are hesitant to seek care for fear of infertility^{4, 59}. They may also face barriers to effective patient-provider discussion of these concerns. For example, healthcare providers may lack knowledge about the specific informational needs of YA cancer survivors or may be uncomfortable discussing sensitive issues, such as fertility, with their young patients^{60–64}. Healthcare providers could benefit from additional training to prepare them to handle these sensitive topics with their cancer survivor patients^{60, 65}.

Important strengths of this study include a nationwide sample of YA reproductive-age female survivors, age 18 to 35 years, with common YA cancers. The study also incorporated a scale designed to measure the range of reproductive concerns experienced by YA female cancer survivors³¹. Although the study sample is diverse across a number of characteristics, participants were mostly White (non-Hispanic), limiting our ability to explore potential racial or ethnic disparities. This will be an important focus of future studies. This study is also limited by self-reported cancer characteristics. Our results indicate the lack of an association between cancer characteristics and depression, which is consistent with other research⁶⁶, and leaves open the possibility for psychosocial or behavioral interventions to improve quality of life in survivorship across a range of cancer types and diagnoses. However, the complex relationship between cancer characteristics and depression is not the focus of the current study and warrants further investigation. We also did not collect data on

use of antidepressants, so we could not include this potential covariate in our analyses. Because our study was specifically interested in exploring fertility and parenthood experiences, our sample may have been biased toward survivors interested in having children and our results may not be generalizable to the wider population of YA female survivors. However, the proportion of participants who reported wanting a child, about three-quarters, is similar to that reported in other studies^{13, 23}. Additional research is needed to further explore potential mediators in the relationship between reproductive concerns (including the six subscales) and depression, such as unmet informational and support needs as well as access to fertility preservation, adoption, and other alternative routes to parenthood. For example, we did not collect information about the specific role of partners or women's partner support needs related to their reproductive concerns. It is possible that partner support could influence women's experiences of reproductive concerns, and this merits exploration in future studies. Finally, we propose a range of mean RCAC scores as exploratory indicators of patient-reported reproductive concerns but additional research is needed to establish clinically meaningful cutoff scores for the RCAC scale and subscales.

Clinical implications

A higher level of reproductive concerns is associated with greater odds of experiencing moderate to severe depression. Almost a quarter of survivors in this sample reported moderate to severe depression, and addressing reproductive concerns represents one potential area of intervention to improve this and other quality of life outcomes for young survivors. Vulnerable groups could benefit from tailored information and counseling to address their concerns, and some may also benefit from referral to a specialist. The results of this study bolster the notion that addressing reproductive concerns through improved care and support is an important element of comprehensive long-term care for YA cancer survivors^{1, 5, 11, 13, 18, 33–35}.

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Table 1

Sample characteristics and bivariate association with PHQ-9 depression score (N=200)

	No. of participants (%) or sample mean	Mean PHQ-9 score ^a (SD)	<i>p</i>
Demographics			
Age at survey (yrs)			0.64
20	11 (5.5)	4.6 (5.3)	
21–25	47 (23.5)	6.3 (6.2)	
26–30	66 (33.0)	6.3 (5.2)	
31–35	76 (38.0)	5.5 (4.8)	
Race			0.64
White	159 (79.5)	5.8 (5.4)	
Non-white	41 (20.5)	6.3 (4.8)	
Ethnicity			
Hispanic/ Latina	19 (9.5)	6.7 (6.8)	0.48
Non-Hispanic/ Latina	181 (90.5)	5.8 (5.1)	
Relationship status			0.94
Married or marriage-like relationship	120 (60.0)	6.0 (5.6)	
Single / Other	80 (40.0)	5.9 (4.8)	
Education			< 0.001
High school graduate	55 (27.5)	8.3 (6.0)	
College graduate	79 (39.5)	5.3 (5.0)	
Graduate or postgraduate degree	66 (33.0)	4.7 (4.4)	
Occupation status			0.002
Full time	105 (52.5)	5.0 (4.5)	
Part time	31 (15.5)	7.3 (6.3)	
Student	33 (16.5)	4.8 (4.6)	
Not employed	31 (15.5)	8.7 (6.2)	
Children and reproductive history			
Biological child(ren)			0.10
Yes	35 (17.5)	7.3 (5.7)	
No	165 (82.5)	5.6 (5.2)	
Adopted child(ren)			
Yes	5 (2.5)	8.0 (7.6)	0.38
No	195 (97.5)	5.9 (5.2)	
Considered adoption after cancer			
Yes	153 (76.5)	5.7 (4.9)	0.31
No	47 (23.5)	6.6 (6.4)	
History of Miscarriage			0.27
Yes	14 (7.0)	7.4 (5.7)	
No	186 (93.0)	5.8 (5.3)	
History of Infertility			0.95

	No. of participants (%) or sample mean	Mean PHQ-9 score ^a (SD)	<i>p</i>
Yes	15 (7.5)	6.0 (4.4)	
No	185 (92.5)	5.9 (5.4)	
Hysterectomy			0.50
Yes	14 (7.0)	5.0 (3.8)	
No	186 (93.0)	6.0 (5.4)	
Past year menstrual periods (missing 6)			0.60
0–3	36 (18.6)	6.8 (5.1)	
4–9	37 (19.1)	5.6 (4.8)	
10–12	121 (62.4)	5.8 (5.5)	
Past year endocrine therapy ^c			0.68
Yes	15 (7.5)	6.5 (7.4)	
No	185 (92.5)	5.9 (5.1)	
Cancer characteristics and treatment			
Life stage at diagnosis			0.009
Childhood (< 14 yrs)	26 (13.0)	3.0 (2.7)	
Adolescence (15–19 yrs)	22 (11.0)	5.9 (5.3)	
Young adulthood (20–35 yrs)	152 (76.0)	6.4 (5.5)	
Duration of survivorship (yrs)			< 0.001
1–4	128 (64.0)	6.9 (5.6)	
5–9	42 (21.0)	5.3 (4.8)	
10 or more	30 (15.0)	2.6 (2.9)	
Cancer type			0.25
Breast	34 (17.0)	6.2 (5.9)	
Hodgkin lymphoma	28 (14.0)	5.3 (4.0)	
Leukemia	27 (13.5)	6.9 (5.1)	
Thyroid	21 (10.5)	8.4 (7.0)	
Non-Hodgkin lymphoma	17 (8.5)	5.9 (6.2)	
Brain	12 (6.0)	5.8 (5.1)	
Soft tissue sarcoma	12 (6.0)	4.4 (4.8)	
Other ^b	49 (24.5)	4.9 (4.4)	
Cancer stage or risk group			0.65
I	35 (17.5)	7.1 (6.8)	
II	52 (26.0)	5.4 (5.1)	
III	33 (16.5)	6.0 (4.7)	
IV	22 (11.0)	6.2 (5.1)	
Low or standard	9 (4.5)	6.0 (3.8)	
High	9 (4.5)	7.6 (4.5)	
Unknown	40 (20.0)	5.0 (5.1)	
Chemotherapy			0.18
Yes	152 (76.0)	5.6 (5.2)	

	No. of participants (%) or sample mean	Mean PHQ-9 score ^a (SD)	<i>p</i>
No	48 (24.0)	6.8 (5.5)	
Radiation			0.27
Yes	103 (51.5)	6.3 (5.7)	
No	97 (48.5)	5.5 (4.8)	
Bone marrow or stem cell transplant			0.53
Yes	21 (10.5)	5.2 (3.8)	
No	179 (89.5)	6.0 (5.4)	
Well-being			
Reproductive concerns after cancer score ^d	58.3 (10.9)	NA	<0.001
Social support score ^e	37.7 (7.1)	NA	<0.001

^aPHQ-9 summary score, range 0–27

^b19 other cancer types represented

^cEndocrine therapy includes use of Tamoxifen, GnRH agonists, and Aromatase Inhibitors

^dReproductive Concerns After Cancer summary score, range 18–90

^eMOS Social Support summary score, range 0–45

Table 2

Logistic regression model of variables related to moderate to severe depression (N = 195)

Variable	Adjusted OR (95% CI)
Reproductive concerns after cancer score ^a (units=5)	1.30 (1.06 – 1.60)
College graduate	0.43 (0.19 – 0.96)
Duration of survivorship (units=5 yrs)	0.42 (0.21 – 0.86)
MOS social support total score ^b (units=5)	0.65 (0.50 – 0.85)

Note: Model adjusted for all variables shown in the table.

^aRCAC scale summary score, range 18–90

^bMOS Social Support summary score, range 0–45

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Table 3

Association between categories of Reproductive Concerns After Cancer (RCAC) scale and subscale scores and depression (unadjusted) (N=200)

	Depression			<i>p</i>
	Total sample <i>N</i> = 200 <i>n</i> (%)	Minimal to mild <i>n</i> = 157 <i>n</i> (%)	Moderate to severe <i>n</i> = 43 <i>n</i> (%)	
RCAC overall scale score				
High ^a	20 (10.0)	10 (6.4)	10 (23.3)	< 0.001
Moderate ^b	110 (55.0)	84 (53.5)	26 (60.5)	
Low ^c	70 (35.0)	63 (40.1)	7 (16.3)	
High RCAC subscale score^a				
Fertility potential	59 (29.5)	43 (27.4)	16 (37.2)	0.26
Partner disclosure	40 (20.0)	22 (14.0)	18 (41.9)	< 0.001
Child's health	71 (35.5)	46 (29.3)	25 (58.1)	0.001
Personal health	53 (26.5)	30 (19.1)	23 (53.5)	< 0.001
Acceptance ^d	16 (8.0)	13 (8.3)	3 (7.0)	1.0
Becoming pregnant	24 (12.0)	13 (8.3)	11 (25.6)	0.006

^a High mean RCAC scale and subscale scores defined as mean score > 4, range 1–5

^b Moderate mean RCAC scale and subscale scores defined as mean score 3 to 4, range 1–5

^c Low mean RCAC scale and subscale scores defined as mean score < 3, range 1–5

^d Reverse coded, higher score indicates lower acceptance of not having children