Published in final edited form as:

Qual Life Res. 2014 March ; 23(2): 585–592. doi:10.1007/s11136-013-0473-y.

Quality of life in female cancer survivors: Is it related to ovarian reserve?

Laxmi A. Kondapalli, MD, MSCE^{1,2,*}, Katherine E. Dillon, BS², Mary D. Sammel, ScD³, Anushree Ray, BS⁴, Maureen Prewitt, RN⁴, Jill P. Ginsberg, MD⁵, and Clarisa R. Gracia, MD MSCE²

¹Section of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Colorado Anschutz Medical Campus, Aurora, United States 80045

²Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, United States 19104

³Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, United States 19104

⁴Center for Research in Reproduction and Women's Health, University of Pennsylvania Perelman School of Medicine, Philadelphia, United State 19104

⁵Division of Oncology, Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, United States 19104

Abstract

Purpose—To assess quality of life scores and possible association with measures of ovarian reserve in female cancer survivors compared to healthy controls of similar age.

Methods—In this prospective cohort study, fifty-nine cancer survivors aged 16–39 years and 66 healthy, similarly aged unexposed women were recruited at the University of Pennsylvania. The primary outcome measures are the generic and cancer-specific domain scores on the Quality of Life in Adult Cancer Survivors (QLACS) instruments, early follicular phase serum hormones (follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), inhibin B (INH), anti-Mullerian hormone (AMH) and ovarian ultrasound measurements (ovarian volume and antral follicle count [AFC])

Results—Cancer survivors had significantly higher total and cancer-specific domain scores compared to unexposed participants. Serum AMH, INH, ovarian volume and AFC were lower while serum FSH was higher in cancer survivors. Although survivors exhibited diminished ovarian reserve, these markers were not independently associated with total QLACS score. Cancer survivors with irregular menstrual function were found to have lower QOL scores than those with regular cycles.

* Address correspondence to: Laxmi A. Kondapalli, MD MSCE, Tel: 303-724-6139, Fax: 303-724-7171, laxmi.kondapalli@ucdenver.edu.

AUTHOR'S ROLES

L.A.K and C.R.G developed the study design. A.R., M.P. and J.G. assisted with participant recruitment and data collection. L.A.K, K.E.D, M.D.S and C.R.G. conducted the data analysis and interpretation. L.A.K, K.E.D and C.R.G. prepared the manuscript. All authors have seen and approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

Presented at the 65th Annual Meeting of the American Society of Reproductive Medicine, Atlanta, Georgia, October 17–21, 2009.

Conclusions—We found that QOL appears to be significantly impaired in cancer survivors compared to controls, even when remote from initial cancer diagnosis. In addition, our study suggests that reproductive aging contributes to QOL in the setting of irregular menses and likely profound impairment of ovarian function.

Keywords

Quality of life; oncology; ovarian reserve; cancer; oncofertility

INTRODUCTION

Survival rates from cancer have steadily increased over the past 40 years. Improved survival is largely due to better understanding of cancer biology, early detection methods, and advances in cancer therapeutics. However, the immediate and late effects of cancer and its treatment remain areas of concern for survivors. Despite promising advances in cancer treatment, quality of life (QOL) for cancer survivors appears to be impaired well beyond the completion of treatment [1]. Oftentimes reproductive and sexual organs are impacted by cancer therapy, and may result in impaired psychosocial and sexual functioning [2, 3]. Furthermore, life-saving treatments may also delay childbearing and cause infertility or premature ovarian failure, thus reducing the chances of having biological children in the future. Indeed, a number of studies from survivor cohorts have demonstrated that long-term cancer survivors have fewer marriages and offspring [4, 5].

While this reproductive impairment is well documented, there are limited data exploring exactly how it affects QOL in reproductive-aged survivors. Aside from concerns about future fertility, it is unclear whether the physiologic reproductive changes that result from gonadotoxic therapies have an independent effect on quality of life. Studies suggest that cancer survivors have impaired ovarian reserve similar to late-reproductive aged women approaching menopause [6]. Given the abundant data concerning the psychosocial impact of ovarian aging [7], we sought to determine if QOL impairment in cancer survivors could be tied to impairment in ovarian reserve. We compared the QOL of cancer survivors to similar-aged healthy controls, and attempted to determine if there was an association between QOL and measures of ovarian reserve. We hypothesized that impaired measures of ovarian reserve may be associated with decreased measures of quality of life in some domains.

MATERIALS AND METHODS

This study is part of an ongoing prospective cohort study at the University of Pennsylvania (Penn) comparing annual measures of ovarian reserve between females exposed to chemotherapy and similarly aged healthy unexposed females [6]. This report compares measures of quality of life and ovarian reserve from the first assessment between these 2 groups.

Participants

Reproductive-aged cancer survivors were recruited from the Children's Hospital of Philadelphia Survivorship Program and the Transition Program at Penn's Living Well after Cancer Program during 2006–2010. Inclusion criteria were (1) chemotherapy treatment, (2) at least 1 year from cancer treatment with no evidence of disease, (3) age 15–39 years, (4) postmenarchal, and (5) presence of uterus and both ovaries. Exclusion criteria included a history of a brain or ovarian tumor, pregnancy or lactation within 3 months, hormonal contraception or hormone therapy within 4 weeks, and any medical condition other than cancer associated with ovarian dysfunction.

Unexposed, reproductive aged controls of similar age to cancer survivors were identified through health practices affiliated with Penn and advertising. Controls were postmenarchal, with regular menstrual cycles (21–35 days), presence of uterus and both ovaries. Exclusion criteria were the same as for survivors. This analysis was restricted to Caucasian participants.

The institutional review board at the University of Pennsylvania approved this study, and informed consent was obtained from all participants. Study visit occurred on days 1–4 of the menstrual cycle. Participants discontinued exogenous hormones for at least 4 weeks and were seen during the subsequent menstrual cycle. Cancer survivors with irregular cycles or no menses for 6 weeks after discontinuing hormones were seen any time.

Questionnaires

During a structured interview, detailed information was collected regarding demographics, medical history, menstrual characteristics, pregnancies, infertility history, contraception, medications, and substance use. Participants were given a menstrual diary and provided the dates of the two most recent menstrual cycles during the interview. Cycle length was calculated as the interval between the two most recent menstrual cycles.

Cancer Treatment

Exposure data were obtained by abstracting medical records. Treatment was summarized for chemotherapeutic type, duration, cumulative dose; radiation dose and location; type of bone marrow transplantation (BMT); and surgery. Chemotherapies categorized as alkylating agents included carmustine, busulfan, lomustine, chlorambucil, cyclophosphamide, ifosfamide, melphalan, nitrogen mustard, procarbazine, and thiotepa. Alkylating agent dose scores (AAD) were determined by assigning a score ranging from 1 to 3 for each agent received and summing the scores over each agent received. We utilized previously published cutoff points to define the scores [8].

Quality of Life Instrument

For this study, we administered the Quality of Life in Adult Cancer Survivors (QLACS) instrument to all participants. The QLACS is a 47-item self-reported questionnaire designed to assess health-related quality of life among long-term cancer survivors [9–11]. There are 5 cancer-specific domains (appearance concerns, financial problems, distress-recurrence, distress-family, and benefits of cancer) along with 7 generic domains (negative feelings, positive feelings, cognitive problems, sexual problems, physical pain, fatigue, and social avoidance). Each item is rated on a 7-point Likert scale (1= never, 7= always). The QLACS has demonstrated good internal consistency (Cronbach's alpha = 0.72 for each domain) [10]. Scores are inversely related to quality of life, such that higher scores reflect worse quality of life.

Physical Examination

Height and weight were measured for calculating body mass index (BMI).

Pelvic Ultrasonography

Uterine volume, ovarian volume and antral follicle counts (AFC) were determined by ultrasonography. Measurements were performed using a Siemens Sonoline G50 machine, 6.8-MHz probe. Transvaginal ultrasonography was preferred, though transabdominal ultrasound was performed in participants uncomfortable with the transvaginal approach. Uterine and ovarian volumes were calculated using the ellipse formula ($A \times B \times C \times 0.5233$). Antral follicle count was determined for participants undergoing transvaginal

ultrasonography when both ovaries were visualized and was defined as the number of follicles between 2 and 10mm in average diameter.

Hormone Analysis

Serum hormones were measured at Penn's Clinical Translational Research Center using LH, FSH and E2 Coat-A-Count kits (Diagnostic Products Corporation) and inhibin B and AMH ELISA kits (Diagnostic Systems). The FSH assay's range is 1.5–100 mIU/mL, with sensitivity of 0.7 mIU/mL and inter- and intra-assay coefficients of variation (COV) <6% and 4%, respectively. The LH assay's range is 1.5–200 mIU/mL, with sensitivity of 0.05 mIU/mL and inter- and intra-assay COV 3.6% and 6.7%, respectively. The E2 range is 20–3,600 pg/mL, with a sensitivity of 7 pg/mL and inter- and intra-assay COV <8.1% and 7%, respectively. The inhibin B ELISA's range is 10–531 pg/mL, with sensitivity of 7 pg/mL and inter- and intra-assay COV <8% and <6%, respectively. The AMH ELISA's range is 0.05–10.0 ng/mL, with a sensitivity of 0.025 ng/mL and inter- and intra-assay COV <8% and 5%, respectively.

Data Analysis

An a priori sample size calculation indicated that 92 participants (46 per group) were required for this study. The sample size calculations were based on the published estimates of mean generic and cancer-specific domain scores in cancer survivors [9, 10], an estimated difference of 25% in mean scores between the survivors and the unexposed groups, type I, α , error of 0.05, power of 80 percent, and equal number of exposed to unexposed. Individual comparisons between demographic and clinical characteristics of the participants based on exposure group were evaluated by Student's t-test or Mann-Whitney U test as appropriate for continuous variables, and chi-square test for categorical variables. Generic and cancer-specific domain scores were the primary outcomes of interest. Secondary outcomes included serum FSH, AMH and Inhibin B levels and total antral follicle count. Multivariable analysis was performed using linear regression to identify significant independent associations between several covariates (age, BMI, income, education, marital status, and pregnancy history) and QLACs overall and domains. Additional models examined the associations between quality of life and reproductive hormones (FSH, LH, estradiol, AMH, inhibin B, ovarian volume and AFC) and interactions between these hormones and exposure status (cancer/control) were also examined. Data analysis was conducted using STATA version 12 (Stata Corp, College Station, TX, USA). Two tailed P value < 0.05 was considered statistically significant.

RESULTS

Cancer survivors enrolled in this study were, on average, 14.1 years from diagnosis. Cancer survivors and healthy controls were similar in BMI, marital status, gravidity, and household income, as well as age (by design) [Table 1]. The majority of participants had not been pregnant. Significantly more cancer survivors reported concerns about fertility than the unexposed group (73 vs. 45%, $p=0.002$). Sixty-four percent of survivors (and all of controls) reported regular menstrual cycles off hormones for the prior year. Of participants with regular menstrual cycles, the mean cycle length was similar between groups. Survivors were assessed an average of 14.1 years (95%CI 11.9, 16.3 years) from the time of cancer diagnosis. Leukemia and lymphoma were the most common cancer diagnoses, comprising two-thirds of survivors in this cohort [Table 2]. Fifty-four survivors (91.5%) received chemotherapy treatment with an alkylating agent, 2 reported pelvic radiotherapy and 9 (15.2%) reported total body irradiation.

Survivors had significantly higher mean total QLACS scores compared to healthy controls (129.7 vs. 97.8, $p<0.0001$) [Table 3]. QOL score was not associated with time since cancer diagnosis. Additionally, survivors had significantly higher mean scores on every cancer-specific domain than the unexposed group, reflecting a lower quality of life. Of note, survivors had higher scores on generic domains scores of sexual problems, physical pain and fatigue. Table 4 compares the baseline markers of ovarian reserve between the 2 groups. Cancer survivors appear to have some element of diminished ovarian reserve as reflected by significantly higher serum FSH (21.9 vs 7.4 mIU/mL, $p<0.001$). While the mean serum AMH and total antral follicle count were significantly lower in the survivor group, these values were in the normal range and remained reassuring, when compared to the unexposed group.

We first evaluated the effect of measures of ovarian reserve on QLACS domain scores in the entire study population using linear regression. While QLACS score did show an association with some measures of ovarian reserve in univariate analyses (data not shown), these associations were no longer significant after adjustment for cancer status. We also examined models with an interaction between cancer status and measures of ovarian reserve and once again demonstrated that the variability in the QLACS score was a result of the case/control group and not the measure of ovarian reserve.

We then performed analyses restricted to the cancer survivor group to investigate the association between individual exposure factors and total, cancer-specific and generic QLACS scores. Among survivors, cancer diagnosis was divided into 3 categories based on prevalence in this cohort: 1= leukemia, 2= lymphoma and 3= other malignancies (sarcoma, Wilm's, breast, and germ cell tumors). Total QLACS score was significantly associated with cancer type. On average, women with lymphoma have higher scores than women with leukemia, though this did not reach significance (β coeff =10.4, $p=0.19$), and the women in the other malignancy category have significantly higher scores than women with leukemia (β coeff=22.7, $p=0.007$) however, there was no association with markers of ovarian reserve. This observation was similar when considering the cancer-specific domain score. Although cancer type was positively associated with cancer-specific QOL score (β =3.2 $p=0.45$ for lymphoma vs. leukemia patients, and β =10.8 $p=0.016$ for 'Other' vs. leukemia patients), exposure to alkylating chemotherapy or pelvic and total body radiation did not correlate with this score. In addition, FSH, AMH and total AFC were not significantly associated with cancer-specific scores. Examination of the general domain score demonstrates a loss of the association with cancer type.

Finally, within the survivor group, the findings that cancer type (a proxy for treatment regimen toxicity) is significant for the total overall score and for total cancer score holds true when adjusted for age and BMI in a multivariate model [Table 5]. Further, the association between total generic score and irregular cycles is also significant when controlled for age, BMI, and cancer type. Survivors with irregular cycles had increased generic scores of 15.6 points compared to women with regular cycles ($p=0.013$) indicating lower quality of life compared to those with regular menstrual cycles. In unadjusted analyses the associations that were significant with menstrual irregularity were domain scores on Negative Feelings, Positive Feelings, Cognitive Problems, and Social Avoidance. These remained significant in models adjusted for age, BMI, and cancer type.

Discussion

To date, few studies have examined the relationship between quality of life and ovarian function after cancer treatment. In this study we assessed the relationship between measures of ovarian reserve and quality of life many years after cancer treatment. Reproductive

concerns, particularly the ability to conceive, can be a source of anxiety and affect long-term quality of life for many cancer survivors. In our study, 73% of survivors report being worried about fertility. Our findings are consistent with previous studies demonstrating that the possibility of parenthood is important to survivors. In fact, approximately 75% of young adults without children at the time of cancer diagnosis report a desire for future fertility [12–14]. Recent studies have indicated that treatment-related gonadotoxicity and potential loss of fertility has a profound impact on young women, and can be more devastating than the cancer diagnosis itself [12, 15, 16]. This suggests that there may be a need for more formalized intensive counseling both prior to and after cancer treatment to aid patients in resolving or managing psychosocial sequelae resulting from infertility.

We found that quality of life appears to be significantly impaired in cancer survivors compared to similarly aged controls, even when remote from initial cancer diagnosis. Survivors enrolled in this study were, on average, 14.1 years from diagnosis, and exhibited lasting adverse effects on long-term well-being. We found that cancer survivors had higher scores on total QLACS domain reflecting a poorer overall quality of life than healthy controls. In addition, survivors had higher scores on every factor included in the cancer-specific domain. Of note, survivors were particularly concerned about appearance, and were distressed about cancer recurrence. Our findings are consistent with other studies of QOL in young cancer survivors. For example, a cross-sectional study of breast cancer survivors indicated that survivors face significant psychological burdens related to fear of recurrence and anxiety [17]. Carver *et al.* examined the effect of demographic, medical and psychosocial factors on different aspects of QOL [18] and found that stage of disease was associated with poor QOL and greater worry about financial problems and physical appearance [18].

The primary goal of the current study was to determine whether ovarian function was independently associated with QOL scores in this population. Overall, we found that measures of ovarian reserve did not appear to be independently associated with quality of life scores. Although cancer survivors had elevated serum FSH and LH levels, and lower AMH levels consistent with diminished ovarian reserve, these markers were not independently associated with QLACS score.

However, we did find that among survivors, the presence of irregular menstrual cycles was associated with QOL scores. Our study suggests that reproductive aging contributes to QOL in the setting of irregular menses. Participants with irregular menstrual cycles most likely had more profound impairment of ovarian function and were later in the menopausal transition, a time when menopausal symptoms begin to occur [19]. Because most of the participants in the present study were menstruating and did not have menopausal symptoms, it was not possible to assess the association between menopausal symptoms and quality of life. We acknowledge this as a limitation of our study. However, it is likely that subclinical changes in ovarian reserve do NOT impact QOL, whereas more obvious clinical manifestations such as irregular cycles and menopausal symptoms contribute to decreased measures of quality of life. We found that survivors' self-assessment of negative and positive feelings, cognitive problems, and social avoidance were associated with menstrual cyclicity. These psychosocial concerns should be addressed in the setting of cancer survivorship care.

Overall, there are few reports of how diminished ovarian reserve and premature ovarian failure impair QOL in cancer survivors. Most studies have assessed the impact of menopausal symptoms on QOL in breast cancer survivors. For example, Ganz *et al.* found that breast cancer survivors reported more frequent menopausal symptoms and general health concerns than healthy controls. Furthermore, Carpenter *et al.* also found that breast

cancer survivors with hot flashes had a lower self-reported QOL and were more likely to have been treated with chemotherapy. In a cross-sectional study of QOL in 291 long-term breast cancer survivors, those with hot flashes were more likely to report that cancer had affected their overall health and QOL [20]. These data indicate that the clinical manifestations of the menopause are associated with impaired measures of quality of life.

Our findings suggest that factors outside of reproductive potential and ovarian function principally impact quality of life experienced by cancer survivors. In addition, baseline characteristics including age and socioeconomic status, such as education level and household income, did not influence quality of life. In this study, cancer type serves as a surrogate marker for severity of treatment and significantly affected the cancer-related QOL but did not demonstrate an influence on generic QOL domains.

We also found that cancer survivors in this study were more likely to report sexual problems compared to similar age healthy women without a history of cancer. This finding is consistent with other reports of psychosexual problems in childhood cancer survivors [21, 22]. Additional studies assessing specific measures of sexual function may help to delineate the mechanisms underlying this association, and potential therapeutic measures that may improve sexual function in this population.

This study has several strengths. Recall bias was minimized by prospective enrolment and valid comparisons were made to an unexposed control population of similar age. Confounding has been reduced by restricting the study to females without other medical causes of ovarian dysfunction, who are not pregnant, lactating or using exogenous hormones. Unlike some other studies, a comprehensive evaluation of measures of ovarian reserve was performed and hormone variability minimized by obtaining early follicular phase measures. Cancer diagnoses and treatments were validated with medical records to diminish misclassification bias. In addition, the use of the QLACS in this population is appropriate since this is a validated questionnaire, which considers functioning and patient satisfaction with functioning [10], developed specifically for cancer survivors 5 years from diagnosis and provides a multidimensional approach to quality of life. In addition, the QLACS is one of the few instruments that explores the late effects of cancer, with emphasis placed on survivorship, not disease. The questionnaire is responsive to long-term follow up of survivors [10] and to life changes[9]. The QLACS provides a useful tool for assessing health-related QOL among cancer survivors that are not addressed by generic instruments or those designed for newly diagnosed patients, which can be applied both to clinical assessment and research purposes.

Several potential limitations should be considered in this study. The study sample consisted primarily of white survivors and lacked ethnic diversity, which limits the generalizability of the findings to other populations. This is a cross-sectional analysis and therefore these data only reflect a single point in time. Longitudinal administration of the QLACS with analyses of repeated measures starting at diagnosis and determined periods of long-term survival, would be helpful to confirm the associations over time. While administering the same questionnaire to diseased and healthy populations is a common approach for assessing the impact of a particular disease on health status, it is difficult to compare general health status scores in cancer survivors with those for the general population. In addition, survivors enrolled in our study were younger at the time of cancer diagnosis than typically assessed by the QLACS instrument, which makes it difficult to compare our results to other studies. It would be helpful to compare our findings with those of other similar studies utilizing different quality of life instruments [23, 24].

There may be a role for in-depth qualitative research in broadening the understanding of the determinant of quality of life in young cancer survivors. Open-ended survey questions and in-person interviews that allow for survivor narratives of quality of life may address issues and problems not identified by instruments like the QLACS. In addition, further investigation into the association between menstrual dysfunction, early menopause and menopausal symptoms on QOL in a larger study of young cancer survivors may be informative.

Over the past few decades, emerging interest in long-term survivorship issues has prompted multiple investigators to explore the physical, emotional, psychosocial, and sexual health of cancer patients. While initial studies focused primarily on assessing outcomes after initial diagnosis, early detection and improved therapeutic options have considerably enhanced long-term survivorship. The large number of women surviving many years to decades beyond their diagnosis has enhanced interest in the late effects of cancer and its treatments on quality of life. Assessment of health-related QOL issues in cancer survivors is widely promoted [10] although a single, validated QOL questionnaire has not been standardized in this patient population. Multidimensional tools such as the QLACS may help identify cancer late effects that clinicians should monitor, and determine which patients may benefit from additional services and interventions. In this study we found that quality of life scores assessed by the QLACS are impaired in young cancer survivors, they do not appear to be associated with measures of ovarian reserve overall. However, QOL scores were lower in women with irregular menstrual cycles, suggesting that more profound changes in ovarian function may impact QOL in this population. Understanding determinants of QOL in this population may help to identify ways to manage late effects of treatment and improve comprehensive survivorship care.

Acknowledgments

Funding/Support: Supported by NIH T32 HD007440 and NIH 5K12HD001271-12 (LAK); Doris Duke Clinical Research Fellowship (KED); NIH K01 L:1-CA-133839-03 (CRG); 1R01HD062797 (CRG,MDS).

REFERENCES

1. Zeltzer LK, Recklitis C, Buchbinder D, Zebrack B, Casillas J, Tsao JC, Lu Q, Krull K. Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009; 27:2396–2404. [PubMed: 19255309]
2. Schover LR. Psychosocial issues associated with cancer in pregnancy. *Semin Oncol*. 2000; 27:699–703. [PubMed: 11130477]
3. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst*. 2012; 104:386–405. [PubMed: 22271773]
4. Janson C, Leisenring W, Cox C, Termuhlen AM, Mertens AC, Whitton JA, Goodman P, Zeltzer L, Robison LL, Krull KR, Kadan-Lottick NS. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:2626–2635. [PubMed: 19815636]
5. Frobisher C, Lancashire ER, Winter DL, Jenkinson HC, Hawkins MM. British Childhood Cancer Survivor Study. Long-term population-based marriage rates among adult survivors of childhood cancer in Britain. *Int J Cancer*. 2007; 121:846–855. [PubMed: 17450524]
6. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, Vance A, Ginsberg JP. Impact of cancer therapies on ovarian reserve. *Fertil Steril*. 2012; 97:134,40.e1. [PubMed: 22137491]
7. Mann E, Singer D, Pitkin J, Panay N, Hunter MS. Psychosocial adjustment in women with premature menopause: a cross-sectional survey. *Climacteric*. 2012; 15(5):481–489. [PubMed: 22335389]

8. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, Donaldson SS, Byrne J, Robison LL. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. 2009; 27:2677–2685. [PubMed: 19364965]
9. Avis NE, Ip E, Foley KL. Evaluation of the Quality of Life in Adult Cancer Survivors (QLACS) scale for long-term cancer survivors in a sample of breast cancer survivors. *Health Qual Life Outcomes*. 2006; 4:92. [PubMed: 17140438]
10. Avis NE, Smith KW, McGraw S, Smith RG, Petronis VM, Carver CS. Assessing quality of life in adult cancer survivors (QLACS). *Qual Life Res*. 2005; 14:1007–1023. [PubMed: 16041897]
11. Pearce NJ, Sanson-Fisher R, Campbell HS. Measuring quality of life in cancer survivors: a methodological review of existing scales. *Psychooncology*. 2008; 17:629–640. [PubMed: 17973235]
12. Schover LR. Patient attitudes toward fertility preservation. *Pediatr Blood Cancer*. 2009; 53:281–284. [PubMed: 19301387]
13. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. *J Clin Oncol*. 2002; 20:1880–1889. [PubMed: 11919248]
14. Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer. A pilot survey of survivors' attitudes and experiences. *Cancer*. 1999; 86:697–709. [PubMed: 10440699]
15. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, Melisko ME, Cedars MI, Rosen MP. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer*. 2012; 118:1710–1717. [PubMed: 21887678]
16. Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, Rosenberg R, Przypyszny M, Rein A, Winer EP. Web-based survey of fertility issues in young women with breast cancer. *J Clin Oncol*. 2004; 22:4174–4183. [PubMed: 15483028]
17. Ferrell BR, Grant MM, Funk BM, Otis-Green SA, Garcia NJ. Quality of life in breast cancer survivors: implications for developing support services. *Oncol Nurs Forum*. 1998; 25:887–895. [PubMed: 9644705]
18. Carver CS, Smith RG, Petronis VM, Antoni MH. Quality of life among long-term survivors of breast cancer: Different types of antecedents predict different classes of outcomes. *Psychooncology*. 2006; 15:749–758. [PubMed: 16304622]
19. Freeman EW, Sammel MD, Lin H, Liu Z, Gracia CR. Duration of menopausal hot flashes and associated risk factors. *Obstet Gynecol*. 2011; 117:1095–1104. [PubMed: 21508748]
20. Carpenter JS, Andrykowski MA, Cordova M, Cunningham L, Studts J, McGrath P, Kenady D, Sloan D, Munn R. Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. *Cancer*. 1998; 82:1682–1691. [PubMed: 9576289]
21. Zebrack BJ, Foley S, Wittmann D, Leonard M. Sexual functioning in young adult survivors of childhood cancer. *Psychooncology*. 2010; 19:814–822. [PubMed: 19862693]
22. van Dijk EM, van Dulmen-den Broeder E, Kaspers GJ, van Dam EW, Braam KI, Huisman J. Psychosexual functioning of childhood cancer survivors. *Psychooncology*. 2008; 17:506–511. [PubMed: 17935145]
23. Grant MD, Piotrowski ZH, Chappell R. Self-reported health and survival in the Longitudinal Study of Aging, 1984–1986. *J Clin Epidemiol*. 1995; 48:375–387. [PubMed: 7897459]
24. Ferrell BR, Dow KH, Grant M. Measurement of the quality of life in cancer survivors. *Qual Life Res*. 1995; 4:523–531. [PubMed: 8556012]

Table I

Baseline Characteristics of Study Participants

		Exposed (n=59)	Unexposed (n=66)	P value
Age (y)		26.8 ± 6.0	28.0 ± 3.9	0.22
BMI (kg/m ²)		23.4 ± 4.7	24.2 ± 5.6	0.46
Marital status- single, n (%)		31 (53.5)	43 (65.2)	0.28
College educated or greater, n (%)		38 (64.0)	51 (77.0)	0.11
Income (>\$75,000), n (%)		25 (42.9)	17 (25.6)	0.40
Previous pregnancy, n (%)	0	40 (75.5)	46 (75.4)	0.40
	1	13 (24.5)	15 (24.6)	
Worried about fertility, n (%)		43 (73.0)	30 (45.0)	0.002
Regular menstrual cycles, n (%)		35 (64.0)	62 (100)	<0.001
Menstrual cycle length (days) ^a		28 2.2	29.0 1.9	0.07

^a only calculated for those with regular cycles

Table II

Cancer Diagnosis and Treatment in 59 survivors, (n,%)

Cancer Type^a	Leukemia	18 (30.5)
	Lymphoma	22 (37.3)
	Sarcoma	11 (18.6)
	Wilm's tumor	2 (3.4)
	Breast	3 (5.1)
	Germ cell	3 (5.1)
Summed AAD	0	5 (8.5)
	1	15 (25.4)
	2	12 (20.3)
	3	11 (18.6)
	4	4 (6.8)
	5	8 (13.6)
	6-9	4 (6.8)
Pelvic Radiation	Yes	2 (3.4)
	No	57 (96.6)
Total body irradiation	Yes	9 (15.2)
	No	50 (84.7)

^a₁= leukemia, 2=lymphoma, 3=other

ADD = alkylating agent dose

Table III

Baseline QLACS Domain Scores

	Exposed (n=59)	Unexposed (n=66)	P value
Total score	129.7 (124.6–138.4)	97.8 (92.8–101.3)	<0.0001
Cancer-specific Domains			
Total cancer score	32.0 (28.7–36.5)	19.9 (18.3–22.3)	<0.0001
Appearance concerns	7.6 (6.4–9.0)	4.3 (3.9–4.8)	<0.0001
Financial problems	6.3 (5.5–8.5)	4.1 (4.0–4.2)	0.0005
Distress-recurrence	9.4 (8.1–10.8)	4.9 (4.2–5.6)	<0.0001
Distress-family	8.6 (7.1–9.8)	6.7 (5.8–8.0)	0.014
Benefits of cancer	17.3 (15.6–19.1)	4.6 (4.0–5.6)	<0.0001
Generic Domains			
Total generic score	70.2 (68.9–80.0)	61.7 (18.3–22.3)	0.016
Negative feelings	11.0 (10.1–12.6)	10.6 (9.1–11.0)	0.6
Positive feelings	19.6 (18.3–20.2)	19.6 (17.9–19.6)	0.97
Cognitive problems	9.8 (8.7–11.0)	8.6 (7.6–9.2)	0.11
Sexual problems	9.1 (7.9–11.2)	6.8 (5.9–7.5)	0.007
Physical pain	7.9 (7.1–9.2)	6.6 (5.8–7.7)	0.049
Fatigue	12.1 (14.2–15.7)	9.4 (12.2–13.4)	0.0002
Social avoidance	7.6 (6.6–9.1)	7.0 (6.0–7.9)	0.35

All values are Mean (95% CI)

Table IV

Baseline Ovarian Reserve Markers

	Exposed (n=59)	Unexposed (n=66)	<i>P</i> value
FSH (mIU/mL)	21.9 (13.9–30.0)	7.4 (6.7–8.0)	0.0003
LH (mIU/mL)	8.0 (3.6–12.4)	4.3 (3.7–4.9)	0.03
E2 (pg/mL)	34.1 (22.5–45.7)	33.9 (29.0–38.8)	0.98
AMH (ng/mL)	2.0 (1.3–2.8)	3.4 (2.8–4.0)	0.006
Inhibin B (pg/mL)	38.5 (30.8–46.3)	46.9 (38.0–55.7)	0.16
Mean ovarian volume (cm³)	7.3 (5.6–8.7)	9.8 (7.9–11.1)	0.22
Total AFC	15.1 (11.0–19.3)	27.9 (24.4–31.4)	<0.0001

All values are Geometric Mean (95% CI)

Table V

Factors associated with QLACS Score in Survivors (n=59)

	Overall Total Score		Total Generic Score	
	Coeff (95% CI)	P value	Coeff (95% CI)	P value
Age at visit	0.46 (−0.73–1.65)	0.44	0.94 (−0.08–2.0)	0.07
Years since diagnosis	−0.23 (−1.1–0.62)	0.59	0.11 (−0.65–0.87)	0.78
Cancer type	11.4 (3.35–19.4)	0.006	3.4 (−4.1–10.9)	0.37
Alkylator exposure	2.7 (−0.9–6.2)	0.14	−10.3 (−31.6–11.1)	0.34
Radiation exposure	−9.0 (−46.0–28.0)	0.63	−29.7 (−61.9–2.4)	0.07
Regular cycles	14.0 (−0.23–28.3)	0.054	15.6 (3.4–27.8)	0.013
BMI (kg/m ²)	0.83 (−0.77–2.4)	0.30	0.44 (−0.95–1.8)	0.53
FSH (mIU/mL)	1.6 (−6.1–9.4)	0.67	2.1 (−4.6–8.9)	0.53
LH (mIU/mL)	−2.4 (−12.5–7.8)	0.64	−0.69 (−8.9–7.8)	0.87
E2 (pg/mL)	−5.9 (−15.8–3.9)	0.23	−3.8 (−12.6–5.0)	0.39
AMH (ng/mL)	−3.2 (−7.5–1.1)	0.14	−2.0 (−5.8–1.8)	0.29
Inhibin B (pg/mL)	−4.8 (−12.7–3.1)	0.23	−5.2 (−11.9–1.6)	0.13
Total AFC	−0.23 (−0.77–0.31)	0.40	−0.08 (0.60–0.40)	0.72