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Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer

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Abstract

Background—We sought to describe the age-specific impact of infertility and early menopause after chemotherapy, among reproductive age women with cancer.

Methods—1041 women diagnosed with cancer between the ages of 18 and 40 responded to retrospective survey on reproductive health history. Five cancer types were included: leukemia, Hodgkin's disease (HD), non-Hodgkin lymphoma (NHL), breast cancer, and gastrointestinal cancer (GI). Survey questions addressed: AOF (cessation of menses after treatment), early menopause (menopause prior to 45 years old) and infertility (failed conception). Logistic regression was used to determine the proportions of AOF and infertility based on age at diagnosis. Censored data methods were used to determine the probability of early menopause.

Results—620 women received chemotherapy alone. The percentage reporting AOF was 8%, 10%, 9%, and 5% for HD, NHL, breast cancer, and GI, respectively. AOF increased significantly with age at diagnosis ($p < 0.05$). If not in AOF, the incidence of infertility was at least 40% at age 35 and increased significantly with age at diagnosis in HD and breast cancer ($p < 0.05$). The estimated probability of early menopause was at least 25% at age 30 and increased significantly with younger age at diagnosis in HD, NHL, and GI ($p < 0.05$).

Conclusions—In order to give patients appropriate counseling, it is important that they understand the potential increased risk of infertility and early menopause beyond that of acute ovarian failure. These findings can provide improved, age-specific counseling regarding reproductive impairment for young women diagnosed with cancer.

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Conflict of Interest Disclosures

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Introduction

According to 2006 SEER statistics, approximately 120,000 women under age 50 develop cancer each year in the United States.¹ Several studies have shown that loss of reproductive potential after cancer treatment can negatively impact quality of life in young survivors.^{2–4} Unfortunately, many young women unknowingly face reproductive compromise.⁵ While about 7% of women across the United States report 12-month infertility,⁶ the rates of infertility in young cancer patients are unknown.

Studies conducted to date about reproductive compromise have focused on the resumption of menses, which may have underestimated the extent of gonadotoxicity.⁷ However, two additional phenomena, primary ovarian insufficiency and premature menopause, may compromise reproductive potential. Primary ovarian insufficiency (also known as premature ovarian failure) can be overt (menses are absent, as in acute ovarian failure, or irregular) or occult (the ovary is damaged but menses remain regular).⁸ Therefore women may still menstruate, yet sustain partial ovarian injury that manifests as infertility when attempting conception.

The time period in a woman's life when conception is possible, her reproductive window, could be shortened if chemotherapy or radiation causes damage to her ovaries and decreases the number of viable eggs after treatment. It has been demonstrated, for instance, that women who continue to menstruate after treatment with chemotherapy for breast cancer remain at an increased risk of entering menopause early.⁹ Furthermore, evidence suggests that early menopause could be a sign of a shortened reproductive window. Before the onset of menopause, while menses are still present, sub-fertility often represents the first manifestation of incipient ovarian failure.¹⁰ In healthy women, fecundity decreases drastically about ten years before the average age of menopause (51 years old).^{11, 12} Therefore, because cancer patients that have been exposed to chemotherapy have a higher incidence of early menopause, they may experience sub-fertility many years prior to what is expected naturally, and thus have a significantly narrowed window of opportunity for attempting conception.⁹

We sought to evaluate the percentage of reproductive age cancer survivors who have experienced some type of reproductive impairment, using a large and diverse sample of women who have undergone chemotherapy treatment for cancer during their reproductive years. We examined reproductive impairment by cancer type and from a comprehensive perspective, including women who have experienced acute ovarian failure, who have experienced infertility, and who have entered menopause early. Furthermore, we sought to examine the effect of age at treatment on the proportion of women who have experienced infertility and early menopause after treatment with chemotherapy.

Patients and Methods

We performed a retrospective survey study, using the California Cancer Registry (CCR) to sample women across the state of California. All study procedures were reviewed and approved by the University of California, San Francisco Committee on Human Research.

Subjects

A computer-generated randomizer was used to sample reproductive age women from the cancer registry that had a history of leukemia, Hodgkin's disease, non-Hodgkin lymphoma, breast cancer, or gastrointestinal (GI) cancer. These cancers were chosen for study because they are common, non-gynecologic cancer groups that can be treated with systemic chemotherapy. Patients were included in the sample if they were 18–40 years of age at

diagnosis, and were diagnosed between 1993 and 2007. Among 6709 patients initially selected for the study, 4147 patients were excluded because their contact information in the cancer registry was outdated. Letters were sent to the primary physicians of each of the remaining women before we attempted to reach the patients. Women were then also excluded if their physician thought participation in the study would cause undue psychological burden (due to severe co-morbid mental illness) (30 patients). After exclusions, 2532 patients were contacted for participation in the study. Analyses of reproductive impairment included only women who reported treatment with chemotherapy alone (i.e., no pelvic radiation, pelvic surgery, or bone marrow transplant).

Survey

A questionnaire was developed to query reproductive history before and after cancer treatment. The survey included information about acute ovarian failure, infertility, and early menopause. Acute ovarian failure was defined as amenorrhea for at least one year that began immediately after treatment. Infertility included only women who resumed menses after treatment and was defined two ways. The first, 12-month infertility, refers to trying to conceive with unprotected intercourse for at least one year with no resulting pregnancy, and is the more conservative estimate of infertility. The second refers to all women who had tried to conceive but were unable and includes both women with 12-month infertility as well as those who tried for less than 12 months but were unable to conceive. Early menopause was defined as entering menopause before age 45 and therefore also includes women who experienced acute ovarian failure.

After an initial draft of the instrument was completed, two independent experts in survey methodology assessed it for readability and content validity – the extent to which our survey accurately assessed reproductive health history. The survey was then piloted on 20 patients from the UCSF Reproductive Endocrinology Clinic and edited for ease of use and readability before being sent to our study population. The survey was made available in both English and Spanish. A professional translation company (American Language Services, Los Angeles, CA) was used to translate the survey and recruitment materials into Spanish. Paper surveys were created using Cardiff Teleform (Vista, CA), an automated scanning utility, allowing patients' selections to questions to be scanned directly into a de-identified database. An online version of the survey was also created (www.surveymonkey.com, LLC, Palo Alto, CA), enabling women to complete the survey online (in English or Spanish).

Recruitment

Women were contacted between January 2010 and September 2010. A contact letter was sent to potential participants, explaining the purpose of the survey, the source of the individual's personal contact information (the CCR), and allowing women to opt out of further contact by reaching the UCSF study coordinator. After one week, a second mailing was sent that included the written survey, a link to the online survey, a written consent form, a postage-paid return envelope, and an optional refusal postcard. Women were asked to complete and return a written consent form by mail and to return the survey by mail or complete it online. Women who did not reply within three weeks received a reminder follow-up phone call. Those who did not reply within two weeks of the reminder call were sent a reminder post-card with a link to the electronic survey.

Data Analysis

Survey data were merged with CCR data using a unique, anonymous identifier code. Statistical analyses were performed using STATA Version 11 (College Station, TX). Differences in diagnoses and demographic characteristics between women who did and did not respond were examined using cancer registry data.

Reproductive impairment was measured in those who reported having been treated with chemotherapy alone (i.e., no pelvic radiation, pelvic surgery, or bone marrow transplant). Descriptive statistics were used to describe the percentage of women who had experienced the following three types of reproductive impairment: acute ovarian failure, infertility, and early menopause. The proportion of women of a given age at diagnosis who experienced reproductive impairment was described two ways and participants were separated by cancer type during analysis to minimize heterogeneity of treatment between different cancer types. Logistic regression was used to estimate the proportions of women with acute ovarian failure and infertility as a function of cancer type and age at diagnosis. It was also used to generate plots of the proportion of women of a given age experiencing acute ovarian failure or infertility. Censored data methods were used to model the probability of early menopause, as some women in our sample had not reached our cut-off age for early menopause by the time of survey. Interval censored regression analysis was used to determine the probability of entering menopause early, based on cancer type and age at diagnosis.

Results

Patient Sample

Of the 2532 women who were contacted, 1378 women replied to our initial contact letter or survey. Of these 337 refused and 1041 (41%) completed our survey. 47% of respondents completed the survey online and 53% completed it on paper. Reasons for declining included: a request to be removed from all cancer registry studies, no interest in further childbearing, the topic was too emotionally difficult to discuss, or the survey was too long. The average time to complete the survey was 26 minutes.

Table 1 compares all the women who completed our survey with those who were contacted, but did not complete it. Patients who completed the survey were 1.4 years younger at diagnosis than those who did not ($P<0.001$), and were diagnosed with more aggressive cancers, as indicated by a SEER summary stage index (range of zero (in situ) to seven (metastatic)) of 3.7 vs. 3.4 ($P<0.001$). There were no differences between responders and non-responders in SEER socioeconomic index (calculated from median income and education for the census block group of residence at diagnosis, $P=0.8$) or years since diagnosis ($P=0.2$).

620 of the 1041 respondents reported having been treated with only chemotherapy (i.e., no pelvic radiation, pelvic surgery, or bone marrow transplant). The age and childbearing desires of patients who were treated with chemotherapy alone are listed in Table 2. Patients with a history of breast and GI cancers tended to be oldest at diagnosis and most likely to have had children before treatment. Between 49–65% of women reported that they would like to have had children after treatment. However, only 30–41% attempted pregnancy, and 9–24% were successful. These 620 patients who received chemotherapy alone were used in our analysis of reproductive compromise.

Acute Ovarian Failure and Infertility after Chemotherapy

The percentage of women treated with chemotherapy alone who experienced acute ovarian failure was the lowest among women with leukemia (3%) and highest among women with breast cancer (9%) and non-Hodgkin lymphoma (10%). Overall percentages of 12-month infertility among women who continued to menstruate after treatment were 20%, 18%, 15%, 27%, and 23% for women with leukemia, Hodgkin's disease, non-Hodgkin lymphoma, breast cancer, and GI malignancies, respectively.

Age as a Predictor of Acute Ovarian Failure and Infertility after Chemotherapy

The proportion of women experiencing acute ovarian failure significantly increased with older age at diagnosis in patients with Hodgkin's disease, Non-Hodgkin lymphoma, breast cancer, and GI malignancies (Figure 1: Panel A). For instance, proportion experiencing acute ovarian failure with Hodgkin's disease was 0.06 at age 20 and 0.3 at age 35 ($p<0.001$). For women with breast cancer, the proportion was 0.32 at age 35 and 0.55 at age 40 ($p<0.001$).

For women whose menses returned within one year of treatment, the proportion experiencing infertility (defined here by our less conservative estimate of infertility) significantly increased with older age at diagnosis in patients with breast cancer and Hodgkin's disease and there was a trend toward increase in women with non-Hodgkin lymphoma (Figure 1: Panel B). The proportion experiencing infertility with Hodgkin's disease treated was 0.18 at age 20 and 0.57 at age 35 ($p=0.007$). For women with breast cancer, the incidence was 0.32 at age 35 and 0.8 at age 40 ($p<0.001$).

Early Menopause after Chemotherapy

For women whose menses returned within one year of treatment, the probability of experiencing early menopause significantly increased with younger age at diagnosis in patients with Hodgkin's disease, non-Hodgkin lymphoma, and GI malignancies, and there was a trend toward increase in women with breast cancer and leukemia (Figure 1: Panel C). The probability of early menopause for women with Hodgkin's disease was estimated to be 0.37 at age 20 and 0.16 at age 35 ($p=0.043$). For women with non-Hodgkin lymphoma, the probability of early menopause was 0.56 at age 20 and 0.16 at age 35 ($p<0.001$).

Discussion

Our findings may have implications for family planning after chemotherapy treatment for cancer. For women diagnosed with cancer during their reproductive years, reproductive impairment can significantly impact quality of life long after cancer treatment. In order to make informed decisions about fertility preservation at the time of treatment, patients should better understand their risk of future reproductive impairment.

In this study, we demonstrate that rates of acute ovarian failure alone likely underestimate the effect of chemotherapy on reproductive function in women of reproductive age. Previous studies have largely focused on amenorrhea as a primary reproductive impairment outcome after cancer treatment.¹³ We have shown here, however, that chemotherapy is additionally associated with infertility and early menopause, essentially narrowing the reproductive window, even in women whose menses resume after treatment.

The percentage of women reporting acute ovarian failure after chemotherapy in our study is consistent with previous work in our field. Among breast cancer patients, the 9% experiencing acute ovarian failure in our patient population is consistent with the rate of 7% in patients younger than age 35 reported by Kil and colleagues.¹⁴ In a prior study of 400 patients with Hodgkin's disease, 7% reported acute ovarian failure, compared to 8% in our study.¹⁵ The relatively low rate of acute ovarian failure seen in leukemia is consistent with what has been learned from in vitro models, where it has been suggested the agents used to treat the most common types of leukemia portend to the least gonadotoxicity.¹⁶ Our age-specific proportions of acute ovarian failure are also similar to those seen by others. For instance, 55% of women who were 40 years old at diagnosis and treated with chemotherapy alone for breast cancer reported acute ovarian failure in our study. This is similar to Goodwin and colleagues' reported rate of approximately 50%.¹⁷

While there is likely a significant biological component contributing to variability in rates of acute ovarian failure among disease and age-matched women,¹⁸ we have shown age to be a significant predictor. Our results, for instance, demonstrate that women who are 40 years old at the time of diagnosis for NHL are three times more likely to experience acute ovarian failure than women who are age 18 at diagnosis.

The majority of women who remain amenorrheic one year post-treatment will not regain ovarian function.^{14,19–21} When women do not become menopausal at treatment and continue to menstruate, infertility and early menopause continue to significantly impact reproductive function. While women age 18 at diagnosis for NHL have a 13% chance of acute ovarian failure, if they do continue to menstruate, they have an additional 9% chance of experiencing infertility and 60% probability of early menopause. It has been suggested that, since the majority of women younger than 35 years of age treated for breast cancer experience only temporary amenorrhea due to chemotherapy, many of these women can maintain fertility.²² In contrast, we found that at least 27% of all women with breast cancer in our study had infertility after treatment, despite the presence of menses.

Literature regarding the impact of chemotherapy on infertility is scarce. There have been numerous studies showing that women with prior diagnosis and treatment for cancer *do* successfully have children.²³ However, there is often no information on the number of women actually *attempting* pregnancy. The percentage of 12-month infertility seen in all cancer types in our study was higher than the 7%, 12-month infertility seen in the United States population. Our results are consistent with rates of infertility seen in the Norwegian Cancer Registry, in which 25% of 184 women with similar time to follow-up for Hodgkin's disease and attempting conception were unable to conceive.²³ Notably, modern treatment for Hodgkin's disease, which commonly includes AVBD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine) or Stanford V (Mechlorethamine, Adriamycin, Vinblastine, Vincristine, Bleomycin, Etoposide, and Prednisone), appears likely to have a significant and negative on impact fertility, in contrast to previous reports.^{24, 25}

Our results suggest that fertility counseling for women who are nearer to 40 years old at the time of diagnosis could be different than for a woman who is 18. For instance, there appears to be a four- to five-fold increase in rates of infertility from age 18 to age 40 in women with Hodgkin's disease. Seventy percent of reproductive age women are concerned about infertility after a cancer diagnosis, and almost one-third of women will adjust their treatment plans based on fertility concerns.³ Our data could contribute to an improved ability to counsel women about future risk of infertility, based on predictors like disease-type and age, and help to make more informed decisions about fertility preservation.

Women concerned about future fertility should also understand their risk of early menopause. Our results demonstrate age-specific rates of early menopause in women treated with chemotherapy for Hodgkin's disease, non-Hodgkin lymphoma, and gastrointestinal malignancies. Consistent with the work of Partridge and colleagues, we have demonstrated that the closer in age one is to natural menopause at the time of diagnosis, the lower the chance that chemotherapy will induce early menopause.⁹ For instance, 18 year-old women with Hodgkin's disease are at a two-fold increased risk of experiencing early menopause versus their 40 year-old counterparts. Although there are previous data alluding to the finding that younger aged patients exposed to chemotherapy are more likely to experience early menopause, this outcome is still quite surprising. Such results argue for the importance of counseling younger women about their risk of a shortened reproductive window. The reasons that young women may experience higher risks of early menopause yet lower risks of infertility and acute ovarian failure, while interesting, are beyond the scope of this paper and likely relate to duration of time elapsed since exposure.

This study has several important strengths and limitations. The outcomes chosen are comprehensive and inclusive, and not just focused on amenorrhea. However, despite controlling for cancer type at diagnosis, lack of clearly defined treatment type and duration for each patient requires us to make generalizations and assumptions about what chemotherapy regimens patients likely received. We are limited to making reasonable inferences about treatment, based on cancer type and practice patterns at that time, as has been done by others with success.²⁶ It is also possible that other, unmeasured, factors may play a role in our findings. For example, women who receive cancer treatment may postpone childbearing, leaving them older at the time they are trying to conceive. Also, while discussing counseling, age is an important prognosticator, but not a perfect predictor of reproductive impairment. Even within a given age group, prior studies have shown wide-variability in individual's ovarian reserve.¹⁸ Another limitation of this study has been the use of a retrospective, rather than prospective, survey, and using a historical cancer registry in which patients may be lost to follow-up.²⁷ Nevertheless, as the National Cancer Institute's working group for the improvement of care of gynecologic malignancies indicated, cancer registries offer an effective means of rapidly acquiring large amounts of data for important cancer issues.²⁸ And our response rate was consistent with those from previously published studies.^{29,30} This study of a cancer registry has been most important in its ability to effectively identify a large sample of patients to demonstrate infertility as a missing metric in cancer survivorship research.

It is fundamental that patients understand their risk of future reproductive compromise – a risk that may include infertility and early menopause, in addition to acute ovarian failure. Counseling based on the risk of amenorrhea alone may give women an unrealistically low perception of their total risk of reproductive impairment - as we know that women can be menstruating and still be infertile. Patients should be given a chance to make an active decision about post-treatment family planning in the presence of the most comprehensive available information.

References

1. NCIFastStats. Statistics stratified by age. Surveillance Epidemiology and End Results(SEER). [online] 2006;<http://seer.cancer.gov/faststats/elections.php>
2. Carter J, Rowland K, Chi D, et al. Gynecologic cancer treatment and the impact of cancer-related infertility. *Gynecol Oncol*. 2005; 97(1):90–5. [PubMed: 15790443]
3. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues in young women with breast cancer. *J Clin Oncol*. 2004; 22(20):4174–83. [PubMed: 15483028]
4. Wenzel L, Dogan-Ates A, Habbal R, et al. Defining and measuring reproductive concerns of female cancer survivors. *J Natl Cancer Inst Monogr*. 2005; (34):94–8. [PubMed: 15784834]
5. Loprinzi CL, Wolf SL, Barton DL, Laack NN. Symptom management in premenopausal patients with breast cancer. *Lancet Oncol*. 2008; 9(10):993–1001. [PubMed: 19071256]
6. Stephen EH, Chandra A. Declining estimates of infertility in the United States: 1982–2002. *Fertil Steril*. 2006; 86(3):516–23. [PubMed: 16952500]
7. Sonmezer M, Oktay K. Fertility preservation in female patients. *Hum Reprod Update*. 2004; 10(3): 251–66. [PubMed: 15140872]
8. Nelson LM. Clinical practice. Primary ovarian insufficiency. *N Engl J Med*. 2009; 360(6):606–14. [PubMed: 19196677]
9. Partridge A, Gelber S, Gelber RD, Castiglione-Gertsch M, Goldhirsch A, Winer E. Age of menopause among women who remain premenopausal following treatment for early breast cancer: long-term results from International Breast Cancer Study Group Trials V and VI. *Eur J Cancer*. 2007; 43(11):1646–53. [PubMed: 17512721]
10. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. *Lancet*. 2010; 376(9744):911–21. [PubMed: 20708256]

11. Gindoff PR, Jewelewicz R. Reproductive potential in the older woman. *Fertil Steril*. 1986; 46(6): 989–1001. [PubMed: 3536609]
12. te Velde ER, Pearson PL. The variability of female reproductive ageing. *Hum Reprod Update*. 2002; 8(2):141–54. [PubMed: 12099629]
13. Schover LR. Patient attitudes toward fertility preservation. *Pediatr Blood Cancer*. 2009; 53(2):281–4. [PubMed: 19301387]
14. Kil WJ, Ahn SD, Shin SS, et al. Treatment-induced menstrual changes in very young (<35 years old) breast cancer patients. *Breast Cancer Res Treat*. 2006; 96(3):245–50. [PubMed: 16555128]
15. Behringer K, Breuer K, Reineke T, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol*. 2005; 23(30):7555–64. [PubMed: 16234521]
16. Soleimani, R.; Heytens, E.; Oktay, K. Prevention of chemotherapy-induced apoptotic follicular death in human ovary by ceramide-induced death pathway inhibitors. Oral abstract presented at: 66th Annual American Society of Reproductive Medicine Conference; 2010 Oct 26–29; Denver, CO. 2010.
17. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol*. 1999; 17(8):2365–70. [PubMed: 10561298]
18. Letourneau JM, Melisko ME, Cedars MI, Rosen MP. A changing perspective: improving access to fertility preservation. *Nat Rev Clin Oncol*. 2011; 8(1):56–60. [PubMed: 20736926]
19. Amir E, Freedman O, Allen L, Colgan T, Clemons M. Defining ovarian failure in amenorrheic young breast cancer patients. *Breast*. 2010; 19(6):545–8. [PubMed: 20615705]
20. Smith IE, Dowsett M, Yap YS, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. *J Clin Oncol*. 2006; 24(16):2444–7. [PubMed: 16735701]
21. Sukumvanich P, Case LD, Van Zee K, et al. Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment: a prospective study. *Cancer*. 2010; 116(13):3102–11. [PubMed: 20564648]
22. Zervoudis S, Iatrakis G, Navrozoglou I. Reproduction after breast cancer. *Best Pract Res Clin Obstet Gynaecol*. 2010; 24(1):81–6. [PubMed: 20170848]
23. Kiserud CE, Fossa A, Holte H, Fossa SD. Post-treatment parenthood in Hodgkin's lymphoma survivors. *Br J Cancer*. 2007; 96(9):1442–9. [PubMed: 17406362]
24. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. *Eur J Cancer Clin Oncol*. 1985; 21(5):601–5. [PubMed: 2408897]
25. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med*. 1992; 327(21):1478–84. [PubMed: 1383821]
26. Cvancarova M, Samuelsen SO, Magelssen H, Fossa SD. Reproduction rates after cancer treatment: experience from the Norwegian radium hospital. *J Clin Oncol*. 2009; 27(3):334–43. [PubMed: 19075285]
27. Arora NK, Hamilton AS, Potosky AL, et al. Population-based survivorship research using cancer registries: a study of non-Hodgkin lymphoma survivors. *J Cancer Surviv*. 2007; 1(1):49–63. [PubMed: 18648945]
28. NationalCancerInstitute. Report of the Leukemia, Lymphoma, and Myeloma Progress Review Group. 2001. <http://planning.cancer.gov/disease/plans.shtml#prg> [serial online]
29. Huyghe E, Sui D, Odensky E, Schover LR. Needs Assessment Survey to Justify Establishing a Reproductive Health Clinic at a Comprehensive Cancer Center. *J Sex Med*. 2009; 6:149–163. [PubMed: 18823323]
30. Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M. Web-based Survey of Fertility Issues in Young Women With Breast Cancer. *J Clin Onc*. 2004; 22(20):4174–4183.

Panel A: Proportion experiencing acute ovarian failure

Panel B: Proportion experiencing infertility despite resuming menses

Panel C: Probability of early menopause despite resuming menses

* $P < 0.05$, ** $P < 0.1$, HD=Hodgkin's disease, NHL=non-Hodgkin lymphoma, GI=Gastrointestinal Malignancy

Figure 1.
Age as a Predictor of Reproductive Impairment after Chemotherapy

Table 1

Comparison of Survey Responders vs. Non-Responders*

	Completed survey (n=1041)	Non-responder (n=1491)	p [†]
Age at diagnosis, years	31.8 (6.7)	33.2 (6.2)	<0.001
Age at survey, years,	41.3 (8.4)	42.5 (8.0)	<0.001
Summary stage index [§]	3.7 (2.1)	3.4 (2.1)	<0.001
Socioeconomic Index [¶]	2.5 (1.4)	2.5 (1.3)	0.8
Time since diagnosis, years	9.5 (4.4)	9.3 (4.4)	0.2

* All data shown are mean (SD)

[†] p-value from t-test comparing responders and non-responders[§] Summary stage index = Surveillance Epidemiology and End Results staging index. Scores range from 0 (in situ) to 7 (metastatic)[¶] SEER Socioeconomic Index calculated from median income and education for the census block group of residence at diagnosis

Table 2

Characteristics of Survey Respondents who Received Chemotherapy

	Total sample (N=620)	Type of cancer				
		Leukemia (n=60)	Hodgkin's (n=218)	non-Hodgkin (n=123)	Breast (n=169)	Gastrointestinal (n=50)
Age at diagnosis, years, mean (SD)	31.2 (6.8)	28.5 (7.2)	27.5 (6.4)	31.3 (6.1)	36.0 (4.3)	34.1 (5.4)
Age at survey, years, mean (SD)	40.6 (8.5)	36.8 (8.9)	35.8 (7.5)	40.3 (7.2)	47.2 (6.0)	44.2 (6.6)
Years since diagnosis, mean (SD)	9.4 (4.4)	8.3 (4.2)	8.2 (4.2)	9.0 (3.9)	11.2 (4.5)	10.1 (3.9)
Children before treatment, %	50	45	32	51	67	72
Desiring children after treatment, %	57	65	65	51	49	56
Attempted pregnancy, %	36	33	41	38	30	36
Had children after treatment, %	19	17	24	21	9	22