Published in final edited form as:

Menopause. 2019 March ; 26(3): 306–310. doi:10.1097/GME.0000000000001199.

Amenorrhea after Lung Cancer Treatment

Elizabeth J. Cathcart-Rake, MD¹, Kathryn J. Ruddy, MD, MPH¹, Ruchi Gupta², Walter Kremers, PhD², Kelly Gast, MD³, H. Irene Su, MD, MSCE⁴, Ann H. Partridge, MD, MPH⁵, Elizabeth A. Stewart, MD⁶, Han Liu, MD^{7,8}, Yanqi He, MD, PhD^{7,9}, and Ping Yang, MD, PhD⁷

¹Department of Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA.

507-284-2511, Cathcart-Rake.Elizabeth@mayo.edu, Ruddy.Kathryn@mayo.edu

²Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN

³Department of Internal Medicine, Mayo Clinic, Rochester, MN

⁴Department of Obstetrics, Gynecology and Reproductive Science, University of California, San Diego, La Jolla, CA

⁵Department of Oncology, Dana-Farber Cancer Institute, Boston, MA

⁶Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN

⁷Department of Epidemiology, Mayo Clinic, Scottsdale, AZ

⁸Department of Respiratory Medicine, The First Hospital of Jilin University, Changchun, China

⁹Department of Respiratory Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, China

Abstract

Objective—More than 5,000 premenopausal women are diagnosed with lung cancer annually in the United States. Limited data exist regarding the risk of treatment-related amenorrhea, a surrogate for infertility and early menopause, after systemic therapies for lung cancer.

Methods—Premenopausal women diagnosed with lung cancer under age 50 were surveyed at diagnosis and annually thereafter about their menstrual status as a part of the Mayo Clinic Epidemiology and Genetics of Lung Cancer Research Program. Types of lung cancer-directed treatments were recorded, and frequencies of self-reported menopause at each survey were calculated.

Results—A cohort of 182 premenopausal women were included in this study, with average age at lung cancer diagnosis 43 years (SD 6). Among the 85 patients who received chemotherapy, 64%

Correspondence to: Elizabeth J. Cathcart-Rake.

Conflicts of interest for the current study: None. Dr. Cathcart-Rake, Dr. Ruddy, Ms. Gupta, Dr. Gast, Dr. Su, Dr. Partridge, Dr. Liu, Dr. He, and Dr. Yang have nothing to disclose. Dr. Stewart reports personal fees from Gynesonics, Redwood City, CA, personal fees from Bayer, Leverkusen, Germany, personal fees from GlaxoSmithKline, London, United Kingdom, personal fees from Astellas Pharma, Tokyo, Japan, personal fees from Welltigs, Minneapolis, MN, and personal fees from AbbVie, North Chicago, IL, all outside the submitted work. Dr. Kremers reports funding from AstraZeneca, Cambridge, United Kingdom, Roche, Basel, Switzerland, and Biogen, Cambridge, MA, outside the submitted work.

self-reported that they had become menopausal within a year of diagnosis. Platinum salts were universally included in these chemotherapy regimens, and the majority of these women also received taxanes within one year of diagnosis. Only 15% of the 94 patients who did not receive systemic therapy within one year of diagnosis experienced self-reported menopause. Three patients received targeted therapy alone, two of whom remained premenopausal at the final qualifying survey, completed a median of 3 years after diagnosis.

Conclusions—Chemotherapy for lung cancer patients appears to increase risk of early loss of menses in survivors.

Keywords

Amenorrhea; menopause; ovarian toxicity; chemotherapy side effects

Introduction:

Approximately 415,000 Americans are lung cancer survivors, with more than 220,000 new cases diagnosed annually in the United States (1, 2). While the rate of new lung cancer diagnoses in men has decreased by 32% since 1975, it has risen 94% for women, and lung cancer has now surpassed breast cancer as the leading cause of cancer death among women in this country (1, 2). While lung cancer is more common in older adults, women are diagnosed at younger ages compared to men, and approximately 5,000 premenopausal women are diagnosed with lung cancer annually in the United States (1, 2). Thus, it is important to study the challenges facing the young female lung cancer patient population.

Unique to the premenopausal survivor population is the concern that chemotherapy may diminish or eradicate the ovarian reserve. Chemotherapy may cause acute amenorrhea by killing growing follicles, and also may cause ovarian failure, i.e. menopause, by destroying remaining quiescent follicles (3–5). Alkylating agents are especially notorious for their gonadotoxic effects. They are thought to destroy quiescent ovarian follicles by triggering follicle activation and apoptosis concurrently, and result in rates of premature menopause between 40–80% among women with breast cancer (5–11). Women who remain amenorrheic two years after chemotherapy do not frequently regain menstrual function (12).

Permanent loss of ovarian function results in infertility, estrogen deprivation symptoms (e.g., hot flashes and vaginal dryness), and bone loss (13). These symptoms may cause significant distress and impaired quality of life in lung cancer survivors. Furthermore, it may influence treatment decisions: in one study of 620 female breast cancer survivors under age 40, over half were concerned about infertility after treatment, and 26% reported that fertility concerns had affected their treatment decisions (4). Thus, understanding the risk for premature menopause after lung cancer-directed therapy is important to inform pre-therapy counseling. Amenorrhea, an absence of normal menses, is frequently measured, as it may help to identify patients at risk for infertility and menopausal symptoms. However, rates of amenorrhea after lung cancer treatment regimens are understudied; a literature search of amenorrhea and lung cancer yielded no results. Extrapolations of risks for amenorrhea must be based on studies of the individual components of the chemotherapy regimens utilized to treat cancers in other populations.

Platinum salts are the frequent backbone of treatment for both non-small-cell and small cell lung cancer. They cross-link DNA with a mechanism of action similar to that of alkylating agents, which suggests they may cause similar, detrimental ovarian function effects (6). This is supported by a recent rat study that reports they are as gonadotoxic as cyclophosphamide (14). However, when given to very young women with germ cell tumors (median age 24.3 years), were not associated with high rates of long-term amenorrhea (15). The effect of platinum on older premenopausal human ovaries has not been well studied. The other components of the “platinum doublet” include topoisomerase inhibitors and taxanes. Etoposide is a frequent cause of amenorrhea in children with Hodgkin’s lymphoma and in young adults with AML (8, 16, 17). It is difficult to ascertain if taxanes contribute to amenorrhea as they are frequently administered in combination with alkylating agents and anthracyclines (18), but one study of paclitaxel and trastuzumab (a nongonadotoxic monoclonal antibody) in women diagnosed with breast cancer at a median age of 44 found a relatively low rate of amenorrhea (28% at 4 years), suggesting that paclitaxel is not highly gonadotoxic (19). In addition, another study that assessed amenorrhea after anthracycline-based chemotherapy for breast cancer did not find that adding a taxane to doxorubicin-cyclophosphamide substantially increased the rate of amenorrhea (20).

While the rates, implications, and risk factors for chemotherapy-induced amenorrhea have been widely studied in survivors of a variety of other cancers (particularly breast cancer and lymphoma), there is a paucity of information regarding amenorrhea in patients with lung cancer. As it has been shown that older premenopausal cancer survivors with a history of tobacco use are more likely to experience premature menopause; as lung cancer is traditionally a disease affecting older tobacco users, it could be posited that risks for amenorrhea may be higher in lung cancer survivors than in the aforementioned populations (20–22). The objective of this study was to evaluate rates of chemotherapy-induced amenorrhea among lung cancer patients.

Methods:

The Mayo Clinic Epidemiology and Genetics of Lung Cancer Research Program is an ongoing clinic-based registry of lung cancer patients (23–25). Since 1997, patients identified with newly diagnosed primary lung cancer and treated at Mayo Clinic in Rochester, Minnesota have been invited to participate in a longitudinal cohort study. Participants are actively followed by mailed questionnaires, beginning 6 months after lung cancer diagnoses, and then annually. Participants included in the study analysis were under the age of 50 and premenopausal at the time of their initial lung cancer diagnosis. Data collection was limited to surveys completed between 1999–2016, with at least one survey completed 1–20 years after the cancer diagnosis. The study was reviewed and approved by the Mayo Clinic institutional review board.

Participants were asked about the types of cancer treatment they underwent, including names of chemotherapies and/or targeted therapies and the dates of treatment. In the survey, patients were asked to identify whether they considered themselves premenopausal, perimenopausal, or postmenopausal at the time of survey completion. Women who self-reported they were postmenopausal in surveys given after the time of diagnosis were considered to

have amenorrhea. “Immediate” treatment-related menopause was defined as reporting age of menopause as the same as the age at diagnosis of cancer or 1 year older. For instance, a woman would be considered to have “immediate” treatment-related menopause if she were 40 years old and premenopausal at the time of diagnosis, and then completed a survey 12 months after diagnosis at age 41 in which she reported she was postmenopausal. Statistical analyses were completed with percentages and averages.

Results:

Out of the 2735 female patients who completed at least one survey between 1999–2016, 182 were under age 50 and reported that they were premenopausal at diagnosis. All surveys that were completed in the cohort were utilized in analysis: some women completed only one survey, and some completed multiple surveys over time. Median time from diagnosis to first survey was 20.4 months (SD 23 months, range 12–202 months). At the time of data analysis in January 2017, there were 101 participants that had provided more than one qualifying questionnaire; the first and last questionnaires were an average of 3.7 years apart (range: 0.4 to 14 years). The average time between diagnosis and last questionnaire was 4.0 years (range 1–17 years), with the last questionnaire having been received between November 1999 and November 2016. There were 81 participants who provided only one qualifying survey, which was obtained an average of 2.6 years after first diagnosis (range 1–17 years).

Table 1 provides participant’s characteristics. Of these 182 participants, 85 (median age at diagnosis 44 years, SD 5, range 34–48) received chemotherapy during the year after diagnosis, 26 of whom also received targeted therapy during that year. Ninety-four women did not receive systemic therapy within a year of diagnosis. Table 2 describes the types and frequencies of chemotherapy agents received, among the 85 women who received chemotherapy. As patients self-reported cancer-directed therapies, occasionally they were not clear on the therapies received, so such treatments were reported as “unknown.” There were a number of different targeted therapy agents utilized by participants, including EGFR, VEGF, CD20, ALK, and HER2 inhibitors.

Among women who received chemotherapy, those who were older at diagnosis reported becoming postmenopausal after fewer years than women who were younger at diagnosis. The menopausal status of women who received chemotherapy is reported in Table 3. Of the women who reached menopause within one year of diagnosis, 44% were never-smokers; of the women who remained pre- or peri-menopausal at their final survey, 85% were never-smokers.

Three patients in the study cohort received targeted therapy alone, two of whom remained premenopausal at the final qualifying survey at a mean age at diagnosis of 40. The third, diagnosed at age 43, became post-menopausal more than two years after her cancer diagnosis. All of these patients had a current or former history of tobacco use.

The remaining 94 women (mean age at diagnosis of 42 years, SD 6 years, range 20–49) received no systemic therapy within a year of diagnosis. The menopausal status of women who did not receive chemotherapy or targeted therapy is shown in Table 4. Of the women

who reached menopause within one year of diagnosis, 71% were never smokers; of the women who remained pre- or peri-menopausal at their final survey, 51% were never-smokers. Due to the differing ages at diagnosis, times to survey completion, variable smoking histories among patients, and sample size, further analyses were unable to be completed.

In order to describe changes in reported menstrual status longitudinally, menstrual status was followed over time for the group of participants who returned multiple qualifying surveys. Of the 54 participants who returned multiple surveys, 31 participants (mean age at diagnosis of 45 years, SD 3, range 39–49) reported becoming postmenopausal at a mean age of 46 years (SD 2, range 41–50). Twelve participants (five who received chemotherapy and seven who had no systemic therapy) reported that they were pre- or peri-menopausal at least once after reporting that they became postmenopausal. Four of these 12 continued to report premenopausal status until their final qualifying survey; five reported peri-menopausal status; and three temporarily reported pre- or peri-menopausal status, but then by the time of the final qualifying survey, again reported postmenopausal status.

Discussion:

While young women comprise an important cohort of lung cancer survivors, their risk of premature amenorrhea has not been previously investigated. Our results suggest that self-reported menopause occurs soon after a lung cancer diagnosis for more than half of all premenopausal women with lung cancer. While our conclusions are limited by the sample size and heterogeneity of the study population, this rate is only slightly lower than the rates of amenorrhea seen in similarly aged breast cancer survivors who received cyclophosphamide-containing regimens (8–11). While prior studies suggest that alkylating agents are responsible for much of the ovarian toxicity experienced by young women with certain cancers, it is clear from these findings and others' that non-alkylating agents can also damage ovarian function (14, 16, 17, 26). It is notable that etoposide and platinum agents have been linked to amenorrhea in prior studies (6, 8, 14, 16, 17, 27).

It will be important to build upon our findings to more thoroughly study the unique consequences of gonadal toxicity in survivors of lung cancer. Unlike in breast cancer, premature menopause is unlikely to improve prognosis in lung cancer, but preservation of fertility and subsequent pregnancies may be complicated by other sequelae of lung cancer treatment, such as chronic dyspnea.

While this study is the first to comment on amenorrhea rates among a premenopausal lung cancer population, it is limited by heterogeneity of reported cancer-directed therapies, number of surveys completed by each participant, and the timing of completion of initial qualifying surveys. This was largely due to the survey from which data was extracted; this survey was initially created to define menopausal status among participants in a lung cancer tumor registry, rather than to evaluate the frequency of chemotherapy-induced amenorrhea. Unfortunately, the resulting heterogeneity precluded further statistical analyses, including correlative studies. Small sample size was also a limitation of this study; there were too few women under the age of 45 to analyze younger women separately. Thus, conversions from

pre- to postmenopausal status may concordantly be explained by variables such as time to follow-up, age, and smoking status.

Further studies are needed to carefully assess the gonadotoxic effects of each different systemic agent and regimen utilized to treat lung cancer. Targeted and immunotherapy agents are increasingly important in lung cancer treatment strategies, but even though many of the signaling pathways that are targeted by these new therapies are also present in ovaries (for instance, the epidermal growth factor receptor, EGFR, pathway), the ovarian effects of these therapies are understudied (28). While this study utilized patient self-report of amenorrhea as the primary outcome measure, further studies should correlate self-reported menstrual status with laboratory evaluations. Laboratory measures of ovarian function such as Anti-Müllerian hormone (AMH) are under investigation in survivors of other cancers, and may reflect the degree of chemotherapy-induced gonadal damage in patients with lung cancer as well (29–38).

Conclusions:

Premenopausal lung cancer patients should be educated about the risk for chemotherapy-related amenorrhea and the aforementioned lung cancer-specific amenorrhea considerations prior to therapy initiation. If future fertility is desired, reproductive endocrinology should be consulted to discuss options for embryo and oocyte cryopreservation, the gold standard techniques for fertility preservation in this setting (39, 40). Gonadotropin-releasing hormone agonist administration could also be considered in light of preliminary data for possible efficacy in patients with other cancers (6, 41–46).

Acknowledgments

Funding: This work was supported by Mayo Foundation funds, and by the National Institutes of Health [grant numbers R01CA80127, R01CA84354, and R01CA115857].

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7–30. [PubMed: 26742998]
2. Health USNIo. National Cancer Institute. SEER Cancer Statistics Review. 1975-2013.
3. Miller JJ, Williams GF, 3rd, Leissring JC. Multiple late complications of therapy with cyclophosphamide, including ovarian destruction. *Am J Med*. 1971;50(4):530–5. [PubMed: 5313910]
4. Nicosia SV, Matus-Ridley M, Meadows AT. Gonadal effects of cancer therapy in girls. *Cancer*. 1985;55(10):2364–72. [PubMed: 3986739]
5. Meiorow D, Biederman H, Anderson RA, Wallace WH. Toxicity of chemotherapy and radiation on female reproduction. *Clin Obstet Gynecol*. 2010;53(4):727–39. [PubMed: 21048440]
6. Roness H, Kashi O, Meiorow D. Prevention of chemotherapy-induced ovarian damage. *Fertil Steril*. 2016;105(1):20–9. [PubMed: 26677788]
7. Kalich-Philosoph L, Roness H, Carmely A, Fishel-Bartal M, Ligumsky H, Paglin S, et al. Cyclophosphamide triggers follicle activation and “burnout”; AS101 prevents follicle loss and preserves fertility. *Sci Transl Med*. 2013;5(185):185ra62.
8. Overbeek A, van den Berg MH, van Leeuwen FE, Kaspers GJ, Lambalk CB, van Dulmen-den Broeder E. Chemotherapy-related late adverse effects on ovarian function in female survivors of

childhood and young adult cancer: A systematic review. *Cancer Treat Rev.* 2016;53:10–24. [PubMed: 28056411]

9. Minisini AM, Menis J, Valent F, Andreetta C, Alessi B, Pascoletti G, et al. Determinants of recovery from amenorrhea in premenopausal breast cancer patients receiving adjuvant chemotherapy in the taxane era. *Anticancer Drugs.* 2009;20(6):503–7. [PubMed: 19339872]
10. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 1996;14(5):1718–29. [PubMed: 8622093]
11. 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]
12. Jacobson MH, Mertens AC, Spencer JB, Manatunga AK, Howards PP. Menses resumption after cancer treatment-induced amenorrhea occurs early or not at all. *Fertil Steril.* 2016;105(3):765–72 e4. [PubMed: 26658130]
13. Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. *J Clin Oncol.* 1995;13(11):2737–44. [PubMed: 7595732]
14. Yuksel A, Bildik G, Senbabaoglu F, Akin N, Arvas M, Unal F, et al. The magnitude of gonadotoxicity of chemotherapy drugs on ovarian follicles and granulosa cells varies depending upon the category of the drugs and the type of granulosa cells. *Hum Reprod.* 2015;30(12):2926–35. [PubMed: 26466914]
15. Gershenson DM, Miller AM, Champion VL, Monahan PO, Zhao Q, Cella D, et al. Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2007;25(19):2792–7. [PubMed: 17602084]
16. Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falk SJ, Gilson D, et al. Risk of premature menopause after treatment for Hodgkin's lymphoma. *J Natl Cancer Inst.* 2014;106(9).
17. Lemez P, Urbanek V. Chemotherapy for acute myeloid leukemias with cytosine arabinoside, daunorubicin, etoposide, and mitoxantrone may cause permanent oligoasthenozoospermia or amenorrhea in middle-aged patients. *Neoplasma.* 2005;52(5):398–401. [PubMed: 16151584]
18. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 2006;24(36):5769–79. [PubMed: 17130515]
19. Ruddy KJ, Guo H, Barry W, Dang CT, Yardley DA, Moy B, et al. Chemotherapy-related amenorrhea after adjuvant paclitaxel-trastuzumab (APT trial). *Breast Cancer Res Treat.* 2015;151(3):589–96. [PubMed: 25981899]
20. Abusief ME, Missmer SA, Ginsburg ES, Weeks JC, Partridge AH. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. *Cancer.* 2010;116(4):791–8. [PubMed: 20052714]
21. Behringer K, Breuer K, Reineke T, May M, Nogova L, Klimm B, 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]
22. Letourneau JM, Ebbel EE, Katz PP, Oktay KH, McCulloch CE, Ai WZ, et al. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. *Cancer.* 2012;118(7):1933–9. [PubMed: 21850728]
23. Sloan JA, Zhao X, Novotny PJ, Wampfler J, Garces Y, Clark MM, et al. Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. *J Clin Oncol.* 2012;30(13):1498–504. [PubMed: 22454418]
24. Schild SE, Tan AD, Wampfler JA, Ross HJ, Yang P, Sloan JA. A new scoring system for predicting survival in patients with non-small cell lung cancer. *Cancer Med.* 2015;4(9):1334–43. [PubMed: 26108458]
25. Yang P, Cheville AL, Wampfler JA, Garces YI, Jatoi A, Clark MM, et al. Quality of life and symptom burden among long-term lung cancer survivors. *J Thorac Oncol.* 2012;7(1):64–70. [PubMed: 22134070]

26. Swain SM, Land SR, Ritter MW, Costantino JP, Cecchini RS, Mamounas EP, et al. Amenorrhea in premenopausal women on the doxorubicin-and-cyclophosphamide-followed-by-docetaxel arm of NSABP B-30 trial. *Breast Cancer Res Treat.* 2009;113(2):315–20. [PubMed: 18302020]
27. Iwase A, Sugita A, Hirokawa W, Goto M, Nakahara T, Bayasula, et al. Anti-Mullerian hormone as a marker of ovarian reserve in patients with ovarian malignancies who have undergone fertility-preserving surgery and chemotherapy. *Gynecol Endocrinol.* 2013;29(4):357–60. [PubMed: 23305483]
28. Jamnongjit M, Gill A, Hammes SR. Epidermal growth factor receptor signaling is required for normal ovarian steroidogenesis and oocyte maturation. *Proc Natl Acad Sci U S A.* 2005;102(45):16257–62. [PubMed: 16260720]
29. Su HI, Sammel MD, Green J, Velders L, Stankiewicz C, Matro J, et al. Antimullerian hormone and inhibin B are hormone measures of ovarian function in late reproductive-aged breast cancer survivors. *Cancer.* 2010;116(3):592–9. [PubMed: 19918920]
30. Rajpert-De Meyts E, Jorgensen N, Graem N, Muller J, Cate RL, Skakkebaek NE. Expression of anti-Mullerian hormone during normal and pathological gonadal development: association with differentiation of Sertoli and granulosa cells. *J Clin Endocrinol Metab.* 1999;84(10):3836–44. [PubMed: 10523039]
31. Anderson RA, Cameron DA. Pretreatment serum anti-mullerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. *J Clin Endocrinol Metab.* 2011;96(5):1336–43. [PubMed: 21325458]
32. Ruddy KJ, Gelber S, Tamimi RM, Ginsburg ES, Schapira L, Come SE, et al. Biomarkers of amenorrhea and ovarian function in breast cancer survivors. *Journal of Clinical Oncology.* 2012;30:9071.
33. Anderson RA, Themmen AP, Al-Qahtani A, Groome NP, Cameron DA. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. *Hum Reprod.* 2006;21(10):2583–92. [PubMed: 16820385]
34. Anderson RA, Mansi J, Coleman RE, Adamson DJA, Leonard RCF. The utility of anti-Mullerian hormone in the diagnosis and prediction of loss of ovarian function following chemotherapy for early breast cancer. *Eur J Cancer.* 2017;87:58–64. [PubMed: 29117576]
35. Krekow LK, Hellerstedt BA, Collea RP, Papish S, Diggikar SM, Resta R, et al. Incidence and Predictive Factors for Recovery of Ovarian Function in Amenorrheic Women in Their 40s Treated With Letrozole. *J Clin Oncol.* 2016;34(14):1594–600. [PubMed: 26884554]
36. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, et al. Impact of cancer therapies on ovarian reserve. *Fertil Steril.* 2012;97(1):134–40 e1. [PubMed: 22137491]
37. Decanter C, Morschhauser F, Pigny P, Lefebvre C, Gallo C, Dewailly D. Anti-Mullerian hormone follow-up in young women treated by chemotherapy for lymphoma: preliminary results. *Reprod Biomed Online.* 2010;20(2):280–5. [PubMed: 20113967]
38. Behringer K, Mueller H, Goergen H, Thielen I, Eibl AD, Stumpf V, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. *J Clin Oncol.* 2013;31(2):231–9. [PubMed: 23150709]
39. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2013;31(19):2500–10. [PubMed: 23715580]
40. Wallace WH, Smith AG, Kelsey TW, Edgar AE, Anderson RA. Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation. *Lancet Oncol.* 2014;15(10):1129–36. [PubMed: 25130994]
41. Clowse ME, Behera MA, Anders CK, Copland S, Coffman CJ, Leppert PC, et al. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. *J Womens Health (Larchmt).* 2009;18(3):311–9. [PubMed: 19281314]
42. Lambertini M, Moore H, Leonard RC, Loibl S, Munster P, Bruzzone M, et al. Pooled analysis of five randomized trials investigating temporary ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients [Abstract GS4–01] In: The San Antonio Breast Cancer Symposium. 12 7, 2017; San Antonio, TX.

43. Donnez J, Dolmans MM. Fertility Preservation in Women. *N Engl J Med*. 2017;377(17):1657–65. [PubMed: 29069558]
44. Chung K, Donnez J, Ginsburg E, Meirow D. Emergency IVF versus ovarian tissue cryopreservation: decision making in fertility preservation for female cancer patients. *Fertil Steril*. 2013;99(6):1534–42. [PubMed: 23517859]
45. Moore HC, Unger JM, Albain KS. Ovarian protection during adjuvant chemotherapy. *N Engl J Med*. 2015;372(23):2269–70. [PubMed: 26039609]
46. Demeestere I, Brice P, Peccatori FA, Kentos A, Gaillard I, Zachee P, et al. Gonadotropin-releasing hormone agonist for the prevention of chemotherapy-induced ovarian failure in patients with lymphoma: 1-year follow-up of a prospective randomized trial. *J Clin Oncol*. 2013;31(7):903–9. [PubMed: 23129737]

Table 1.

Participant Characteristics.

Characteristic	All participants, N=182
Age	Mean: 42.7 ± 5.7 Median: 44.0 Range: 20–49
Years from diagnosis to first survey	Mean: 2.2 ± 1.9 Median: 1.7 Range: 1.0–16.8
Cigarette Smoking	
Never	48.4%
Former	24.1%
Current	27.5%
Chemotherapy within 1 year of diagnosis	
Yes	46.7%
No	16.5%
Unknown	36.8%
Targeted therapy within 1 year of diagnosis	
Yes	15.9%
No	9.9%
Unknown	74.2%

Table 2.

Chemotherapy agents administered within one year of diagnosis.

Chemotherapy Agents	Number of Chemotherapy Recipients (N=85)
Platinum (<i>cisplatin, carboplatin</i>)	85 (100%)
Taxane (<i>paclitaxel, docetaxel</i>)	54 (64%)
Antimetabolite (<i>pemetrexed, gemcitabine</i>)	27 (32%)
Topoisomerase inhibitor (<i>etoposide, topotecan</i>)	25 (29%)
Other (<i>epothilone, vinorelbine</i>)	10 (12%)

Table 3.

Menopausal status of patients who received chemotherapy.

	Percentage who reached menopause		Percentage who did not reach menopause
Years after diagnosis	Within 1 year	2+ years	Time of final survey Mean: 3 years $\pm$ 2 [1–10]
Percentage who reached menopause	46%	9%	45%
Mean age at diagnosis	47 $\pm$ 2 [41–49]	43 $\pm$ 5 [35–48]	40 $\pm$ 5 [25–48]

Table 4.

Menopausal status of patients who did not receive chemotherapy and/or targeted therapy.

	Percentage who reached menopause		Percentage who did not reach menopause
Years after diagnosis	Within 1 year	2+ years	Time of final survey Mean: 4 years± 3 [1–10]
Percentage who reached menopause	15%	16%	69%
Mean age at diagnosis	45±3 [41–49]	43±4 [36–49]	41±7 [20–49]