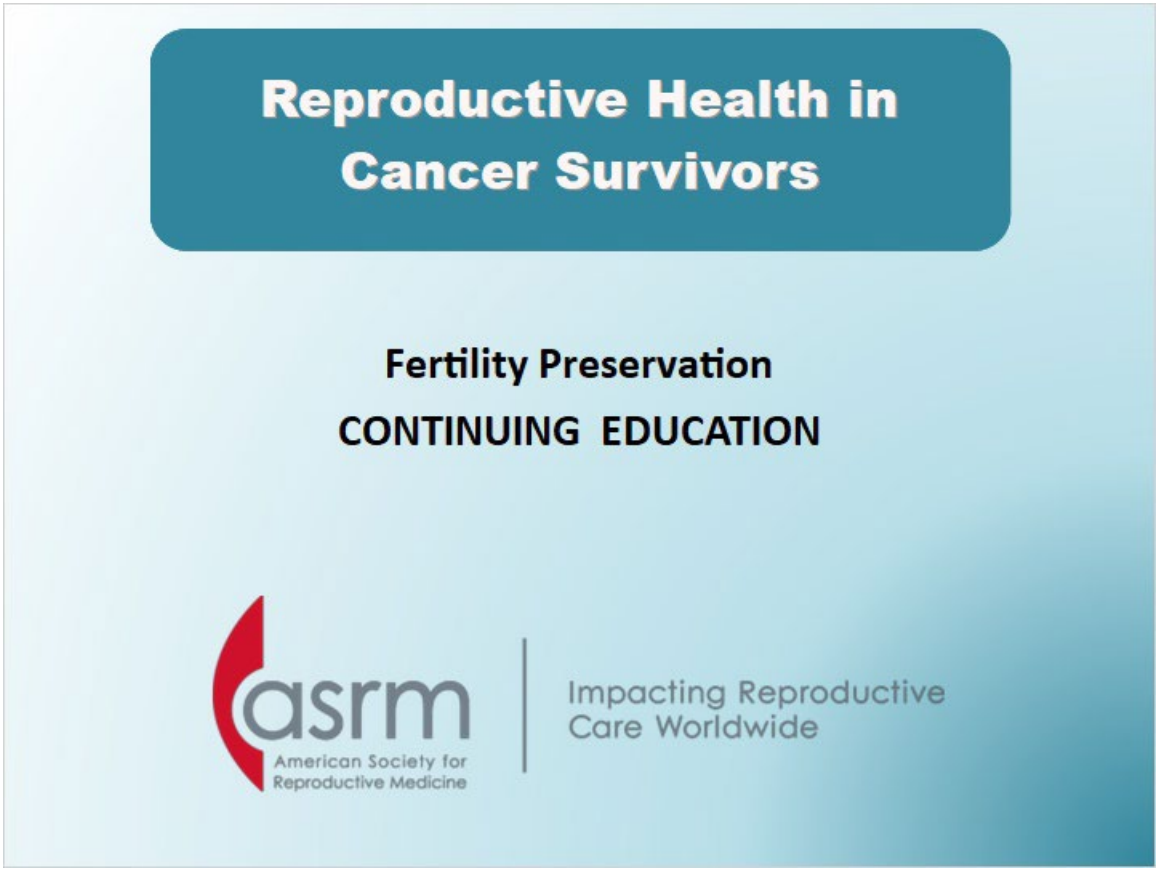
# MD120 Lesson 8

## 1. MD120_L8

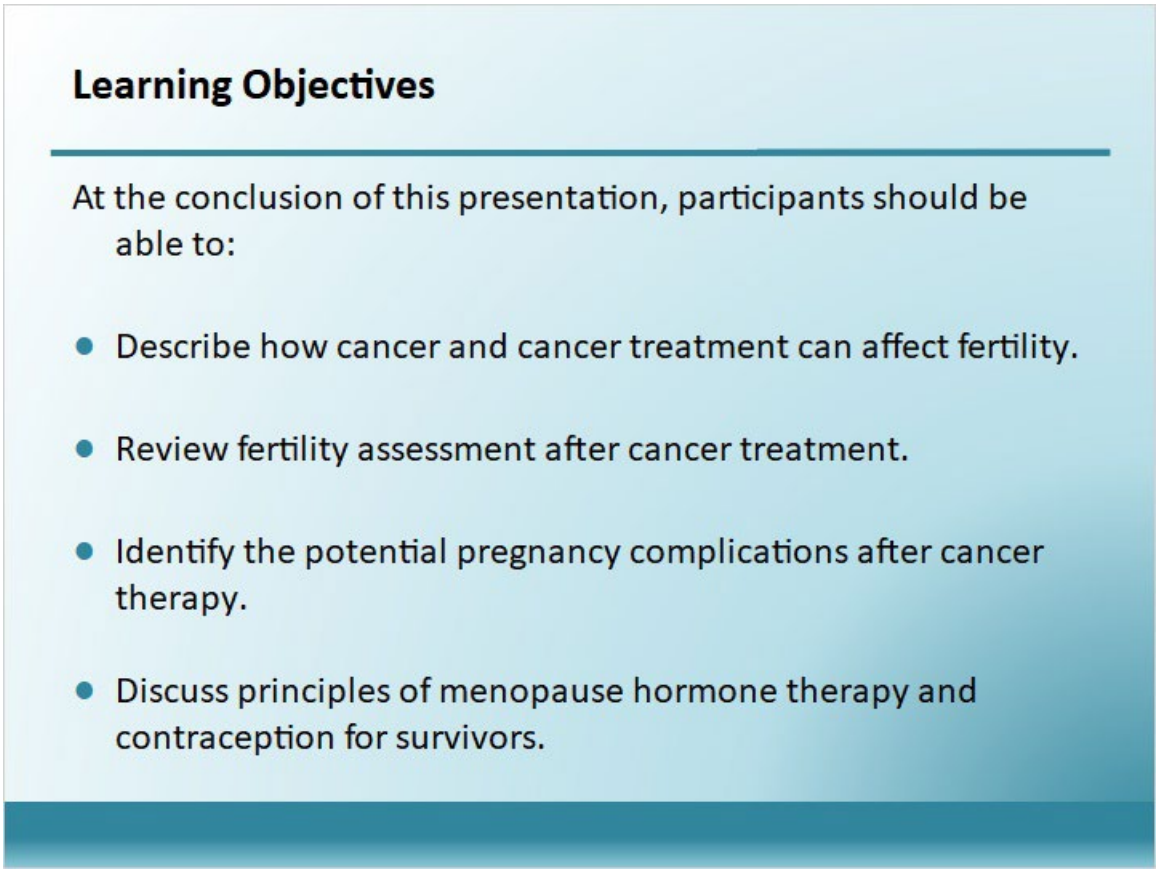
### *1.1 Reproductive Health in Cancer Survivors*




**Notes:**

Welcome to the American Society for Reproductive Medicine's eLearning modules. The subject of this presentation is "Reproductive Health in Cancer Survivors."

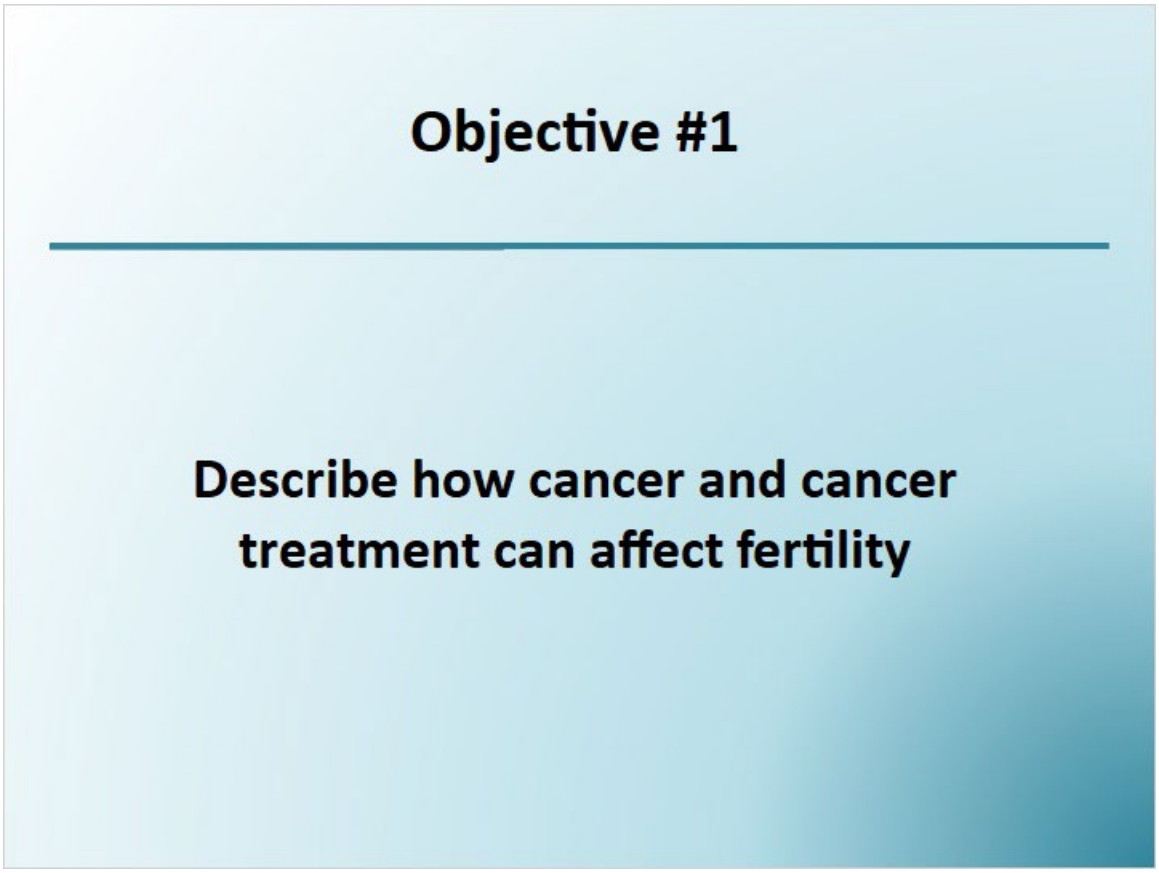
## *1.2 Learning Objectives*




**Notes:**

Upon completion of this module, participants should be able to describe how cancer treatment affects fertility, review fertility assessment after cancer treatment, identify the potential pregnancy complications after cancer therapy, and discuss principles of menopause hormone therapy and contraception for cancer survivors.

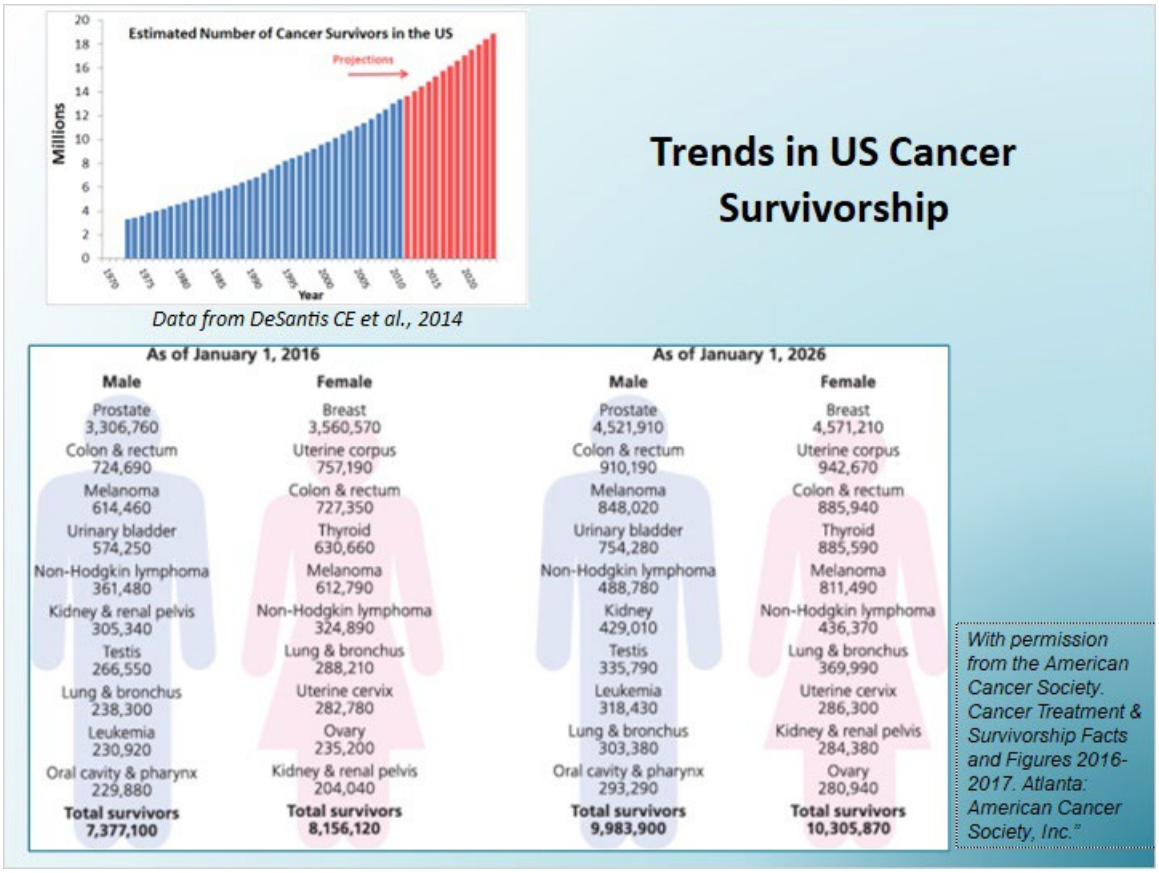
### *1.3 Objective #1*




**Notes:**

We will begin by reviewing trends in cancer survivorship and describing how cancer and cancer treatment can impact fertility.

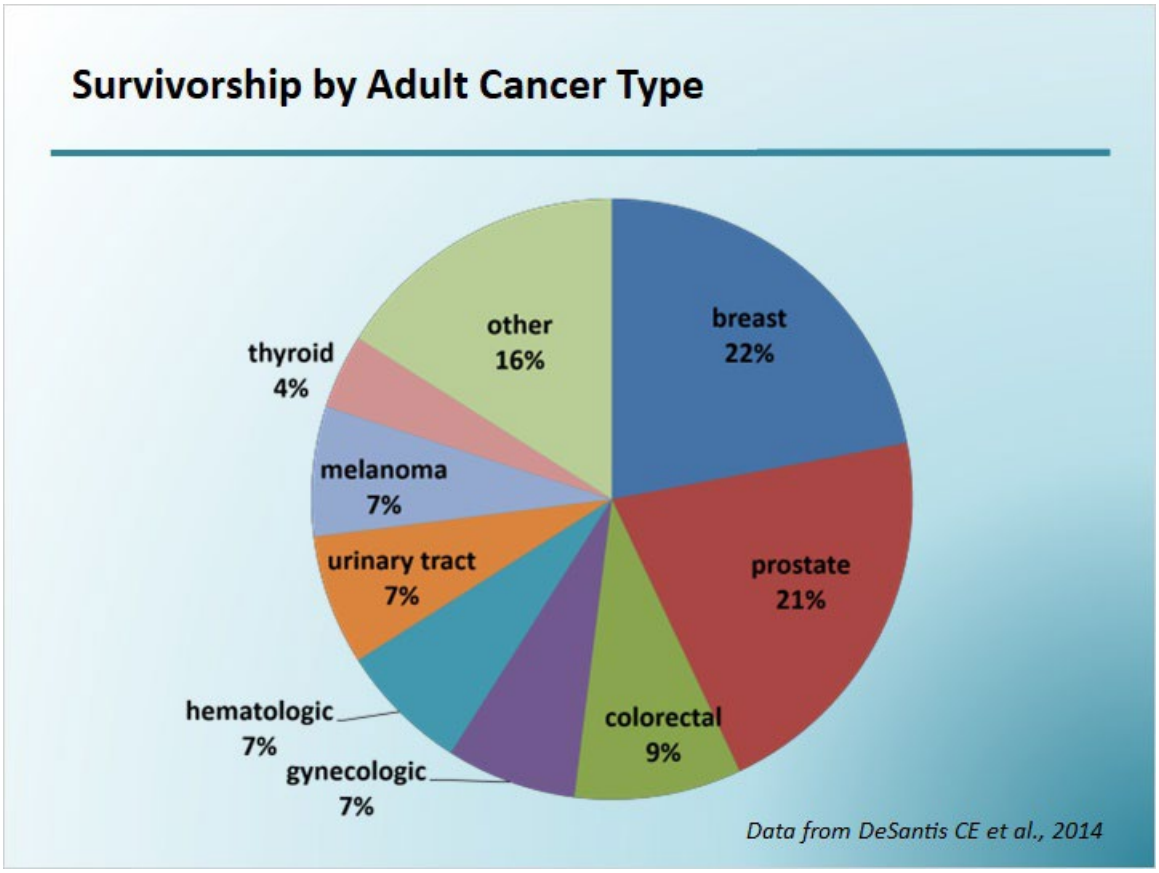
## *1.4 Trends in US Cancer Survivorship*




**Notes:**

Largely due to advancements in cancer therapeutics and early detection, there is a growing population of cancer survivors in the United States. In fact, nearly 14.5 million Americans alive in 2014 had a personal history of cancer. As seen here, there continues to be a projected rise in cancer survivorship for the next decade.

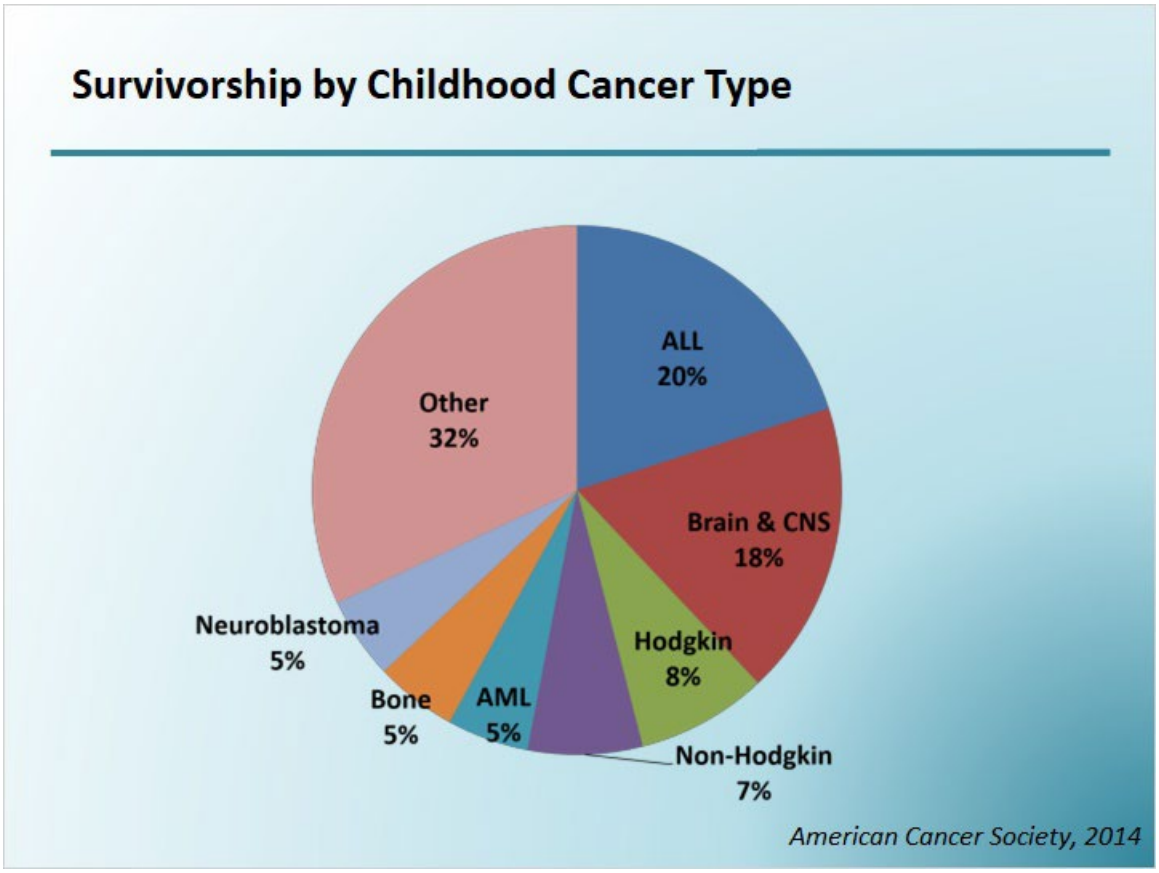
## *1.5 Survivorship by Adult Cancer Type*




**Notes:**

Here is a breakdown of adult cancer survivors by the type of malignancy. Twenty-two percent are survivors of female breast cancer, 21% from prostate cancer, and 9% from colorectal cancer. Gynecologic, hematologic, urinary tract, melanoma, and thyroid and other cancers comprise the rest.

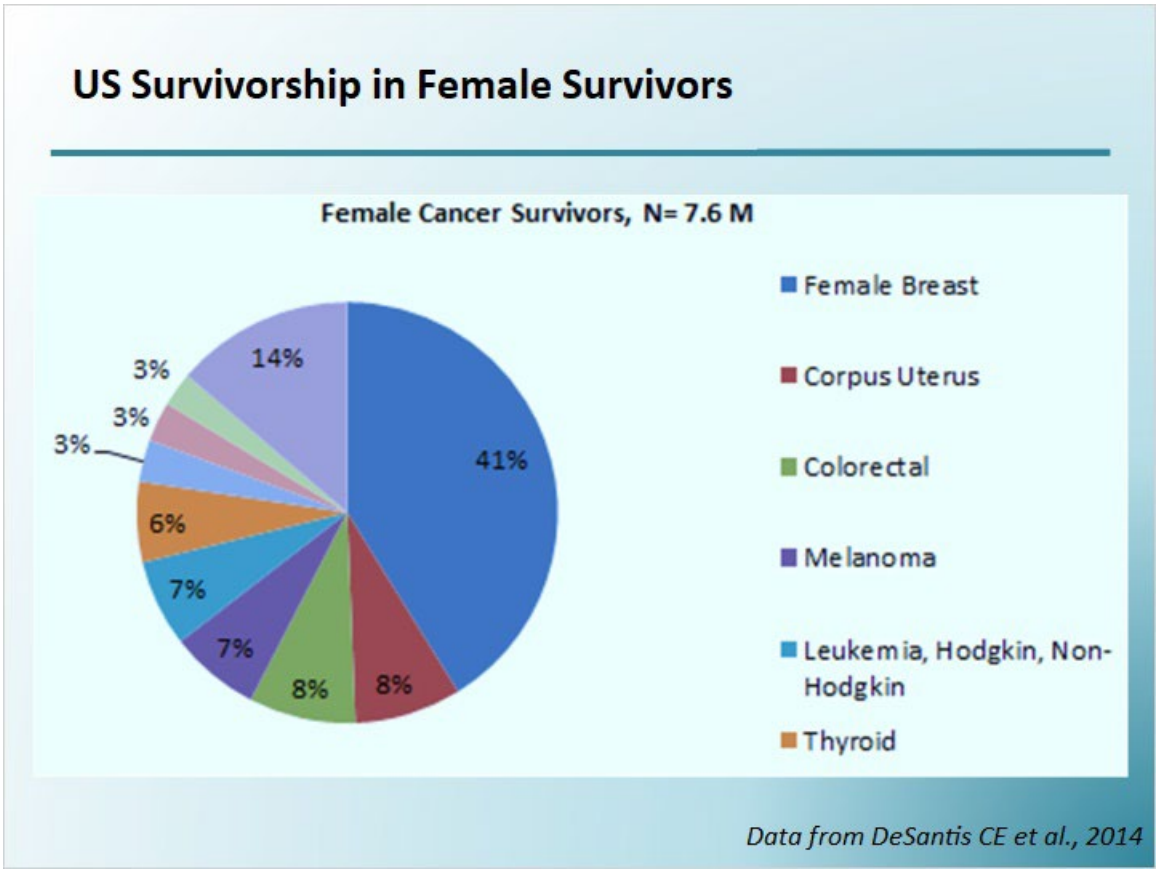
## *1.6 Survivorship by Childhood Cancer Type*




**Notes:**

Childhood cancer remains the leading cause of death by disease in the United States. Each day, 43 children are diagnosed with cancer and the average age of diagnosis is 6 years. This graph demonstrates the distribution of common cancer diagnoses. The most common types of cancer diagnosed in children and adolescents are leukemia, brain and other central nervous system tumors, lymphoma, bone tumors and neuroblastoma. Other common cancer types include thyroid, Wilms tumor, germ cell tumors and retinoblastoma. In the last 40 years, the overall survival rate for childhood cancer has increased from 10% to nearly 90%.

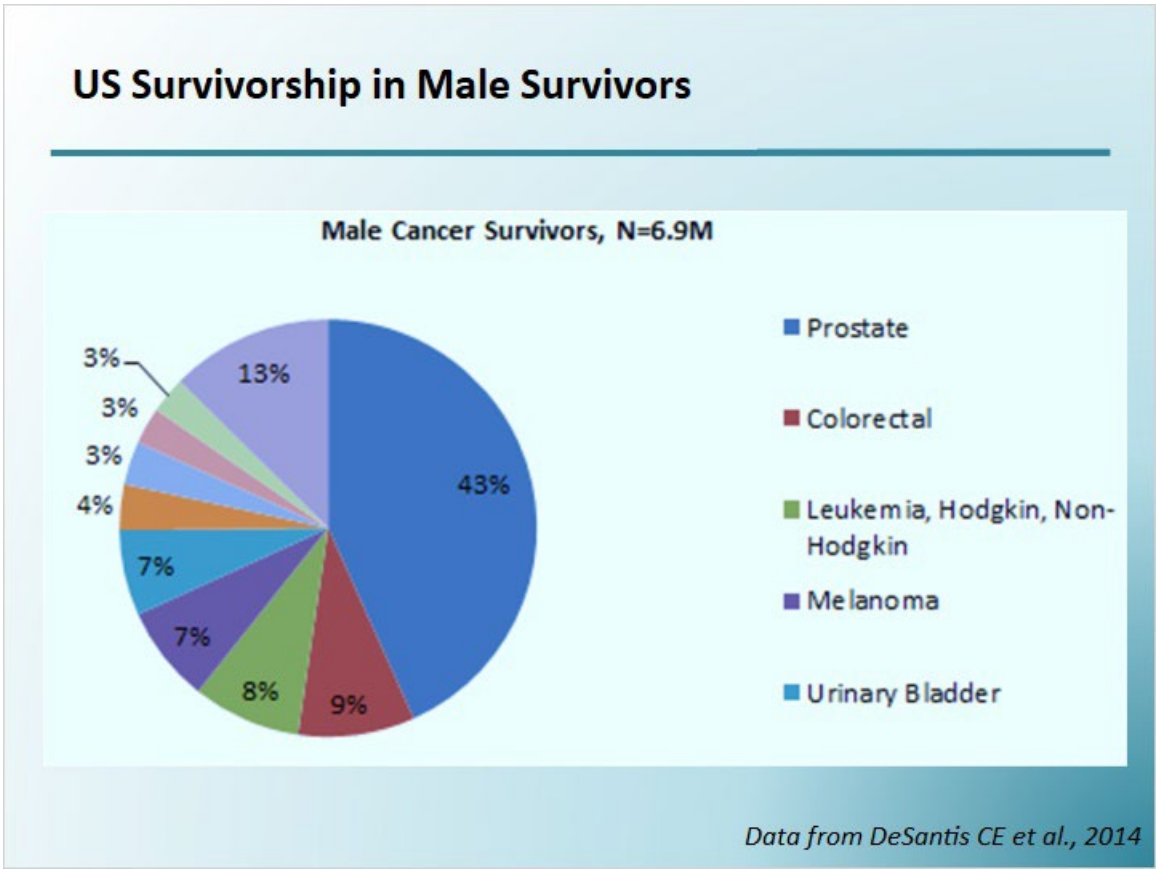
## *1.7 US Survivorship in Female Survivors*




**Notes:**

When examining survivorship on a gender-specific basis, of the 7.6 million female cancer survivors, 41% are breast cancer survivors. Among young adult female survivors aged 18 to 40 years, the most common cancer types are breast, lymphoma, melanoma and cancers of the genital tract.

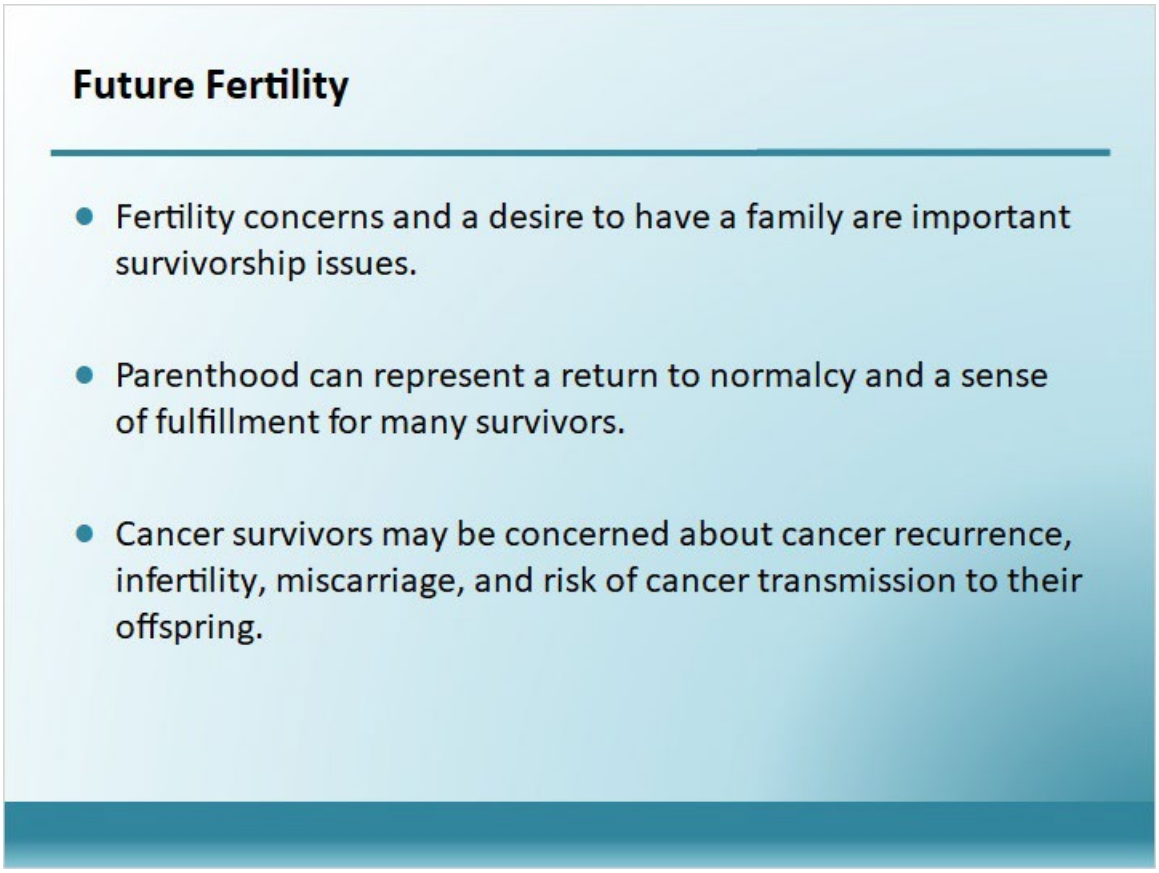
## *1.8 US Survivorship in Male Survivors*




**Notes:**

Among the 6.9 million male cancer survivors, prostate cancer survivors comprise the largest cohort, followed by colorectal and hematologic cancers. However, among young adult males, lymphoma, leukemia, melanoma and testicular cancers are among the most common cancer types.

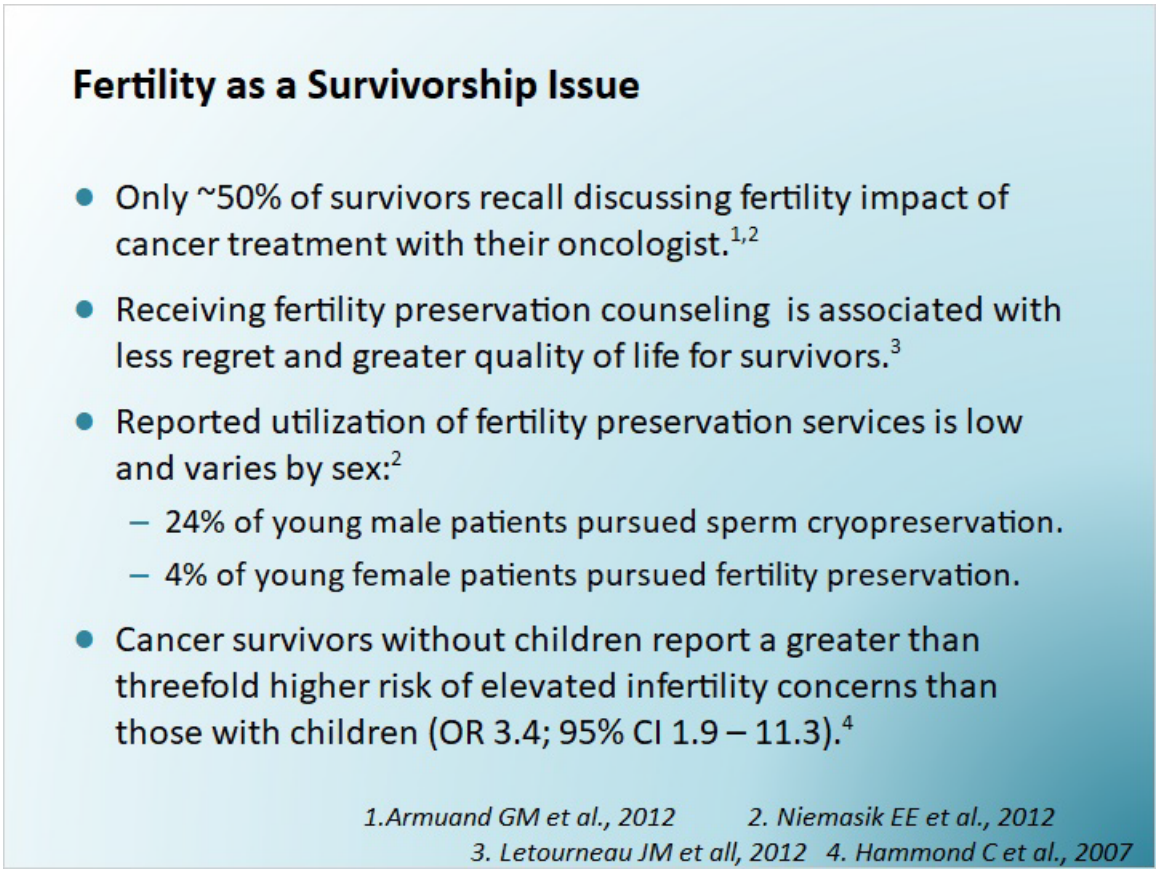
## *1.9 Future Fertility*




**Notes:**

Today, many young cancer patients can expect long-term survival; however, the quality of their lives may be hampered by gonadotoxicity, infertility, and negative psychosocial effects. One of the strongest predictors of emotional well-being in cancer survivors is the ability to be a good parent. Fertility concerns and a desire to have a family are important survivorship issues. Parenthood can represent a return to normalcy and a sense of fulfillment for many. Cancer survivors may be concerned about cancer recurrence, infertility, miscarriage and the risk of cancer transmission to their offspring .

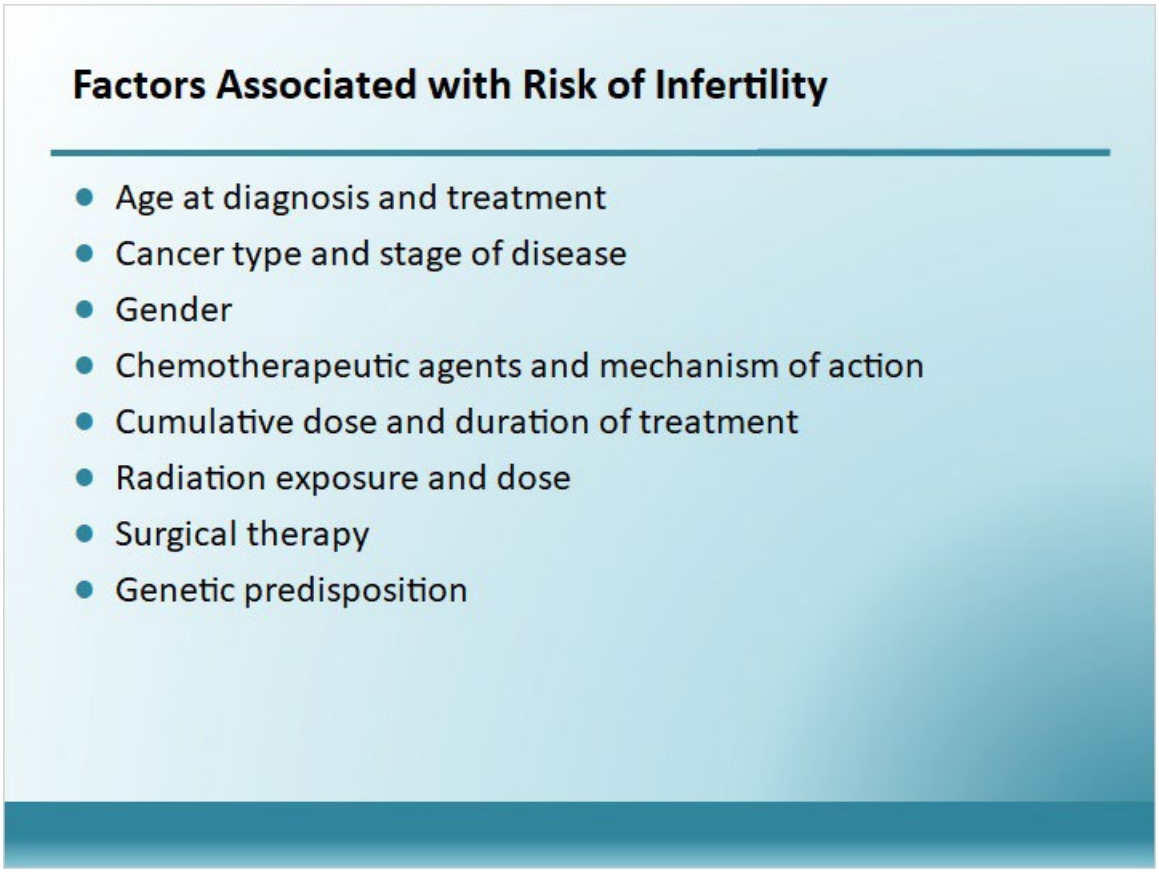
## *1.10 Fertility as a Survivorship Issue*




**Notes:**

Despite concerns about future parenthood, surveys of cancer survivors in California and Sweden revealed that only 50% of participants recall receiving reproductive health counseling from their oncology team. Receiving specialized counseling about reproductive loss and fertility preservation is associated with less regret and greater quality of life for survivors. Additionally, utilization of fertility preservation services is low and may differ by biologic sex. In a survey of California survivors, 24% of young male cancer patients pursued sperm cryopreservation while only 4% of young female patients pursued oocyte or embryo banking. The psychosocial impacts of infertility are especially distressing for cancer survivors without children. A study of cancer survivors 10 years after stem cell transplant reported that those without children before their transplant had a greater than threefold higher risk of elevated concerns about infertility than those who had children prior to transplant (OR 3.4, 95% CI 1.93-11.30).

## *1.11 Factors Associated with Risk of Infertility*



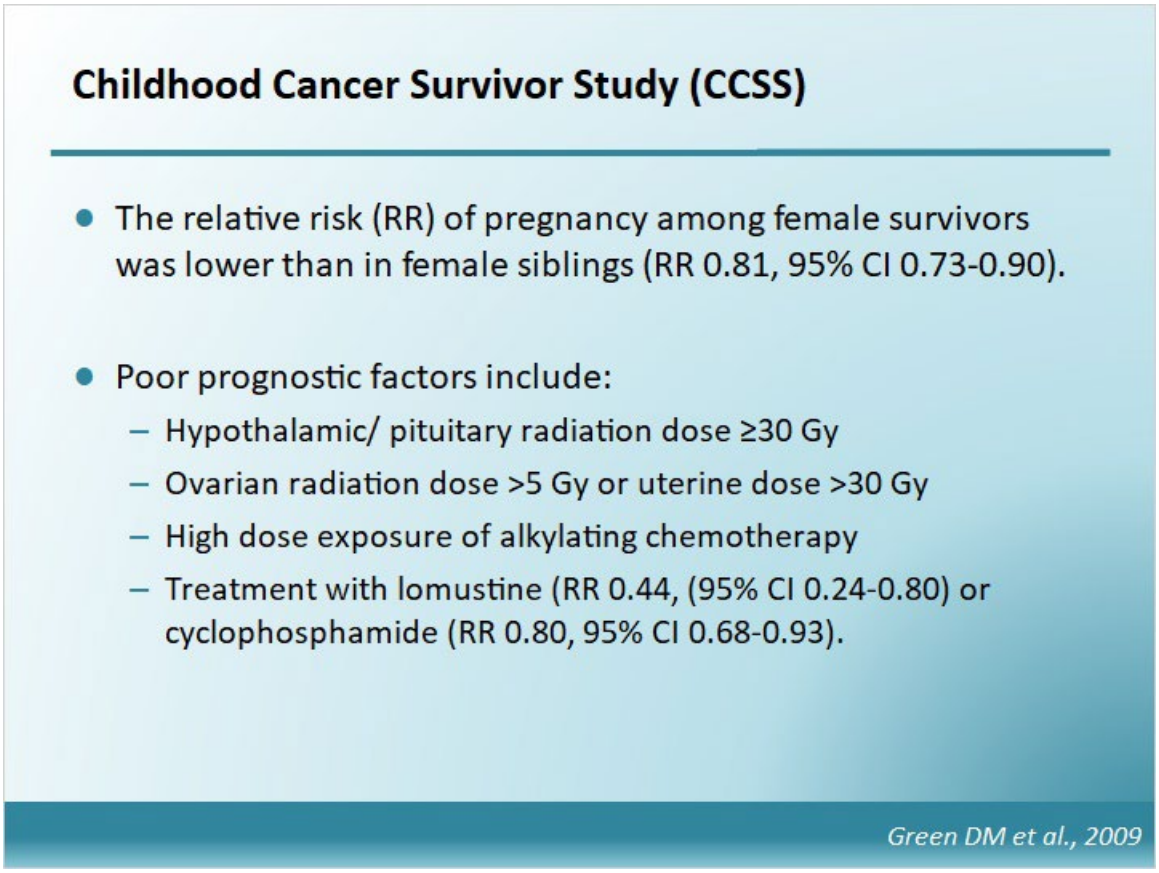

**Notes:**

Several factors impact an individual's risk of infertility after cancer diagnosis or treatment.

Infertility can be caused by injury to the hypothalamic-pituitary-gonadal axis, as well as direct damage to pelvic organs. Chemotherapy, radiation, surgery, and the malignancy itself can result in infertility. The reproductive impact may be transient or permanent.

The magnitude of infertility risk depends on multiple factors, including the age of diagnosis and treatment, the cancer type and stage of disease, gender, the specific chemotherapeutic agents and mechanism of action, the cumulative dose and duration of treatment, exposure to radiation and dose, surgical therapy, and genetic predisposition.

## *1.12 Childhood Cancer Survivor Study (CCSS)*

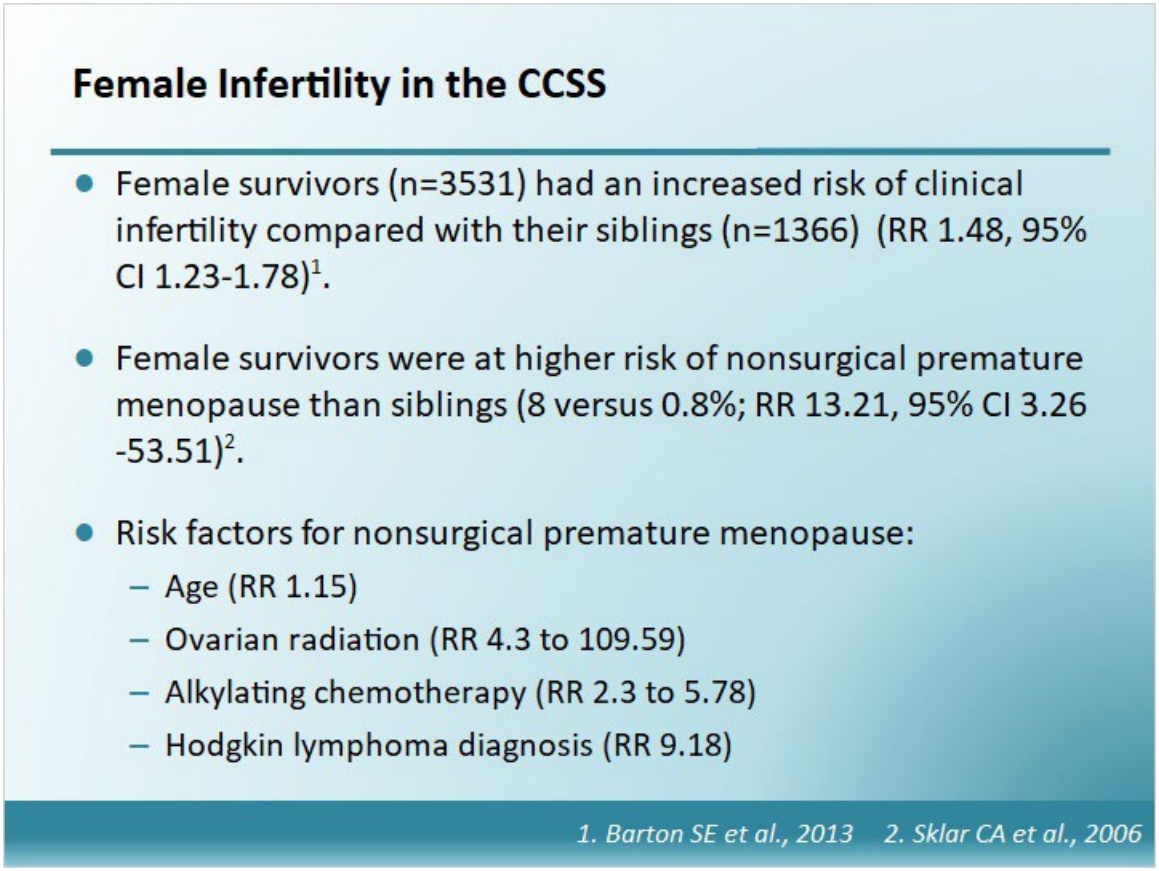



**Notes:**

The largest database examining long-term consequences of cancer therapy including the risk of infertility in cancer survivors is the Childhood Cancer Survivor Study (CCSS). A total of 14,000 childhood cancer survivors diagnosed between 1970 and 1986 were surveyed and followed for this long-term cohort study from 26 centers in the United States and Canada. In addition, about 4,000 of their siblings were recruited as comparison subjects. Due to the significant changes in pediatric cancer therapy over the past 30 years, a second group of 10,000 survivors diagnosed between 1987 and 1999 and 1,000 of their siblings were also recruited.

In a series of publications, fertility rates in female cancer survivors and female partners of male cancer survivors were compared with fertility rates in the sibling cohort. This study found that female cancer survivors had a 19% lower relative risk of achieving pregnancy compared with their female siblings (RR 0.81, 95% CI 0.73-0.90). Poor prognostic factors for infertility included exposure to hypothalamic or pituitary radiation doses greater than 30 Gy, ovarian doses greater than 10-15 Gy in pre-pubertal females and 5 Gy in adult women, uterine doses greater than 30 Gy, or high doses of alkylating chemotherapy with agents such as lomustine or cyclophosphamide.

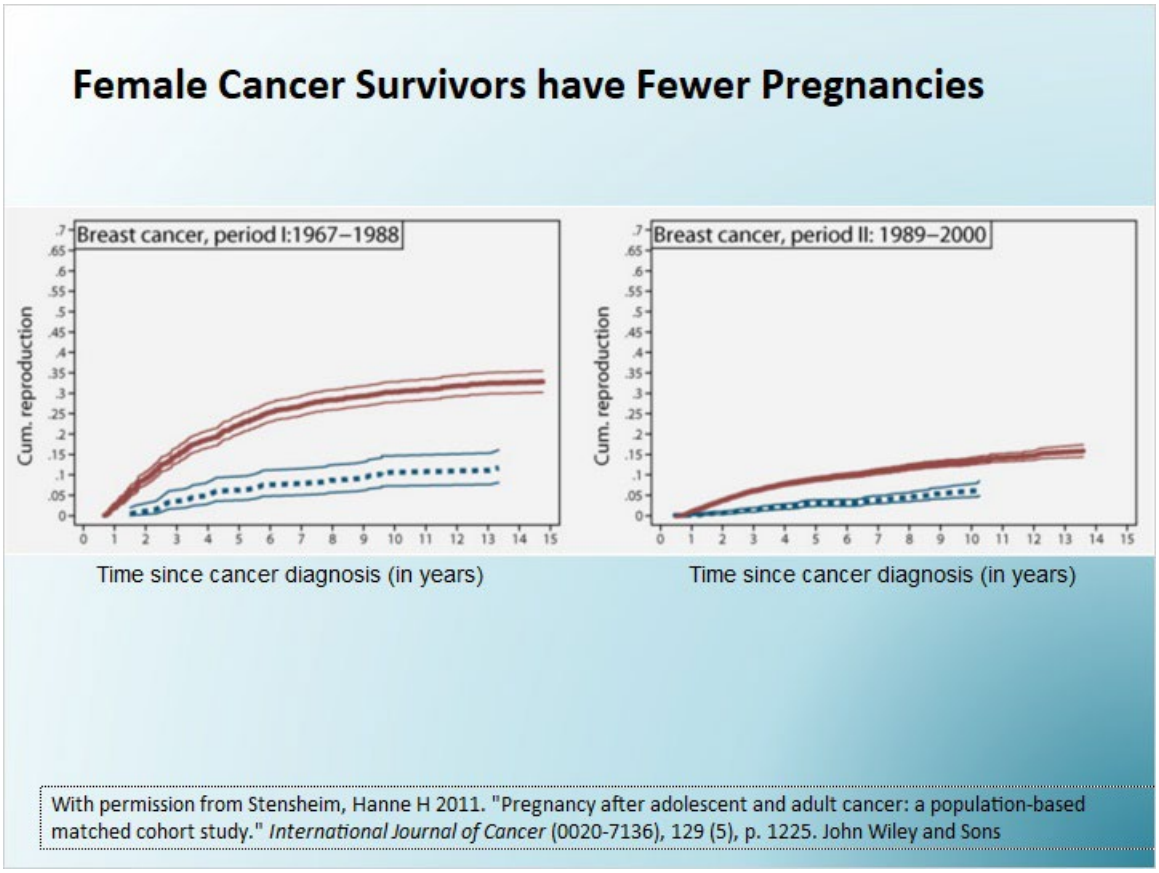
## *1.13 Female Infertility in the CCSS*




**Notes:**

The relative risk of infertility among female cancer survivors was 48% higher as compared with their siblings (RR 1.48, 95% CI 1.23-1.78). The difference in risk was most pronounced at early reproductive ages. Female survivors were also at higher risk of nonsurgical premature menopause than siblings (8 versus 0.8%; RR 13.21, 95% CI 3.26-53.51). The risk factors associated with premature menopause included age at treatment, exposure to ovarian radiation, higher dose or number of alkylating agents used, and a diagnosis of Hodgkin lymphoma. Exposure to more than one risk factor conferred additional risk. For example, survivors who were treated with alkylating agents as well as pelvic radiation were noted to have a cumulative incidence of nonsurgical premature menopause approaching 30%.

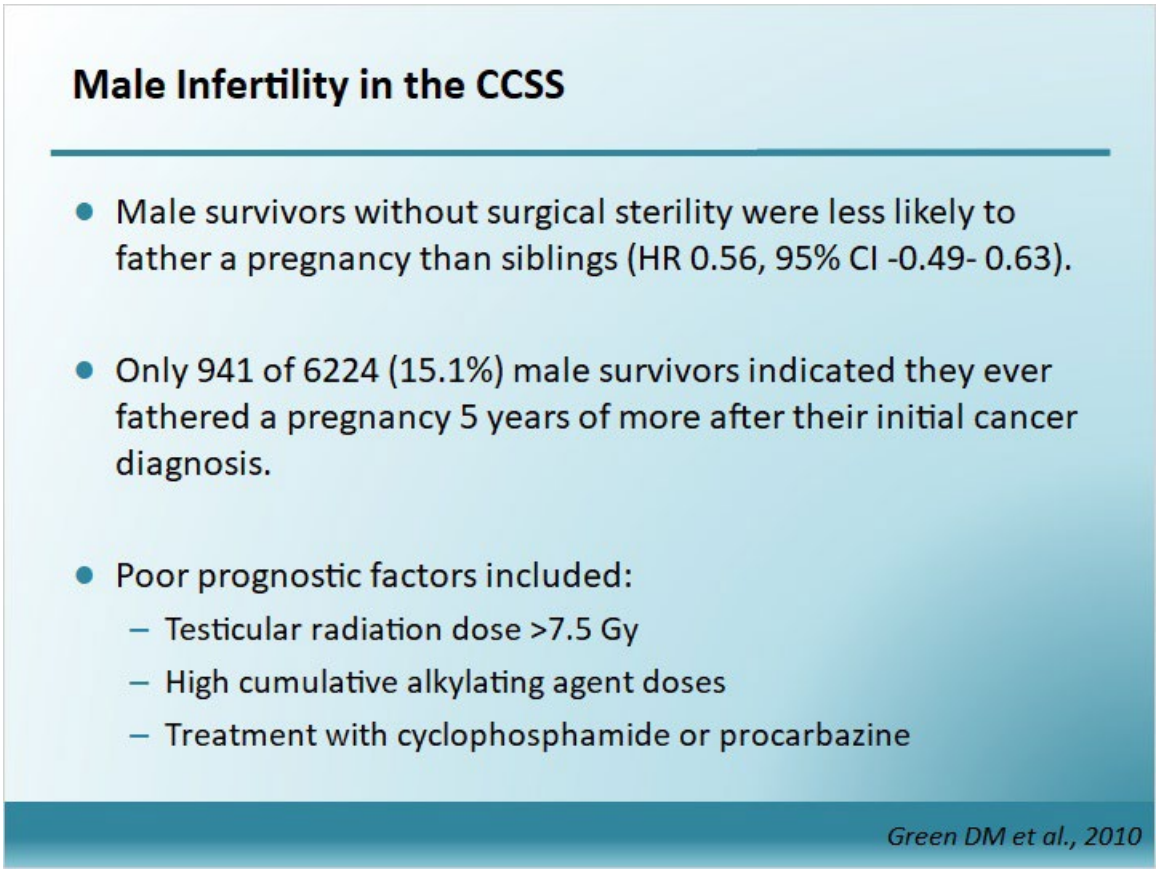
## *1.14 Female Cancer Survivors have Fewer Pregnancies*




**Notes:**

In a population-based study from Norway of 16,00 female cancer survivors and 85,000 controls, female cancer survivors had a 40% less chance of becoming pregnant as compared with the general population when adjusting for age, previous parity, and level of education. The chances of subsequent pregnancy were dependent on the type of cancer as seen in this box plot.

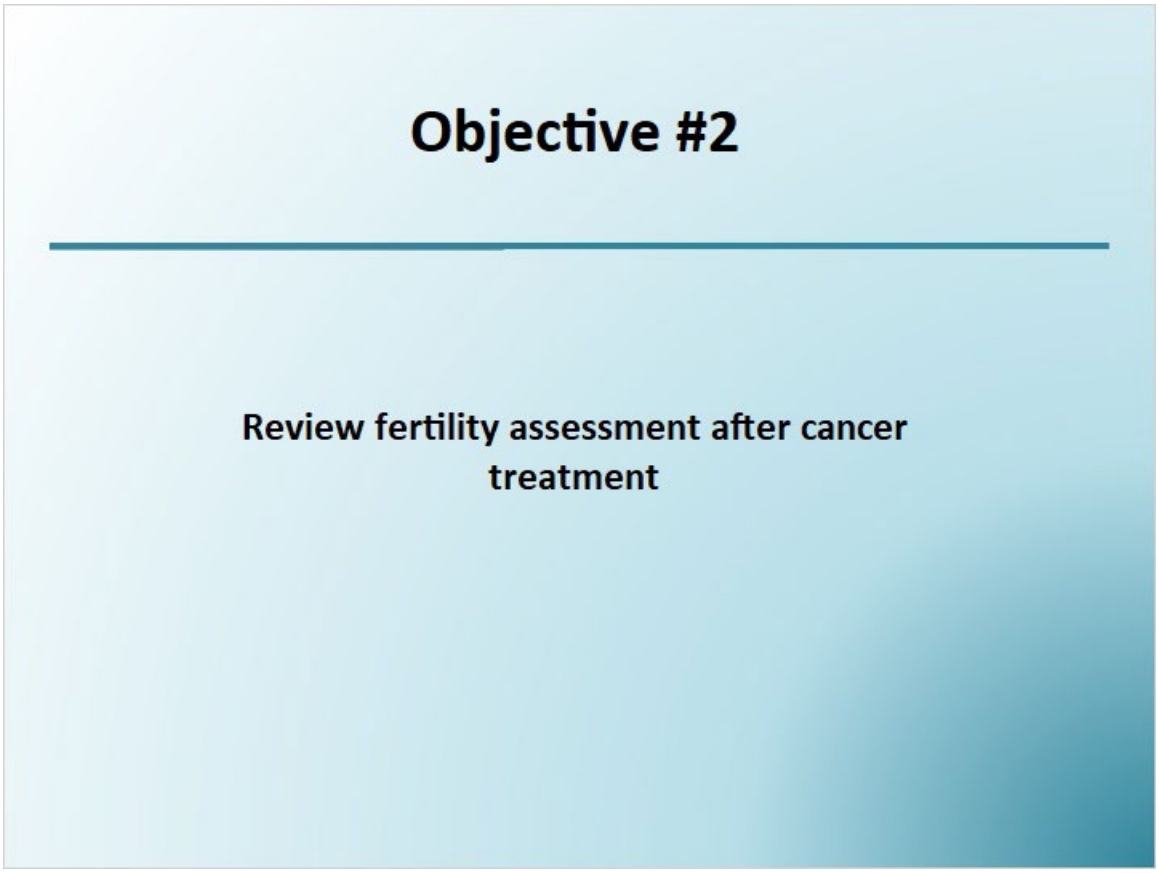
## *1.15 Male Infertility in the CCSS*




**Notes:**

Male survivors who did not have surgical sterility were also less likely to father a pregnancy than siblings. In fact, only 15.1% of male survivors indicated they ever fathered a pregnancy five years or more after their initial diagnosis. Poor prognostic factors included testicular radiation doses greater than 7.5 Gy, higher cumulative alkylating agent doses, and exposure to cyclophosphamide or procarbazine.

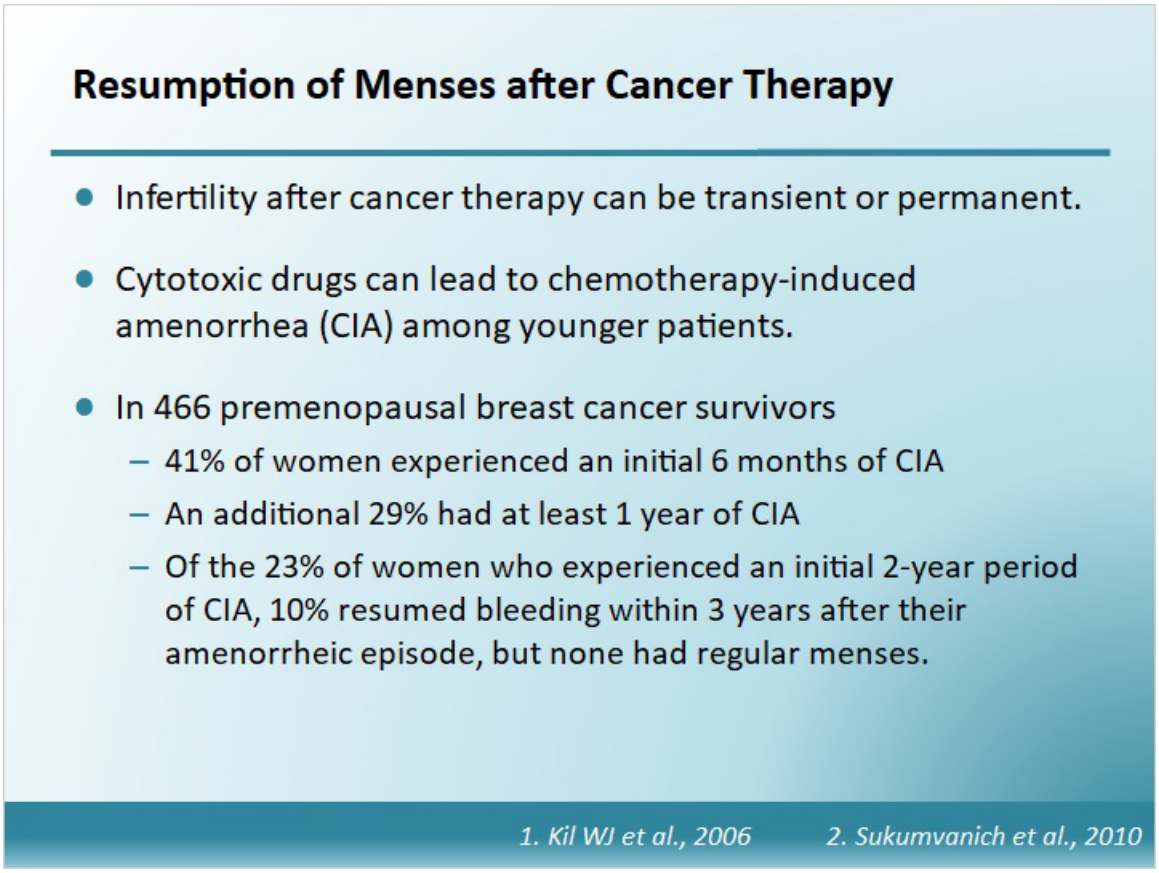
## *1.16 Objective #2*




**Notes:**

We will now review methods and limitations of assessing fertility potential after cancer treatment.

## *1.17 Resumption of Menses after Cancer Therapy*

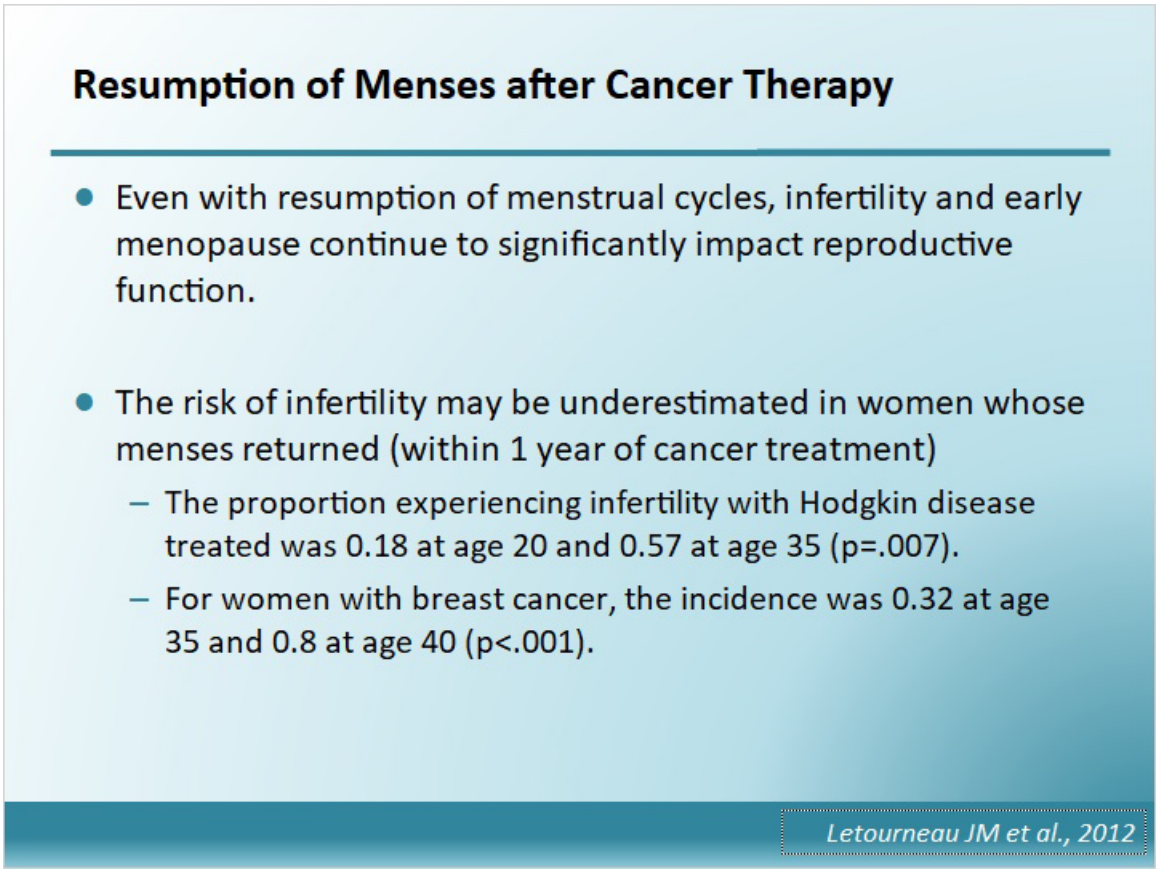



**Notes:**

The assessment of fertility potential after cancer therapy is challenging because infertility may be transiently impaired. Unfortunately, the duration of transient infertility or even whether infertility is transient or permanent, cannot reliably be predicted. The presence of functioning ovaries or testes does not reliably predict that pregnancy will occur.

Many survivors will experience menstrual dysfunction after completion of cancer therapy. Cytotoxic drugs can lead to chemotherapy-induced amenorrhea (CIA) among younger patients. In a study of chemotherapy-induced amenorrhea and time to resumption of menstrual bleeding in 466 premenopausal breast cancer patients, approximately 41% of women experienced an initial 6 months of chemotherapy-induced amenorrhea, and an additional 29% had at least 1 year of chemotherapy-induced amenorrhea. Of the 23% of women who experienced an initial 2-year period of chemotherapy-induced amenorrhea, 10% resumed bleeding within 3 years after their amenorrheic episode, but none had regular menses.

## *1.18 Resumption of Menses after Cancer Therapy*

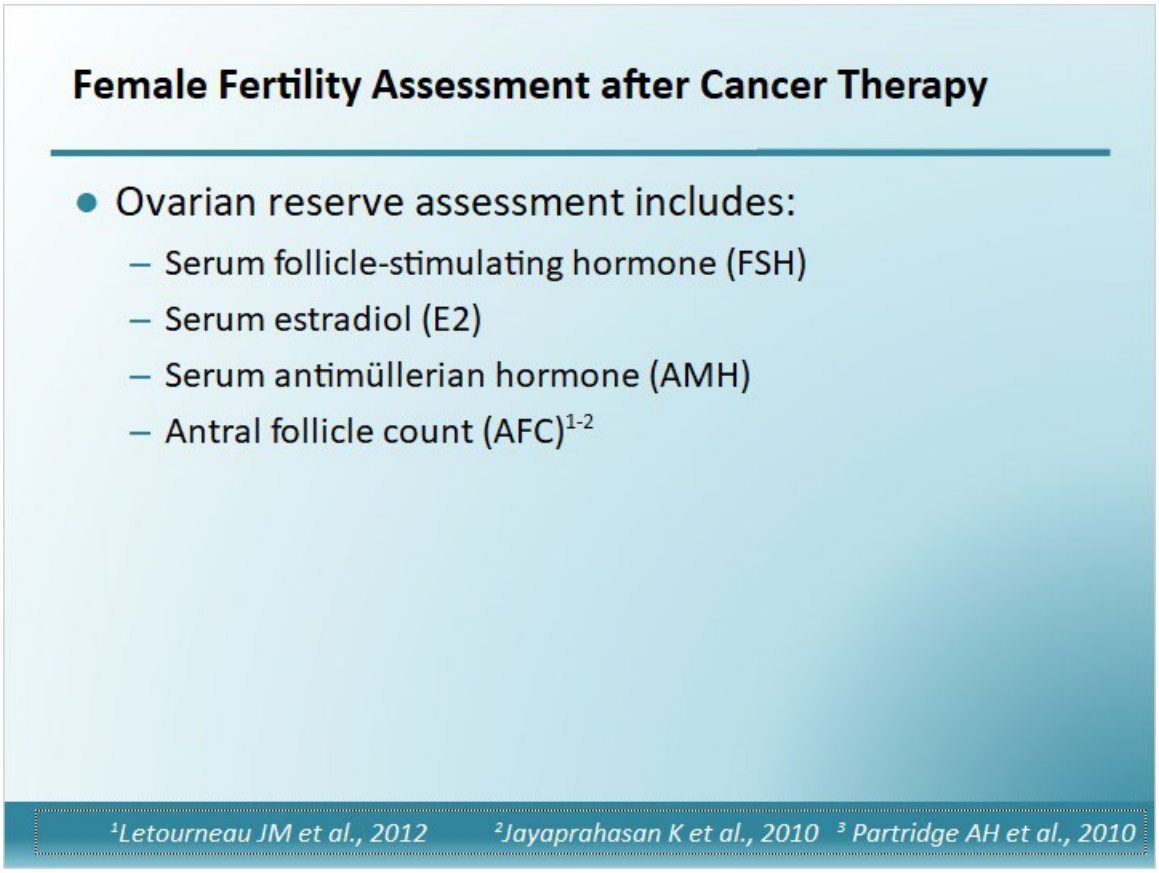



**Notes:**

Even in women who continue to menstruate regularly, infertility and early menopause may significantly impact reproductive function.

It is important not to rely on menstrual cyclicity alone to reassure survivors as we may be underestimating their infertility risk. For women whose menses have returned within 1 year of cancer treatment, the proportion experiencing subsequent infertility increases significantly with older age at cancer diagnosis in patients with breast cancer and Hodgkin disease. A trend towards a similar association between age at diagnosis and risk of infertility was noted in women with non-Hodgkin lymphoma.

## *1.19 Female Fertility Assessment after Cancer Therapy*




**Notes:**

The fertility evaluation of cancer patients necessitates an assessment of ovarian reserve with serum follicle-stimulating hormone (FSH), estradiol, antimüllerian hormone (AMH) and/or pelvic ultrasound with antral follicle counts.

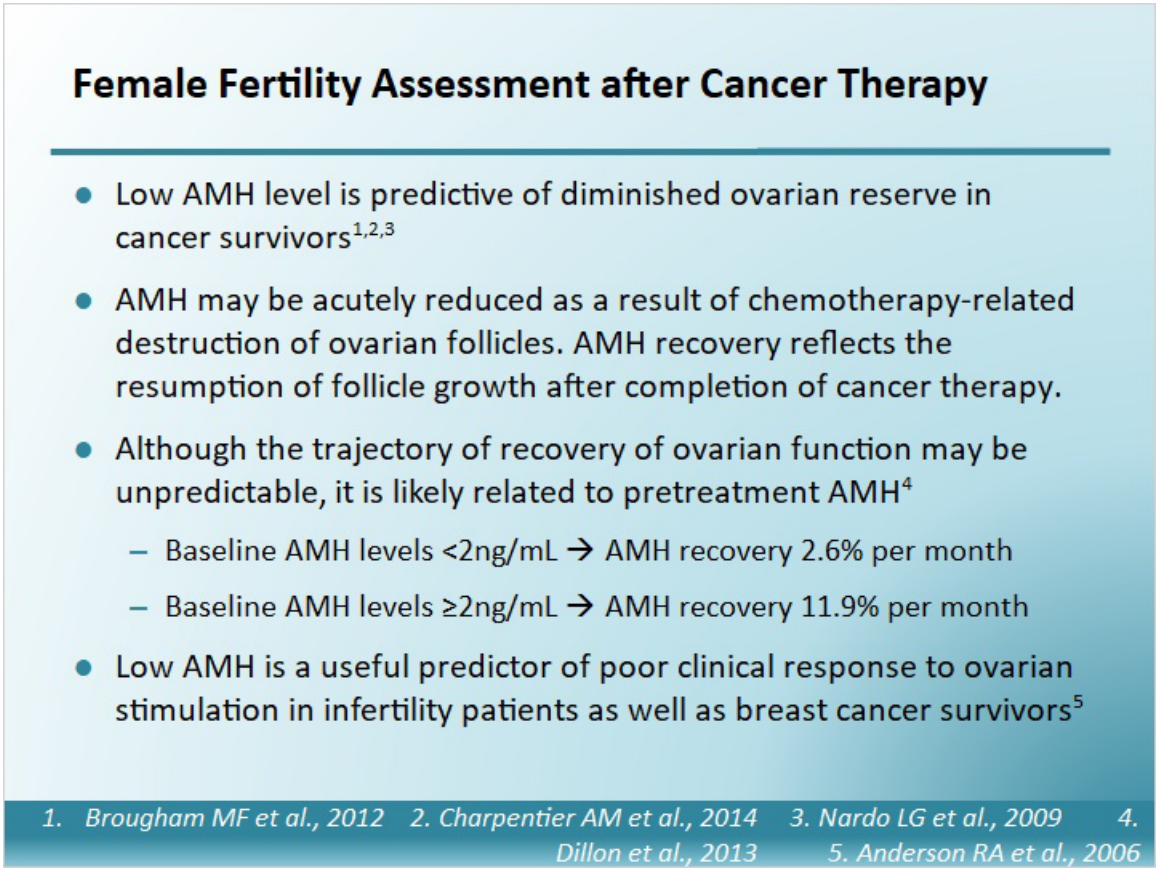
Serum FSH is the most commonly used marker of ovarian reserve but can fluctuate throughout the menstrual cycle. Oftentimes, FSH can acutely rise to menopausal levels in the setting of gonadotoxic therapy. Although it may decrease after completion of cancer treatment, FSH rarely returns to pre-chemotherapy levels. Estradiol is secreted from granulosa cells of developing ovarian follicles. Due to central feedback mechanisms, obtaining an estradiol level will allow for the correct interpretation of a normal FSH level.

AMH is a glycoprotein hormone that is produced by the granulosa cells of primary, preantral, and antral follicles, and therefore reflects the size of the primordial oocyte pool. A decrease in the number of ovarian follicles results in lower AMH levels, indicating oocyte depletion and reduction in ovarian reserve.

The antral follicle count records the number of visible ovarian follicles measuring 2-10 mm that are observed during transvaginal ultrasound in the early follicular phase (cycle days 2-5). The

antral follicle count correlates with the quantity of remaining follicles and with the ovarian response during controlled ovarian stimulation. In addition, good inter-cycle and inter-observer reliability has been demonstrated. In a cross-sectional study comparing markers of ovarian reserve between early stage breast cancer survivors and matched controls, there were significant differences in AFC and AMH, and nonsignificant differences in FSH, indicating better ovarian reserve in controls. Furthermore, AFC and AMH levels were highly correlated (r=0.72).

## *1.20 Female Fertility Assessment after Cancer Therapy*



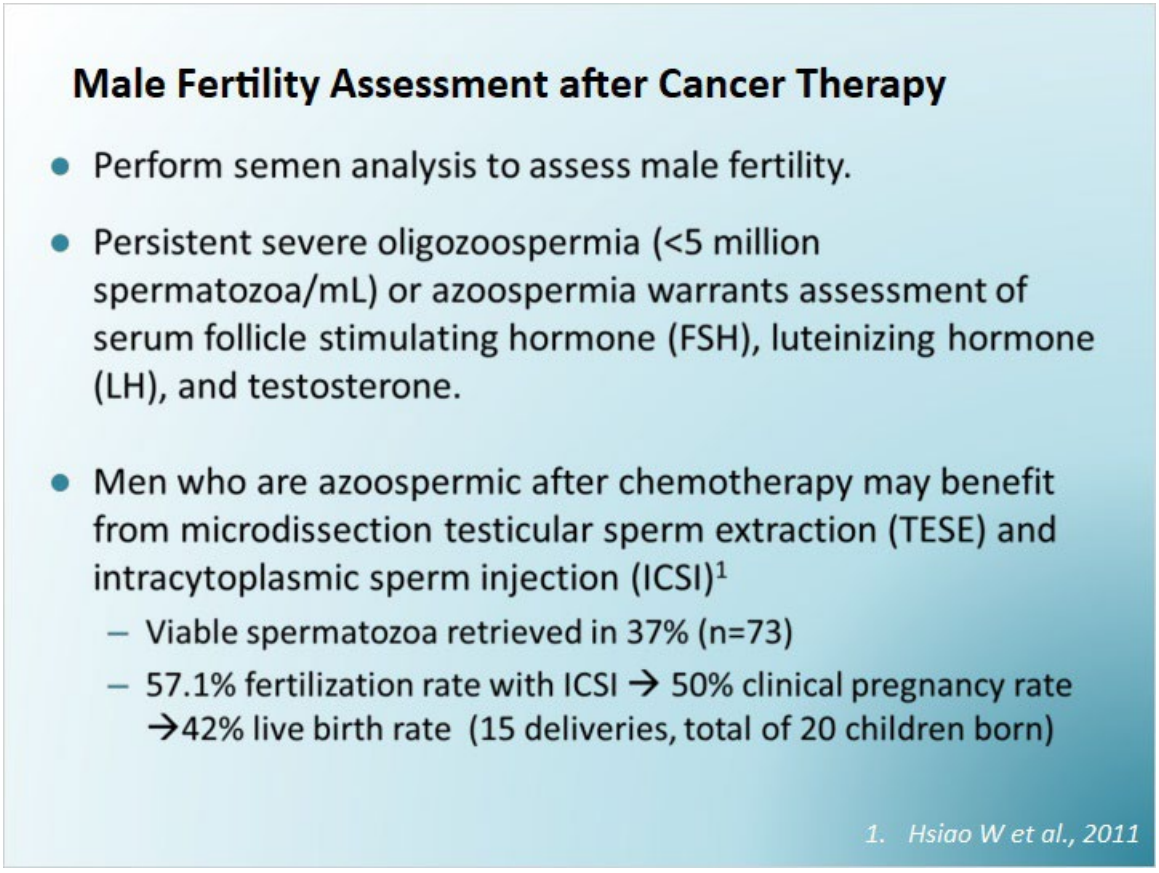

**Notes:**

Premenopausal women with regular menstrual cycles should undergo ovarian reserve testing. A low AMH level may be the best test for prediction of diminished ovarian reserve in this population. Serum AMH has been found to be useful as an early indicator of ovarian aging, including the assessment of chemotherapy-induced ovarian follicle loss in premenopausal breast cancer survivors.

In addition, AMH has been observed to be acutely impaired during treatment and begin to recover during the post-treatment period. This acute decline in AMH appears to occur as a result of chemotherapy-related destruction of ovarian follicles. The recovery

in these measures reflects the resumption of follicle growth after cancer therapy. The window of recovery can often be unpredictable but is likely related to pretreatment ovarian reserve. Women with baseline AMH levels <2ng/mL have demonstrated a recovery in AMH of 2.6% per month whereas those with baseline AMH levels ≥2ng/mL demonstrated a recovery rate of 11.9% per month. Low AMH is a known predictor of poor response to ovarian stimulation during in vitro fertilization among patients with infertility, and has demonstrated similar clinical utility among breast cancer survivors.

### *1.21 Male Fertility Assessment after Cancer Therapy*

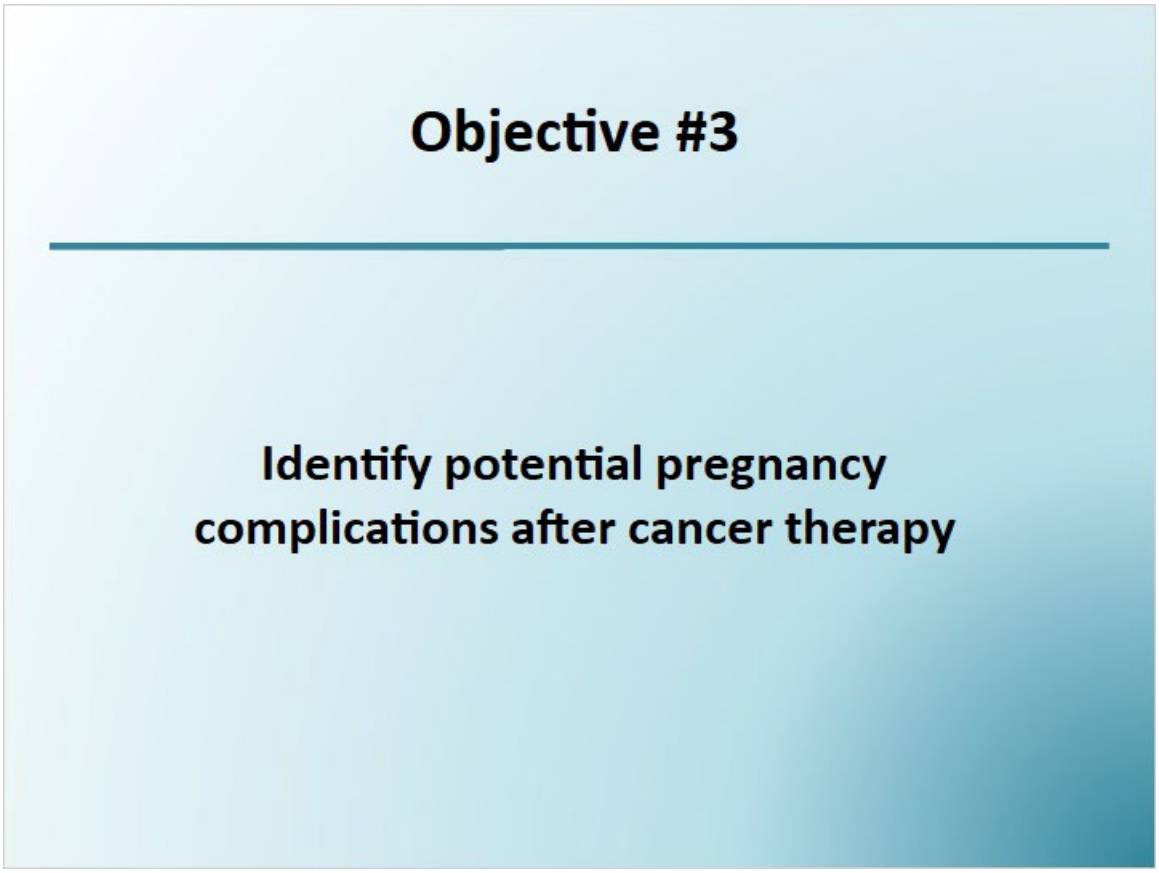



**Notes:**

In men, fertility potential is evaluated by a semen analysis. If repeated semen analyses demonstrate severe oligozoospermia or azoospermia, basal serum follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone should be measured. These patients may benefit from a referral to a urologist specializing in fertility. Traditionally, men who are azoospermic after cancer therapy were considered sterile. However, microdissection testicular sperm extraction (TESE) with intracytoplasmic sperm injection (ICSI) may offer an effective treatment option for some. Viable spermatozoa were

retrieved in 37% of 73 men who underwent microdissection testicular sperm extraction an average of 19 years post-chemotherapy. The fertilization rate with ICSI was 57.1%, resulting in a 50% clinical pregnancy rate and a 42% live birth rate (15 deliveries, with a total of 20 children born).

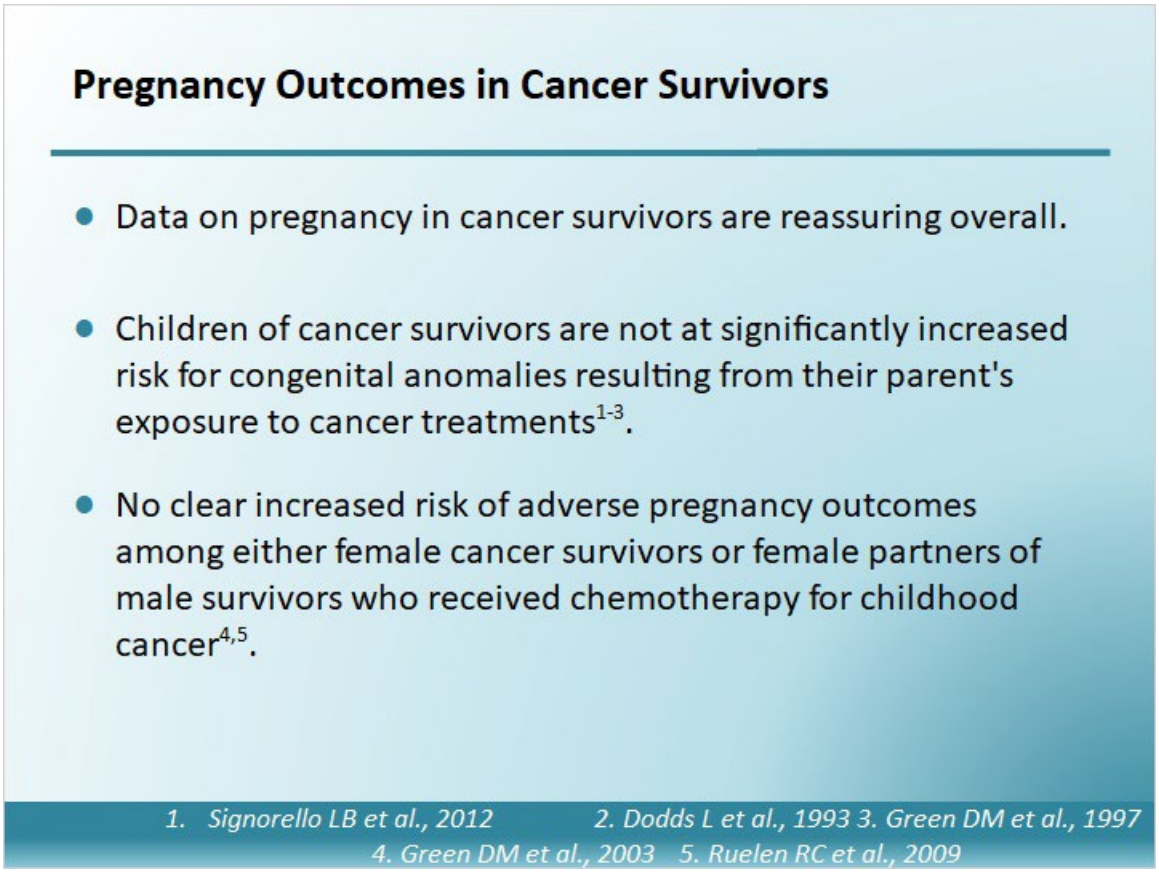
### *1.22 Objective #3*




**Notes:**

It is important to understand the impact of cancer and its therapy on pregnancy and fetal health.

## *1.23 Pregnancy Outcomes in Cancer Survivors*

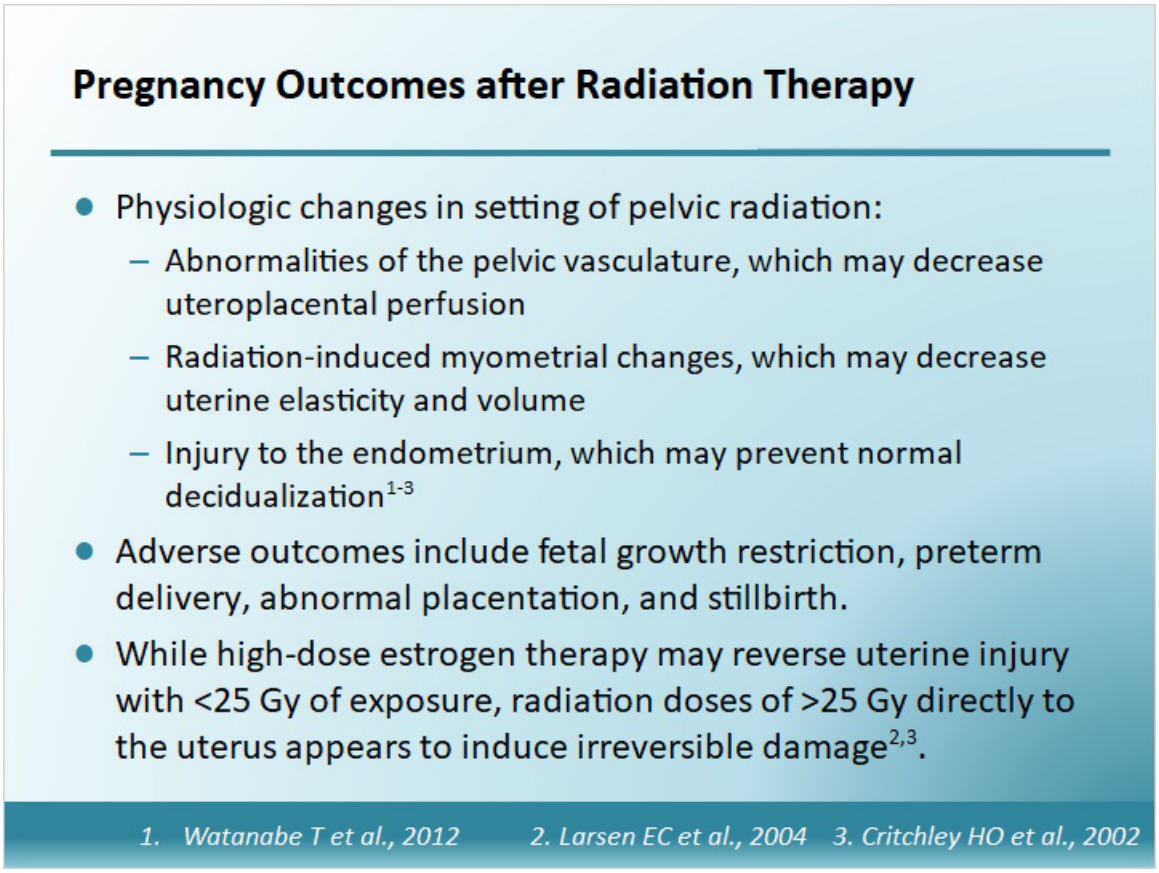



**Notes:**

Overall, the available data on pregnancy and offspring outcomes among cancer survivors are reassuring. Survivors should be reassured that research to date does not support an excess risk of congenital malformations, genetic disorders, or chromosomal syndromes in offspring born to childhood cancer survivors. In fact, multiple studies demonstrate the risk of congenital anomalies is not higher than that in the general population.

There does not appear to be strong evidence of an increased risk of adverse pregnancy outcomes among either female cancer survivors or female partners of male survivors who received chemotherapy for childhood cancer.

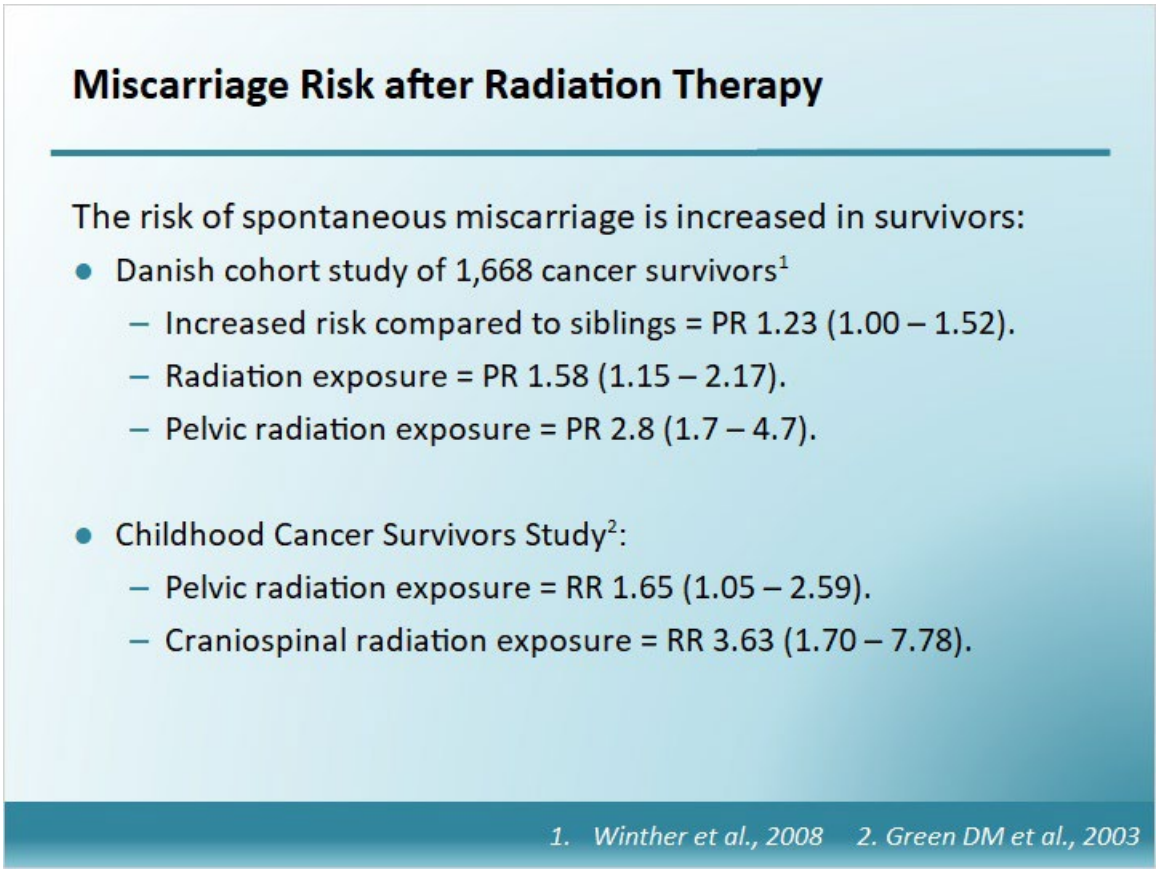
## *1.24 Pregnancy Outcomes after Radiation Therapy*




**Notes:**

One notable exception is female cancer survivors with a history of pelvic radiation exposure. Girls and young women who undergo pelvic radiation are at risk of a number of physiologic effects that alter pelvic organ function. For example, abnormalities of the pelvic vasculature may decrease uteroplacental perfusion. Radiation-induced myometrial changes, such as fibrosis, may decrease uterine elasticity and volume. Finally, injury to the endometrium may prevent normal decidualization. These changes may account for some adverse pregnancy outcomes such as fetal growth restriction, preterm delivery, placenta accreta, and stillbirth that have been reported in pregnancies occurring in women with a history of pelvic radiation. While high-dose estrogen therapy may reverse uterine injury in women exposed to less than <25 Gy of pelvic radiation, doses greater than 25 Gy directly to the uterus appears to induce irreversible damage[2,3].

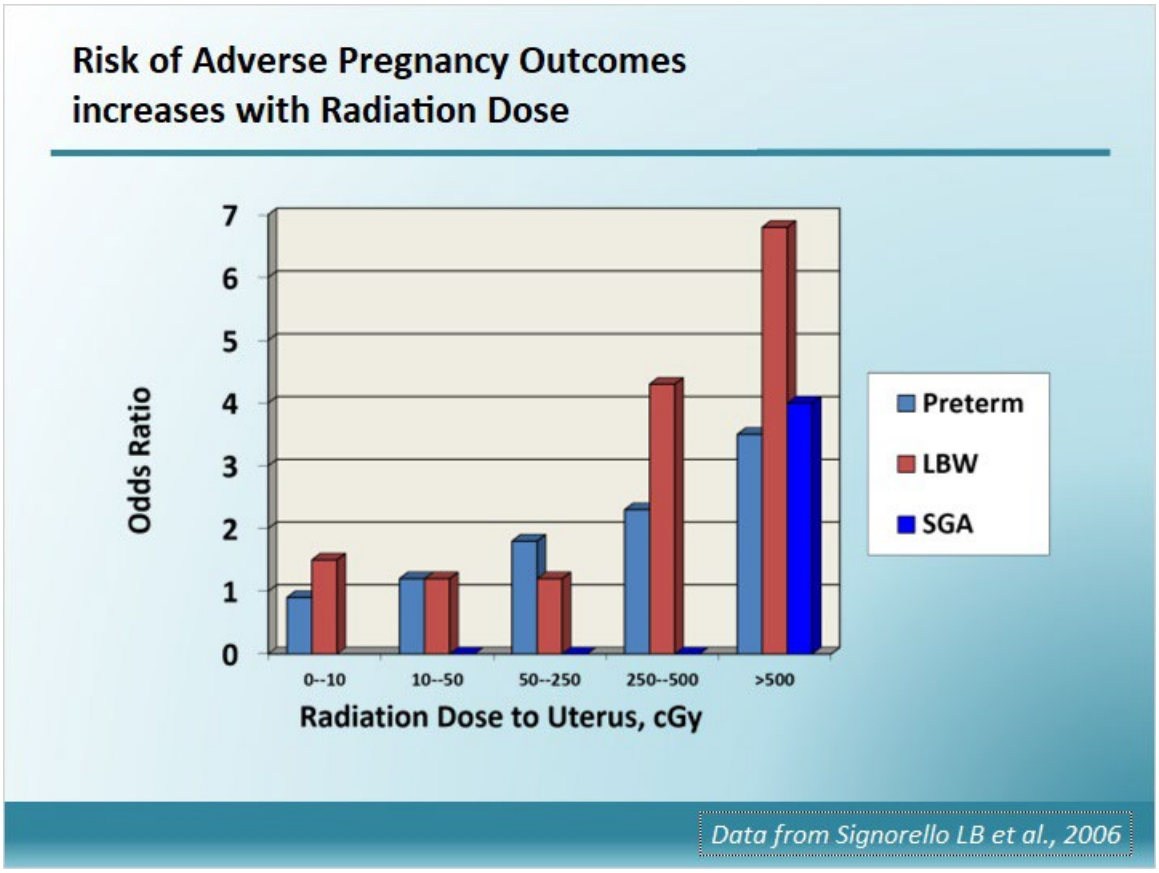
## *1.25 Miscarriage Risk after Radiation Therapy*




**Notes:**

Radiation exposure is also associated with higher rates of miscarriage among cancer survivors compared to their healthy siblings. In a population-based cohort study of 1,688 female childhood cancer survivors in Denmark, survivors had a 23% higher risk of spontaneous abortion (PR, 1.23; 95% CI 1.0 to 1.5) compared to their siblings, primarily related to previous radiation exposure (PR, 1.58; 95% CI, 1.2 to 2.2) and in particular with high-dose radiotherapy to the ovaries and uterus (PR, 2.8; 95% CI 1.7 to 4.7) [1]. The Childhood Cancer Survivors' Study demonstrated a similar increase in miscarriage risk with pelvic and craniospinal radiation therapy carrying a relative risk of 1.65 (95% CI 1.05 to 2.59) and 3.63 (1.70 to 7.78), respectively[2].

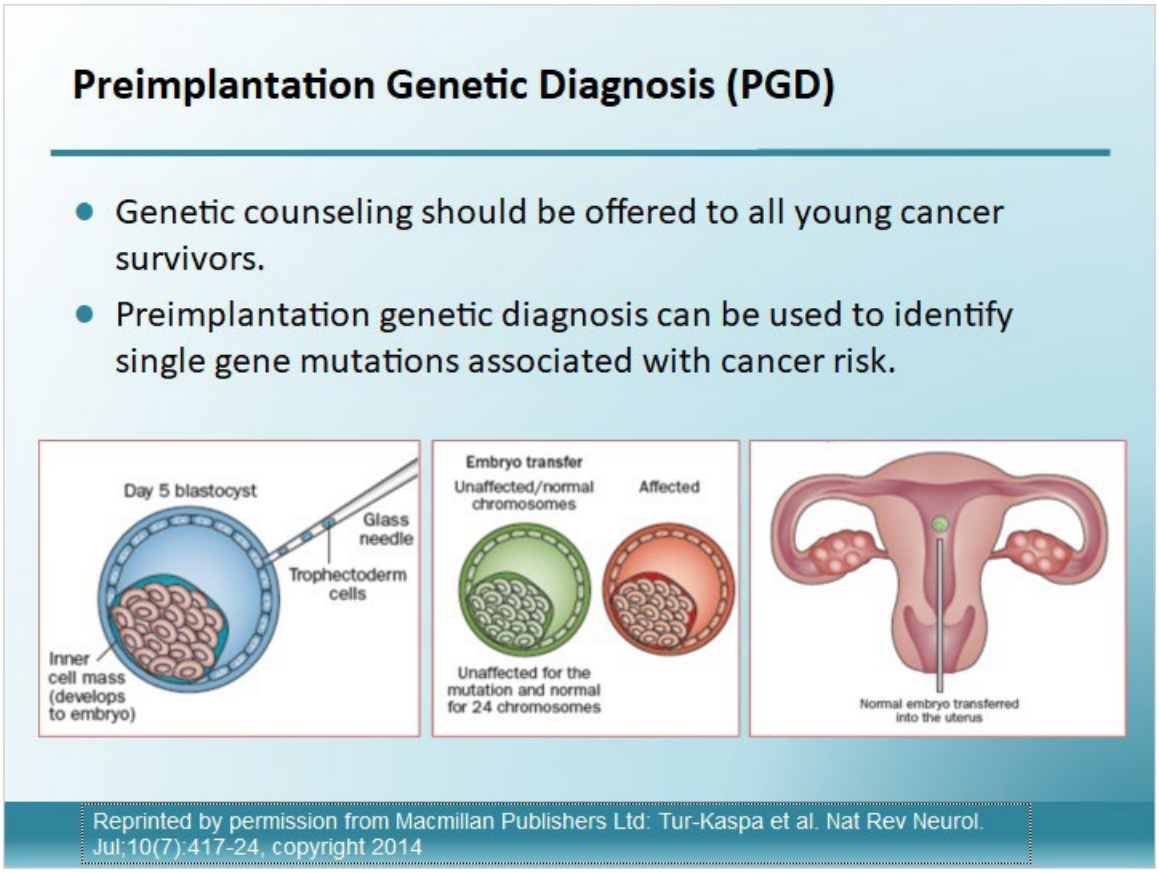
## *1.26 Risk of Adverse Pregnancy Outcomes*




**Notes:**

Data from the Childhood Cancer Survivor Study were used to investigate whether radiation exposure is associated with increased risk of preterm birth or intrauterine growth restriction in children born to cancer survivors. The findings are summarized in this graph and suggest a dose-dependent association between pregnancy complications and cumulative radiation exposure. Compared with the children of survivors who did not receive any radiotherapy, the children of survivors treated with high-dose radiotherapy to the uterus had increased risks of preterm birth (50.0% versus 19.6%; OR = 3.5), low birth weight (36.2% versus 7.6%; OR = 6.8), and small for gestational age (SGA) infants (18.2% versus 7.8%; OR = 4.0).

## *1.27 Preimplantation Genetic Diagnosis (PGD)*

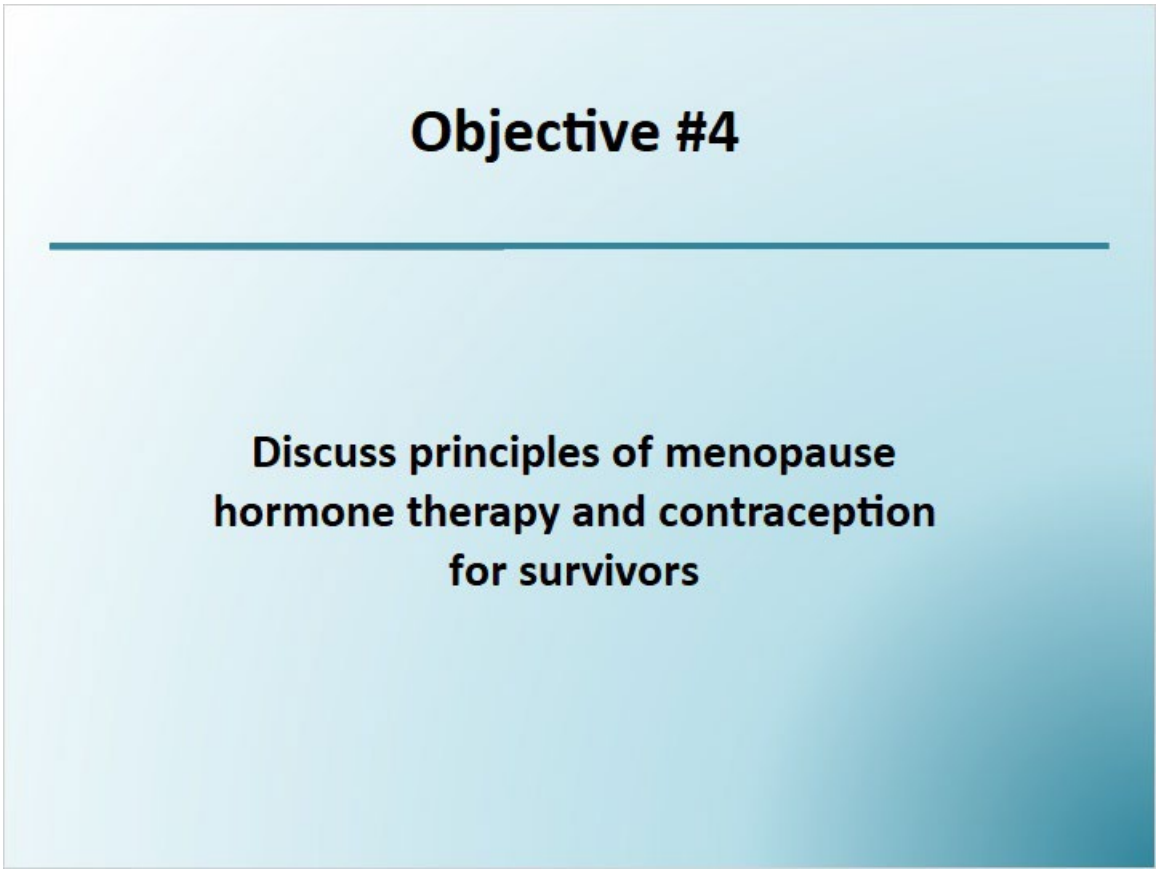



**Notes:**

Genetic counseling with a focus on genetic cancer risk assessment should be offered to all young cancer survivors as it may not have been offered in the past. Furthermore, some patients may have undergone genetic screening with outdated panels and may benefit from repeat testing with expanded screening.

Preimplantation genetic diagnosis (PGD) can been offered to patients with an inherited predisposition for familial cancer predisposing mutations. Controlled ovarian stimulation and in vitro fertilization is performed. The resultant embryos are cultured to the blastocyst stage and 5 to 10 cells of the eventual placenta (trophectoderm) are biopsied. Genetic analysis is often accomplished with amplification of the entire genome and analysis with microarray-based comparative genomic hybridization or genome sequencing. PGD for single gene defects is frequently combined with comprehensive chromosome screening for aneuploidy to avoid transfer of an unaffected but aneuploid embryo.

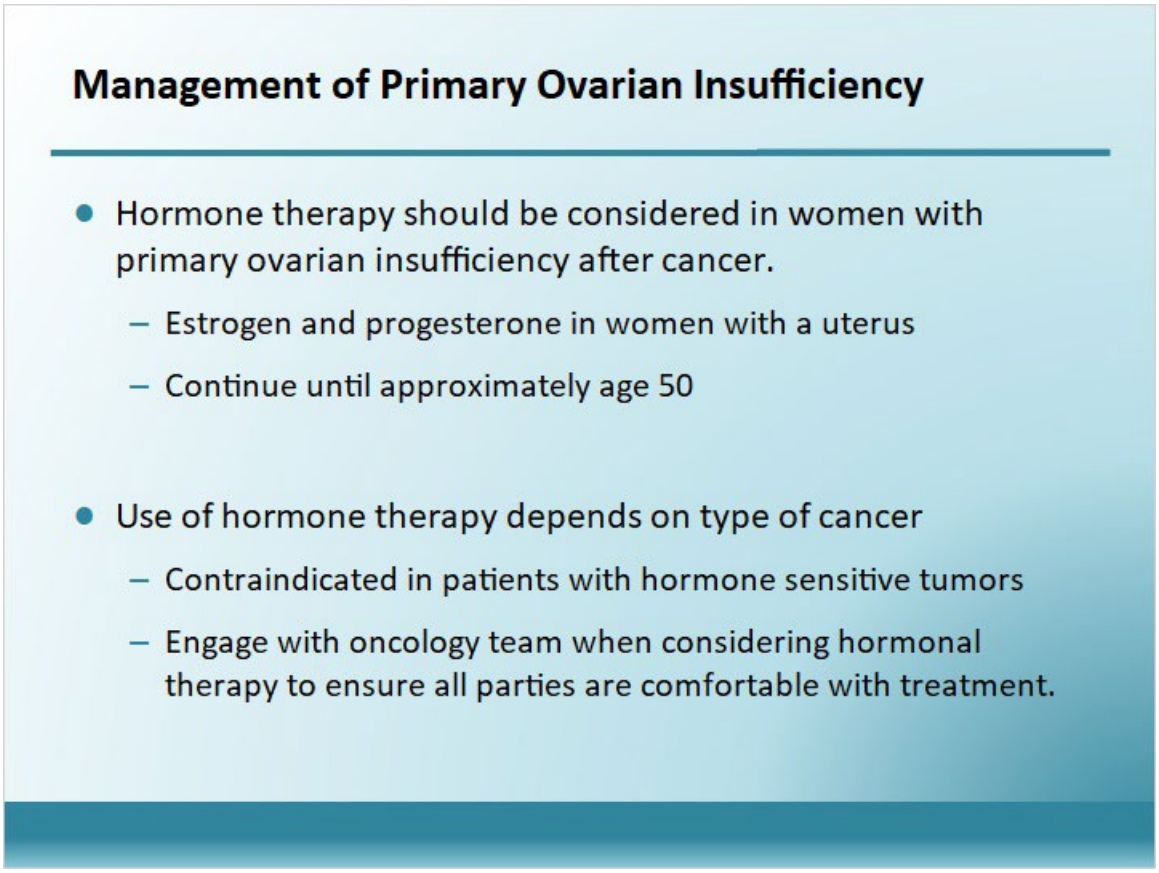
### *1.28 Objective #4*




**Notes:**

We will end by discussing principles of menopausal hormone therapy and contraception for cancer survivors.

## *1.29 Management of Primary Ovarian Insufficiency*




**Notes:**

Unless there is a contraindication to hormone therapy, women with premature ovarian insufficiency due to cytotoxic drugs or radiation therapy should receive estrogen to prevent bone loss. In women with an intact uterus, this should be combined with a progestin to avoid the risks of unopposed estrogen to the endometrium. Other lifestyle measures to promote bone health should also be emphasized, including exercise, a healthy diet, adequate calcium and vitamin D intake, and avoidance of smoking. Like women with other causes of premature ovarian insufficiency, the current approach is to continue hormone therapy until approximately age 50 years, the average age at natural menopause.

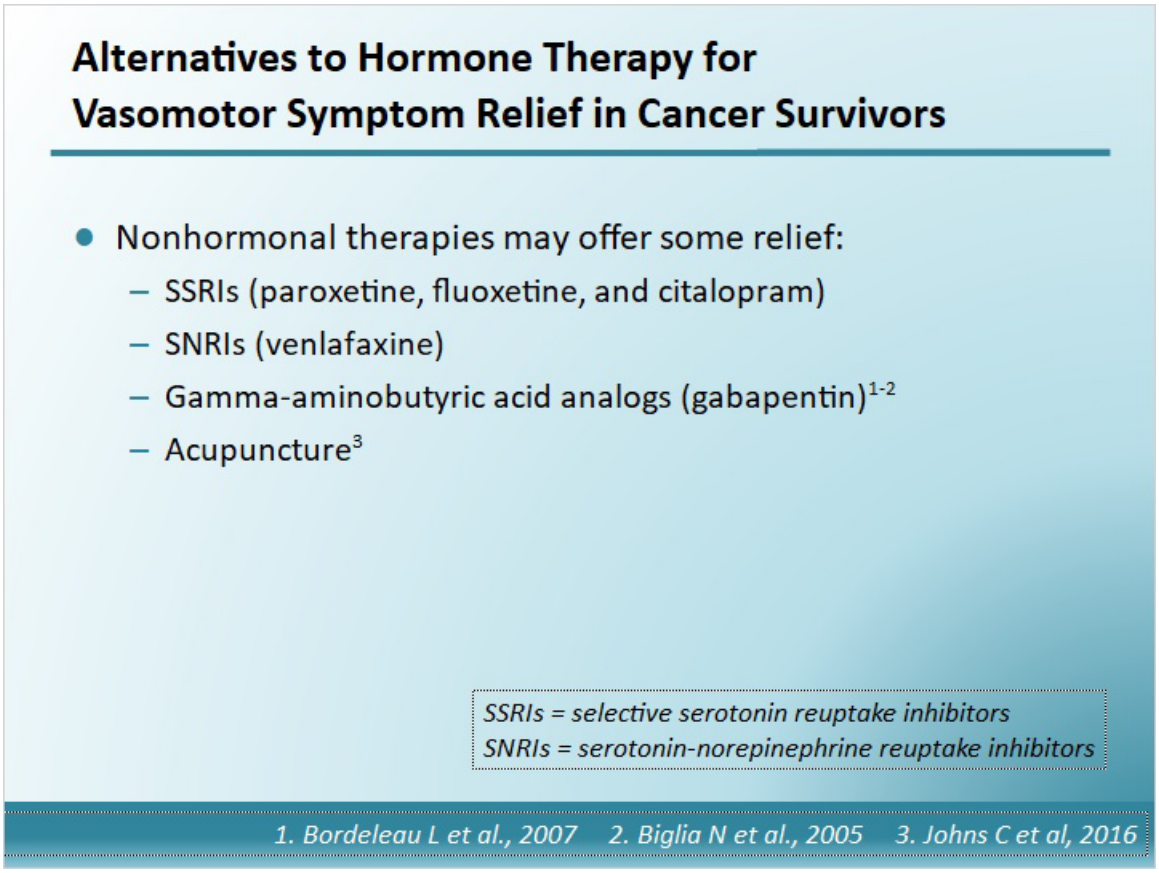
The decision of whether to initiate hormonal therapy depends greatly upon the type of cancer. For example, estrogen is contraindicated in women with breast cancer and other hormone sensitive tumors. By contrast, women with premature ovarian insufficiency after treatment for Hodgkin lymphoma are frequently prescribed estradiol to preserve bone health and prevent cardiovascular disease. It is helpful to engage the patient's oncology team in this decision to ensure that all parties are comfortable with the treatment plan.

## *1.30 Alternatives to Hormone Therapy for*


**Notes:**

Menopausal symptoms are common among patients with breast cancer, either as a result of temporary or permanent anovulation, ovarian suppression from chemotherapy, or as an adverse effect from hormonal therapies such as tamoxifen. The safety of estrogen and progesterone therapy for the treatment of vasomotor symptoms in breast cancer survivors is unclear, as early randomized controlled trials were terminated early when findings indicated an increase in recurrence. However, a large systematic review demonstrated that hormone therapy was not associated with an increased risk of cancer recurrence, cancer-related mortality, or total mortality.

## *1.31 Alternatives to Hormone Therapy for*

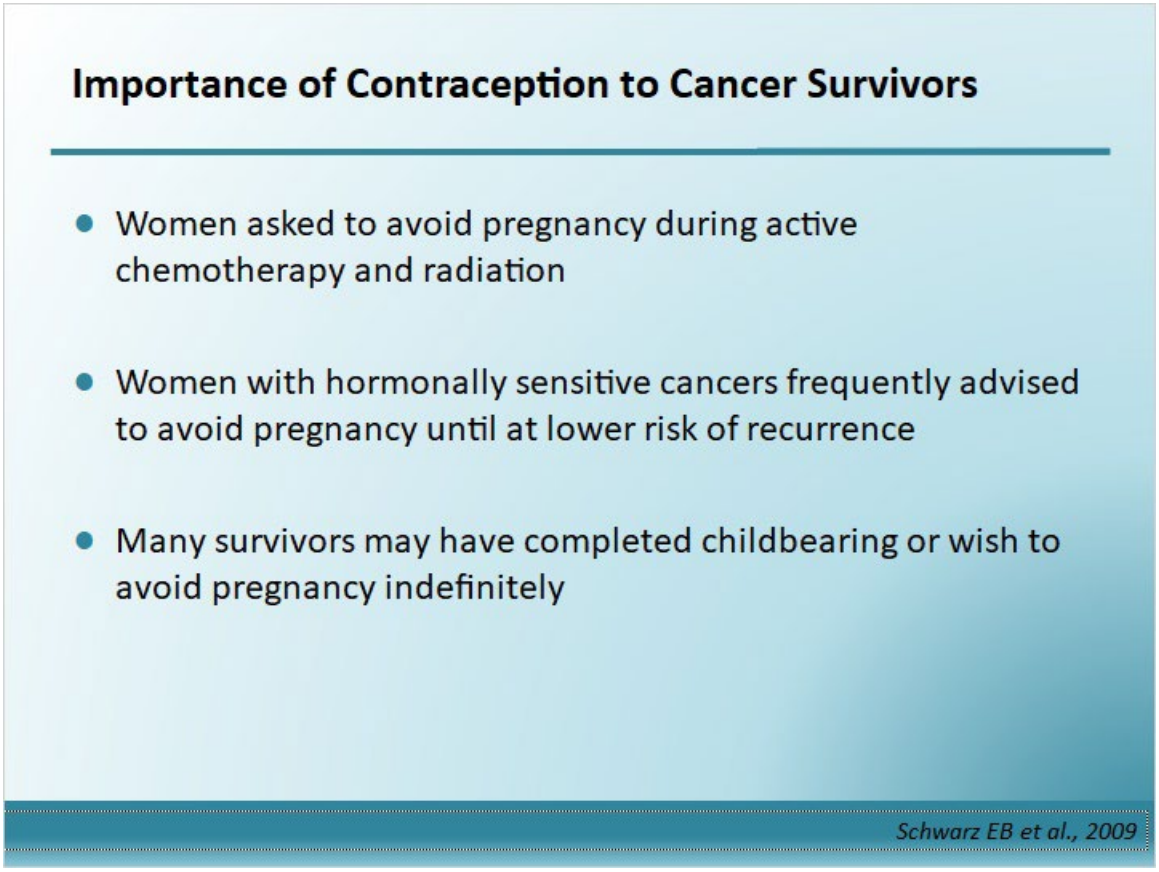



**Notes:**

There are a number of non-hormonal pharmacologic treatments that have been investigated for the treatment of vasomotor symptoms in cancer survivors. Overall, most of these treatments are not as effective as hormone therapy, but they do offer some relief for symptomatic hot flushes. Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, fluoxetine, and citalopram, have shown to reduce vasomotor symptoms compared with placebo. However, SSRIs may interfere with tamoxifen metabolism, thus reducing the drug's efficacy. This effect does not appear to be present with serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine. The effective dose of venlafaxine for treatment of vasomotor symptoms is lower than the typical treatment dose for depression. Low doses of the gamma-aminobutyric acid analog gabapentin have shown benefit for the management of vasomotor symptoms and to improve sleep quality. Lastly, acupuncture has similar efficacy to venlafaxine and gabapentin but may have longer efficacy after completing treatment.

It is important to note that though widely used as alternative treatment for relief of vasomotor symptoms, none of these compounds has been formally approved by the Food and Drug Administration for this indication.

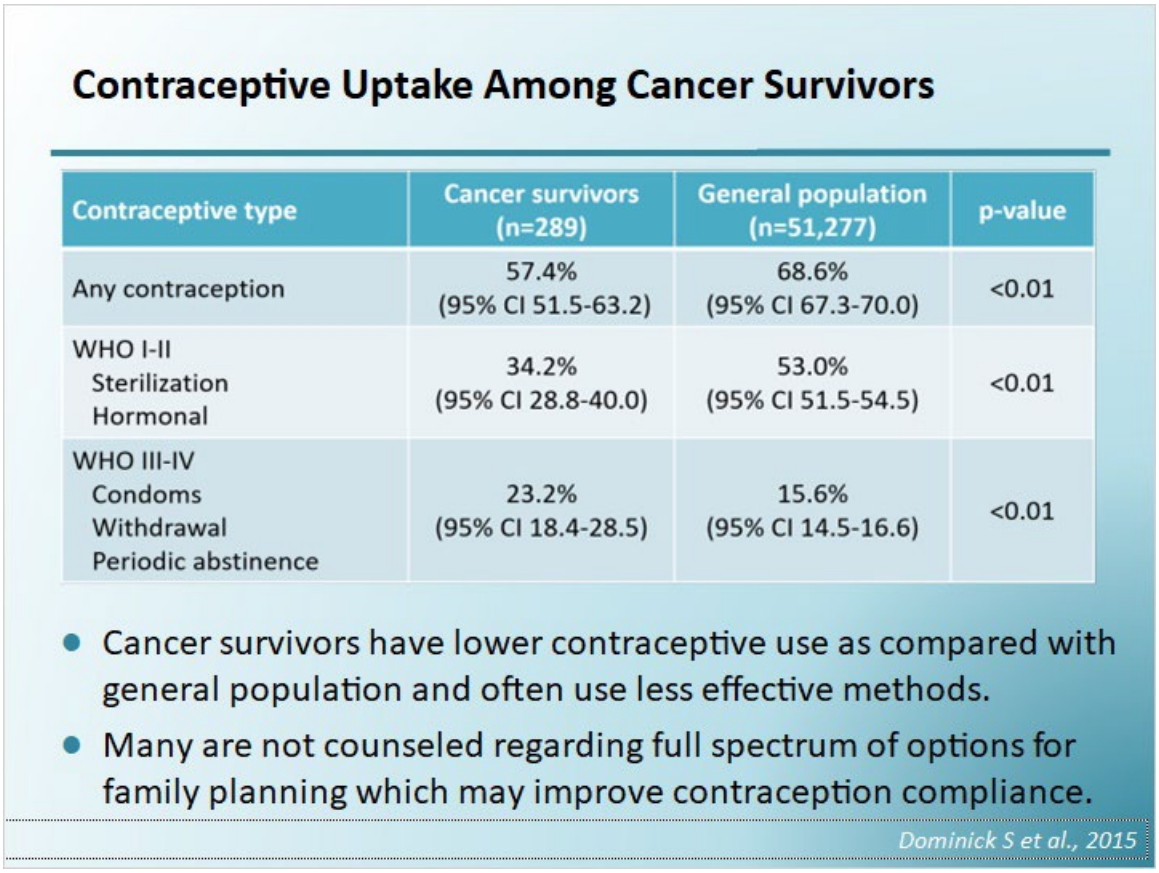
## *1.32 Importance of Contraception to Cancer Survivors*




**Notes:**

Contraception is another significant issue in cancer survivors. Most women are advised to avoid pregnancy during chemotherapy or radiation treatments that may be teratogenic. In addition, women with hormonally sensitive cancers are frequently advised to avoid pregnancy until they have passed the period of peak recurrence or until their overall health status permits. Alternatively, some women may desire to avoid pregnancy indefinitely.

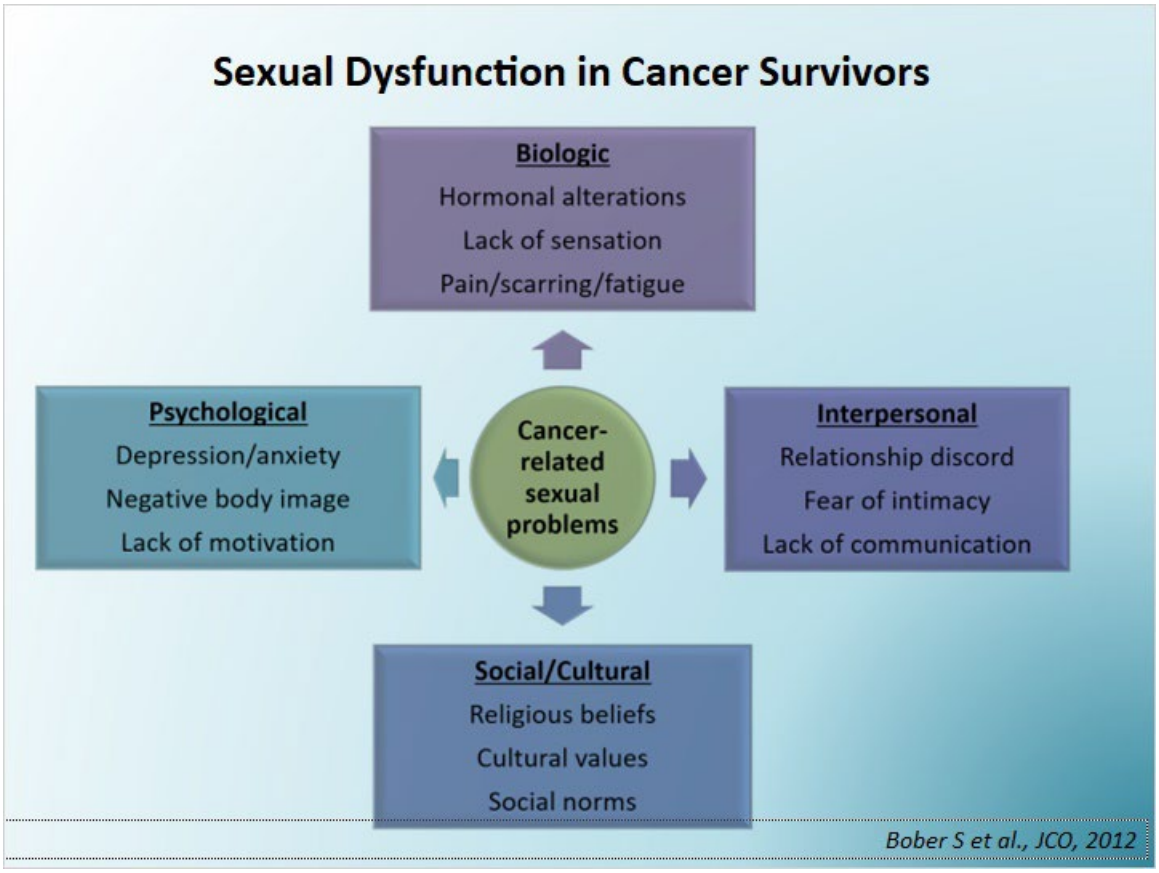
## *1.33 Contraceptive Uptake Among Cancer Survivors*




**Notes:**

Despite its importance, contraception is a frequently neglected part of survivorship counseling among cancer survivors. A study of enrollment data from an ongoing national prospective cohort study on reproductive health after cancer entitled the Fertility Information Research Study compared current contraceptive use in survivors with that of the general population ascertained by the National Survey for Family Growth. Age-adjusted rates of using sterilization or hormonal methods of contraception (classified as tiers I-II contraceptive methods by the World Health Organization (WHO) were significantly lower in survivors as compared with the general population. Cancer survivors were comparatively more likely to rely on less effective WHO tiers III-IV contraceptive methods such as condoms, withdrawal, or periodic abstinence. Only 56% of survivors reported receiving any family planning services since the time of their cancer diagnosis.

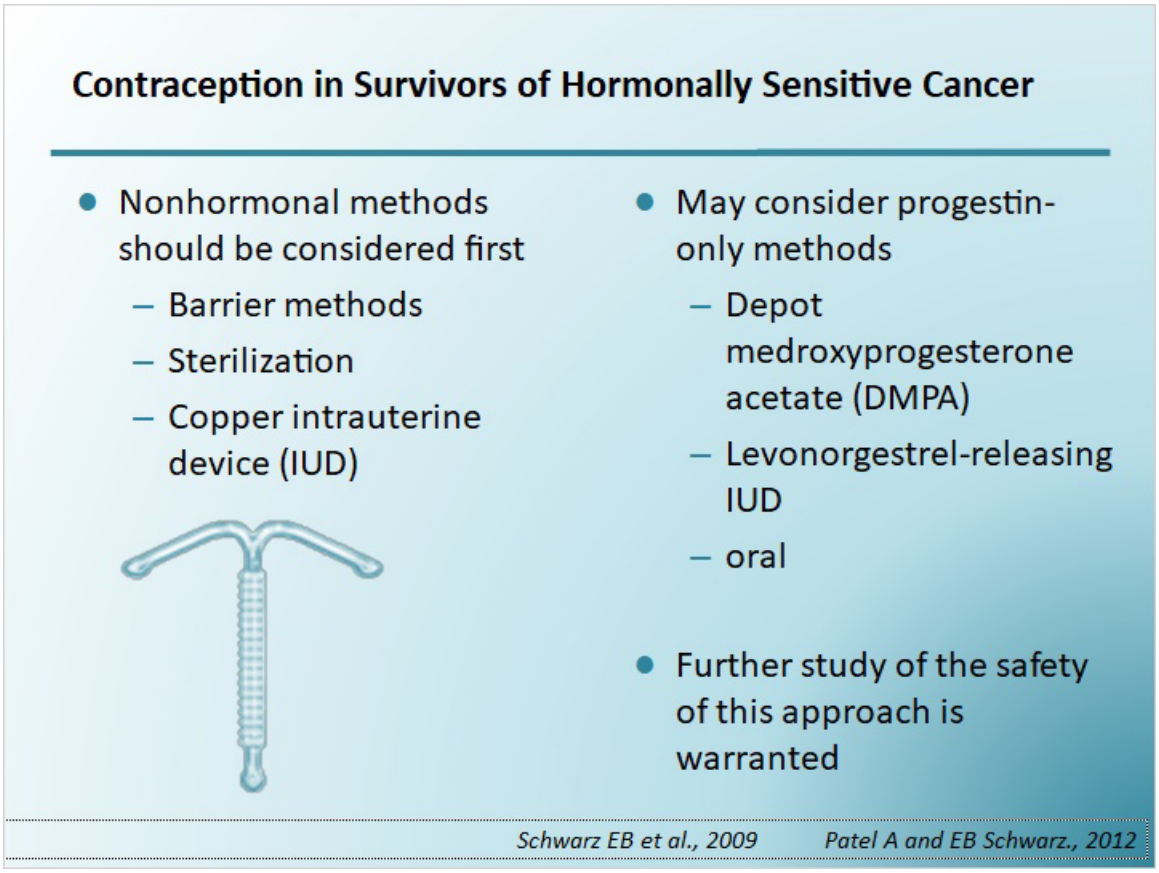
## *1.34 Sexual Dysfunction in Cancer Survivors*




**Notes:**

Sexual dysfunction in cancer survivors has been well documented. However, it is infrequently discussed among survivors and may further contribute to the reduced uptake in contraceptive services in this population. While a full exploration of sexuality in cancer survivors varies based on cancer and treatment type and is beyond the scope of this course, it is worth noting that many cancer treatment modalities including surgery, chemotherapy, radiation, and hormonal therapies have the potential to impair sexual function. Given that sexuality comprises psychological, relational, and cultural elements, in addition to physiologic factors, it is critical to embrace an integrative bio-psycho-social approach to understanding and addressing this fundamental aspect of survivors 'experience.

## *1.35 Contraception in Survivors of Hormonally Sensitive Cancer*

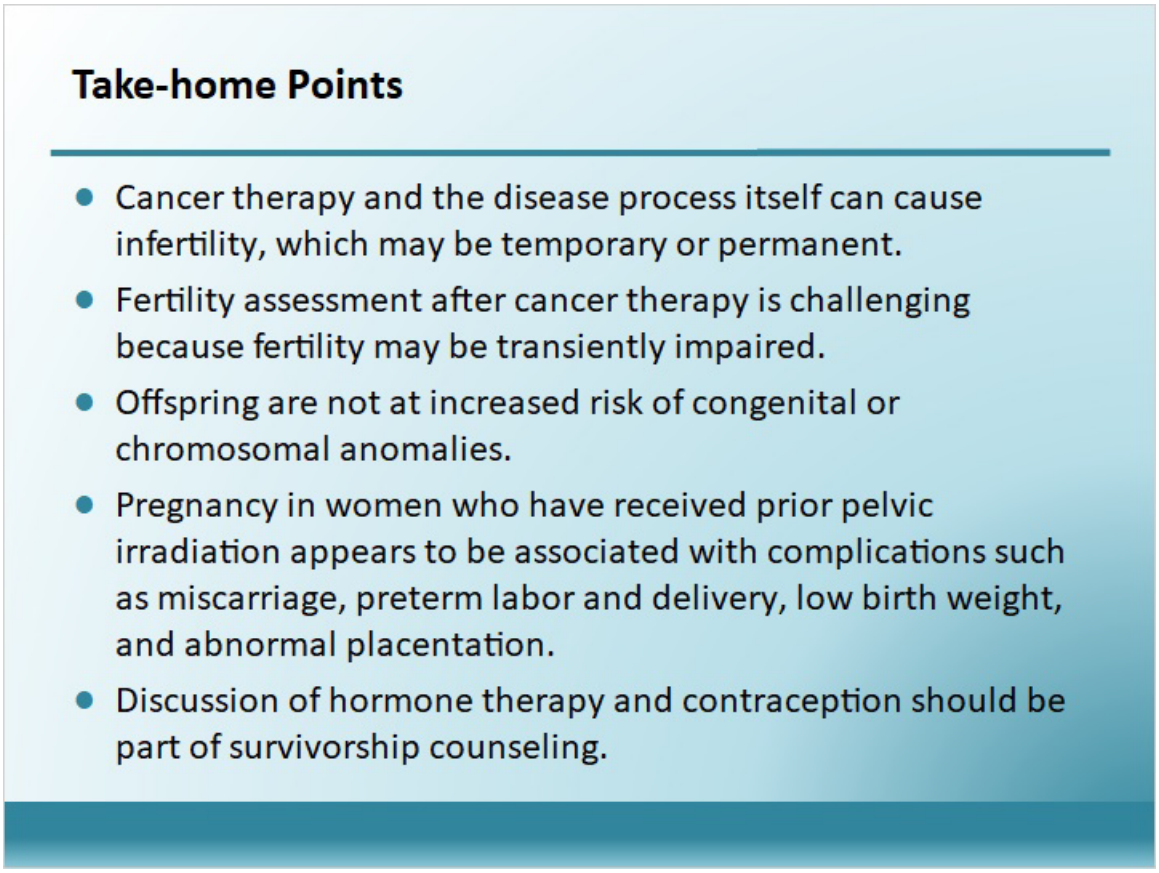



**Notes:**

Non-hormonal contraceptive methods should be considered first-line therapy for women with a history of hormonally mediated cancer. Barrier methods and sterilization are examples, although the copper intrauterine device (IUD) offers the triple advantage of being long-acting, reversible, and highly effective.

Women who do not find any of these methods acceptable may wish to consider a progestin-only method such as pills, IUD, or depot medroxyprogesterone acetate (DMPA) injection. Progestins have been shown to have a proliferative, antiproliferative, or neutral effect on breast tissue, depending on the type, timing, and dose of progestin used. DMPA injections do not increase the risk of breast cancer. Progestin-only pills and the levonorgestrel-releasing IUD do not appear to increase the risk of breast cancer in the general population although further safety studies are required before this approach can be summarily recommended.

## *1.36 Take-home Points*




**Notes:**

In summary, cancer therapy and the disease process itself can cause infertility, which may be temporary or permanent. Fertility assessment after cancer therapy is challenging because fertility may be transiently impaired. Offspring are not at increased risk of congenital or chromosomal anomalies. Pregnancy in women who have received prior pelvic irradiation appears to be associated with complications such as miscarriage, preterm labor and delivery, low birth weight, and abnormal placentation. Hormone replacement can be considered for promotion of bone health and treatment of vasomotor symptoms in survivors of certain cancers. Finally, assessment and provision of contraceptive care should be an integral part of survivorship counseling.

***1.37 Thank you!***


**Notes:**

Thank you for your participation.  We hope you enjoyed this presentation.