Starting a family is a life goal for many, as being a parent is a significant source of meaning and happiness. Unfortunately, some survivors may be unable to get pregnant or to father a child because of their childhood illness and treatment. Others may worry about the possibility that treatments they received will have harmful effects on their children.

The good news is that children of survivors don't inherit a higher genetic risk for cancer from their parents, unless the person's cancer was caused by a known genetic mutation. However, it's unknown whether certain types of treatments might cause harm to the children of survivors who received those treatments. LTFU Study investigators recently published results of a project looking at possible effects of radiation therapy on the offspring of childhood cancer survivors. We report those results in this issue of the newsletter. We also report on two detailed studies of fertility among male and female survivors.

Thank you. As always, we want to thank you, our participants, for being our partners in research. Scientific findings such as those reported in this newsletter are a direct result of your continuing participation in the LTFU Study.

Just Released!
Childhood Cancer Survivors, 3rd Edition

The third edition of Childhood Cancer Survivors provides state-of-the-art information for survivors on topics such as:

- Medical late effects from treatment
- Emotional aspects of surviving cancer
- Schedules for follow-up care
- Challenges in the healthcare system
- Lifestyle choices to maximize health
- Discrimination in employment or insurance

Woven throughout the text are stories from more than 100 survivors and parents. Authors Keene, Hobbie, and Ruccione are experts in the field of childhood cancer. Keene is the mother of a survivor of childhood leukemia and the author of several books including Childhood Leukemia, Childhood Cancer, Educating the Child with Cancer, and Chemo, Craziness & Comfort. Hobbie is Associate Director of the Cancer Survivorship Program at Children’s Hospital of Philadelphia. Ruccione is Co-Director of the HOPE (Hematology-Oncology Psychosocial and Education) Program in the Children’s Center for Cancer and Blood Diseases at Children’s Hospital Los Angeles. Available from online booksellers or at:

http://shop.oreilly.com/product/9781457118678.do
Since many survivors desire to have a child, issues related to fertility and offspring are highly important ones for the LTFU Study. We do know that some treatments in childhood, including radiation and some types of chemotherapy, can cause people to be unable to have children. We wanted to learn more about this risk and about the specific treatments that lead to infertility. In addition, we wanted to find out if radiation treatment in childhood or adolescence could affect a person's offspring when they conceived or fathered a pregnancy as an adult.

Fertility of male and female survivors

Dr. Dan Green led a team that investigated fertility issues in separate studies of male and female survivors. The research team compared the fertility rates of the survivors to those of participants in the LTFU Study sibling comparison group. They also looked at specific treatment exposures. They found that:

- Overall, female survivors were 20 percent less likely to become pregnant than the female siblings.
- Male survivors who did not have any of the high-risk treatments were just as likely as the siblings to father a pregnancy.
- Radiation treatment to areas of the body that included the testicles in males or the ovaries and uterus in females led to a higher risk of infertility.
- Treatment with high doses of alkylating agent chemotherapy drugs increased the likelihood of infertility for both males and females.

Also at increased risk of infertility were:

- Men who were diagnosed at older ages (15-20 years) or who were treated with the alkylating agent procarbazine or with high doses of cyclophosphamide (Cytoxan).
- Women who were exposed to radiation doses of more than 30 Gray to the hypothalamic/pituitary area of the brain or who were treated with the specific chemotherapy agents lomustine (CCNU) or cyclophosphamide.

Why results are important. Knowing the effects of specific treatments can help survivors and their health care providers understand their reproductive consequences and fertility options. The results of this study may also be used to counsel future patients about fertility problems that are linked to cancer treatments.

About the study. Participants in this study were between the ages of 15 and 44 years. The male study included 7,516 men (6,224 survivors and 1,292 siblings); the female study included 6,590 women (5,149 survivors and 1,441 siblings).

Alkylating agents . . .

. . . are a common type of chemotherapy drugs. They have been linked to damage to the gonads (ovaries and testicles). They are used to treat many different types of diseases, including leukemia, Hodgkin and Non-Hodgkin lymphoma, and solid tumors. Alkylating agents include drugs like:

- BCNU (Carmustine)
- Busulfan
- CCNU (Lomustine)
- Chlorambucil
- Cyclophosphamide (Cytoxan)
- Ifosfamide
- Mechlorethamine (Nitrogen Mustard)
- Melphalan
- Procarbazine
- Thiotepa

Effects of treatment on offspring

It is not known whether radiation treatment causes genetic damage to human germ cells (sperm cells and egg cells) that can harm a person's offspring. Scientific advances may soon make it possible to directly determine whether such damage occurs. In the meantime, LTFU Study investigators, led by Dr. Lisa Signorello, have come up with an indirect method to assess the possibility that radiation treatment damages germ cells. The investigators reasoned that genetic mutations in germ cells might lead to a higher rate of stillbirth or neonatal death. So studying the occurrence of stillbirth and neonatal deaths could be used as a way of finding out “by proxy” if radiation treatment is likely to cause genetic damage to germ cells.

The researchers wanted to find out if stillbirth or neonatal death occurred more often among children of survivors who had received radiation to the testicles or the ovaries and uterus or to the pituitary gland. Stillbirth is defined as a fetal death after 20 weeks of pregnancy. Neonatal death refers to
death immediately after birth or in the first four weeks of life. The pituitary gland is a pea-sized structure in the brain that regulates the production of the sex hormones, testosterone in boys and estrogen in girls.

The research team found that:

- Radiation exposure to the testicles in males did not increase the risk of stillbirth or neonatal death among the children conceived after they received this treatment.
- Radiation exposure to the pituitary gland did not increase the risk of stillbirth or neonatal death among the children of males or females.
- Radiation exposure to the ovaries and uterus of females, however, did greatly increase the risk of stillbirth or neonatal death among the children of males or females. The higher rate of stillbirth and neonatal death among the children of girls treated with radiation was felt to result from damage to the uterus and its blood vessels rather than to mutations in the egg cells.

In spite of the increased risk among female survivors, the research team concluded that this study did not provide evidence that radiation therapy causes mutations to either sperm or egg cells leading to genetic damage to the offspring of either men or women. Stillbirths and neonatal deaths did occur more often among the children of girls whose ovaries and uterus had been irradiated. However, the researchers believed this was because of radiation damage to the uterus and its blood vessels. This uterine damage likely led to the loss of offspring, rather than any genetic damage to the girls' egg cells.

This study found that treatment with alkylating agent chemotherapy did not increase the risk of stillbirth or neonatal death among children of male or female survivors, even at high doses.

**Why results are important.** The results of this study are reassuring for male survivors. There does not seem to be an increased risk of stillbirth or neonatal death among the offspring of men who received radiation to treat their childhood illness. Women who received high-dose radiation to the ovaries and uterus, however, do face a higher risk. Knowledge of this finding can help health care providers deliver the best possible care to these survivors if they conceive a child.

**About the study.** The study analyzed information about 1,148 men and 1,647 women who had survived childhood cancer. Among the participants, there were 4,946 pregnancies.

**References:**


Resources are available to help with fertility issues and with grieving the loss of a child. If you're facing either of these situations, please investigate the assistance offered by the organizations listed below:

**For help with infertility issues:**

www.livestrong.com/fertility-information

A project of the Lance Armstrong Foundation (LAF), the LIVESTRONG site provides in-depth articles on many different aspects of fertility.

www.fertilehope.org

This site is another project of LAF. It offers calculators for infertility risk and for reproductive options based on risk, information for health care professionals, a searchable database of resources, including doctors, financial resources, legal assistance, and more.

www.resolve.org

The website of the National Infertility Association offers a newsletter, information sheets, and access to support groups.

www.fertileaction.org

Started by a cancer survivor, the mission of this organization is to eradicate the cost of fertility preservation for female cancer survivors.

**If you are grieving the loss of a child:**

www.nationalshare.org

This site offers resources for bereaved families as well as for health care professionals. It includes a network of support groups, organized by US State, that are often associated with local hospitals.

www.compassionatefriends.org

This national volunteer organization offers grief support after the death of a child and has chapters in most US states, as well as a presence on Facebook.
Fertility Issues after Childhood Cancer Treatment
(Adapted from the Children's Oncology Group Health Links)

In females

Childhood cancer treatment can lead to . . .

**Estrogen deficiency.** Estrogen deficiency occurs when the immature eggs (egg follicles) in the ovaries are depleted or damaged. It can be a result of alkylating agent chemotherapy, radiation therapy to the ovaries or the pituitary gland, or surgical removal of the ovaries. If this happens to a young girl, she will need hormones prescribed by a doctor to go into puberty. Estrogen is also needed to help maintain strong bones, a healthy heart, and overall well-being. Young women who are estrogen deficient should discuss the potential risks and benefits of hormone replacement therapy with their doctor.

Women with depleted egg follicles are at risk of . . .

**Ovarian failure.** This means that the ovaries completely stop making estrogen and that menstrual periods stop permanently. Ovarian failure occurs in women at menopause as part of normal aging. The average age of menopause is 51.

**Premature menopause.** This means that menstrual periods stop permanently before age 40. If a woman is currently having periods but received chemotherapy or radiation that can affect ovarian function, she may still be at risk of entering menopause at an early age.

**Infertility (the inability to get pregnant).** Infertility can be caused by depletion of or damage to egg follicles, and the reduced production of ovarian hormones. Radiation therapy may cause scarring that reduces blood flow to reproductive organs and affects their ability to sustain a pregnancy. There may also be other reasons for infertility that are unrelated to cancer therapy.

**Pregnancy risks.** Radiation therapy can lead to an increased risk of miscarriage, premature delivery, or problems during labor. Chemotherapy with anthracycline drugs (such as doxorubicin or daunorubicin) and radiation therapy to the upper abdomen or chest may lead to heart problems. If a woman has heart problems, pregnancy and labor can make them worse.

In males

Childhood cancer treatment can lead to . . .

**Testosterone deficiency.** This means that the testicles can’t produce enough of the male hormone testosterone. It can be caused by alkylating agent chemotherapy, by radiation therapy to the testicles or the pituitary gland, or by surgical removal of both testicles. If this happens to a young boy, he will need hormones prescribed by a doctor to go into puberty. If it happens after puberty, a man will need testosterone therapy to maintain a healthy body composition of muscle, bone, and fat, as well as a healthy sex drive and the ability to have erections.

**Infertility (the inability to father a pregnancy).** Infertility can be caused by reduced testosterone, decreased, damaged, or absent sperm, damage to the duct system that transports the sperm, or to the nerves that control sexual function. There may also be other reasons for infertility that are unrelated to cancer therapy.

Is treatment-related infertility permanent?

Men who had both testicles surgically removed will not be able to make sperm and infertility will be permanent. The same is true for women who had both of their ovaries removed. Infertility following radiation is likely permanent.

Some men may recover sperm production months or years after the completion of chemotherapy. For others, the damage from chemotherapy may be permanent. This means you should use birth control if you don’t want to make someone pregnant.

Women who were already menstruating will stop having monthly periods during their cancer therapy. In most cases, menstrual periods will start up again after treatment ends. It can sometimes take up to several years to restart menstruation. If you don’t want to get pregnant, birth control should be used, even if you’re not having monthly periods.

If a woman wants to have children but is at risk of premature menopause because of the treatment she received, it is best not to delay getting pregnant beyond the early thirties.

For complete information, please see the following Children’s Oncology Group Health Links:

http://www.survivorshipguidelines.org/pdf/FemaleHealthIssues.pdf
http://www.survivorshipguidelines.org/pdf/HeartHealth.pdf