

## CANCERS LINKED TO THE DEVELOPMENT OF SECOND CANCERS

No matter what type of cancer is treated, treatments such as radiation and chemotherapy can lead to a second cancer in the long run. Because it can take many years for treatment-related cancers to develop, they have been studied best in those who have lived a long time after being treated. Successfully treating a first cancer gives a second cancer the time (and the chance) to develop. The cancers discussed in this section were some of the first cancers in which treatment led to long-term survival. It is likely that we will see second cancers developing after some other cancers as treatment and survival improves.

### HODGKIN DISEASE

Survivors of Hodgkin disease (HD) have a risk of developing another cancer that is more than 3 times that of the general population. Overall, the risk of a second cancer is more than 20% in the first 20 years after treatment. An increased risk of acute leukemia has been seen in HD patients treated with chemotherapy, especially if an alkylating agent was used, for example, in the combination of drugs known as MOPP [mechlorethamine, vincristine (Oncovin), prednisone, and procarbazine]. Leukemia is much less common in people treated with the combination known as ABVD [doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine]. Treating HD with radiation alone has little effect on leukemia risk, but adding radiation to MOPP chemotherapy increases the risk further. The chance of getting leukemia after HD is related to the patient's age when they were treated, with the highest risk seen in those treated after age 40. The risk also seems to go up as the amount of chemotherapy used increases.

The risk of non-Hodgkin lymphoma (NHL) is also higher in survivors of HD. Because this risk does not seem to change based on the type of treatment used, many experts do not think that NHL seen after HD is caused by cancer treatments.

Radiation therapy for HD has been linked to an increased risk of developing solid tumor cancers. The risk is highest in the areas that were in the path of the radiation beam. The most common second cancer in female survivors of HD is breast cancer. The risk is highest in those who had radiation to an area in the center of the chest called the mediastinum before age 30. (The mediastinum is the area between the lungs where the heart and its vessels, the trachea, the esophagus, the thymus, and some lymph nodes are found.) Early in the treatment of HD, many patients got radiation to the

mediastinum as a part of mantle field radiation. Some patients also went into early menopause from radiation or alkylating agent chemotherapy. In women who went through menopause before age 40 because of HD treatment, the risk of breast cancer went down.

If you were treated with chest radiation therapy at a dose of 20 Gy (2000 cGy/rads) or higher you should:

1. Perform monthly breast self-examination. Report any lumps or changes to your healthcare provider right away.
2. Have a clinical breast exam performed by your healthcare provider — at least once a year until you reach age 25 - then every 6 months thereafter.
3. Have a yearly mammogram\* - starting at age 25 or 8 years after you received radiation (whichever comes last).

\*Note: Breast tissue in younger women (prior to menopause) tends to be more dense than breast tissue in older women. Because of this, some healthcare providers may recommend other tests (such as an MRI or breast ultrasound) to monitor for breast cancer in younger women.

Lung cancer risk is also higher after treatment for HD. This higher risk is related to chest radiation treatments as well as chemotherapy with alkylating agents. Patients that have both chemotherapy and radiation are even more likely to develop lung cancer. Smoking also increases the risk. The risk of lung cancer goes up more if the patient smoked before treatment, but the risk is even higher if the patient continues to smoke after radiation therapy. The risk of thyroid cancer is also increased in HD patients who were treated with radiation to the neck. Other cancers that are seen after radiation include gastrointestinal (stomach) cancer and sarcoma.

Over time, treatment for HD has changed. Chemotherapy with alkylating agents has become much less common, and when radiation is needed, lower doses are used. These changes seem to have helped lower the cancer risks after treatment, but long-term follow-up studies are still needed. Since there is an increased risk for a second cancer following treatment for Hodgkin disease, survivors of HD should be carefully followed-up. Your doctors should look for the development of solid tumors, leukemia, and non-Hodgkin lymphoma along with recurrence of Hodgkin disease.

All patients should be encouraged to reduce their risk of lung cancer by not smoking. Women who were treated with radiation to the chest (such as mantle field radiation therapy) should start breast cancer screening early if they were treated before age 35. There are no standard guidelines, but many experts recommend that patients treated with this type of radiation start screening 5 to 8 years after finishing their HD treatment. This screening should include regular breast exams and mammograms. Breast MRI (magnetic resonance imaging) could also be helpful.

Patients who had radiation to their abdomen (belly) should pay special attention to any abdominal problems and report them to the doctor right away. Problems like unplanned weight loss, ongoing diarrhea, or other

bowel problems could be a sign of a serious condition.

#### NON-HODGKIN LYMPHOMA

Survivors of non-Hodgkin lymphoma (NHL) are at increased risk of developing some second cancers, but less so than patients who were treated for Hodgkin disease. Overall, NHL survivors get new cancers about 15% more often than the general population. Increased risks of malignant melanoma, lung cancer, and kidney cancer have been seen in patients who had been treated for NHL.

Survivors of NHL are also at risk for several other cancers such as Kaposi sarcoma; cancers of the head/neck area (this includes the tongue, floor of the mouth, throat, and voice box); colon cancer; thyroid cancer; bone and soft tissue cancer; and bladder cancer. Leukemia and Hodgkin disease are also more common after treatment for NHL. Radiation therapy increases the risk of breast cancer in women who were treated before age 25. Mesothelioma, a rare cancer of the outer lining of the lung, is also increased in those who were treated with radiation.

A higher risk of bladder cancer has only been seen in those who were treated with chemotherapy. The drug cyclophosphamide (Cytoxan), especially if used in higher doses, is linked to bladder cancer.

Low-dose total body irradiation (TBI), which was once used to treat NHL, has been linked to an increased risk of leukemia. The risk of leukemia is also higher in those treated with chemotherapy, with the highest risk seen in those treated with both radiation and chemotherapy.

Patients who had autologous bone marrow transplants (meaning the patient's own bone marrow was used -- not someone else's) are also at increased risk for developing acute myelogenous leukemia (AML) and an early form of leukemia called myelodysplastic syndrome (MDS).

#### TESTICULAR CANCER

The most common cancer seen in testicular cancer survivors is a second testicular cancer. Overall, 2% to 5% of men who have had cancer in 1 testicle will eventually have it in the other testicle. The second cancer is not from treating the first cancer with radiation or chemotherapy. In fact, those treated with surgery alone still have an increased risk of a second testicular cancer. Also, the chance of getting a second testicular cancer is actually lower in men who were treated with chemotherapy. The rest of this section is about new cancers other than testicular cancer.

Patients treated for testicular cancer have less than one-half the risk of second cancers than those treated for Hodgkin disease. Compared with the general population, testicular cancer survivors are up to twice as likely to develop a new cancer outside the testicle. The chance of a second cancer goes up over time and also depends on which treatments were used.

The risk of a solid tumor cancer starts going up within 5 years and doubles after 10 years in those who were treated with radiation alone. This risk remains high for more than 35 years after treatment. The most common

cancers seen after abdominal radiation for testicular cancer are cancers of the bladder, colon, pancreas, and stomach. Radiation to the abdomen also increases the risk of cancers of the rectum, kidney, and prostate. If the radiation field includes the chest (or mediastinum), the risks of lung cancer and thyroid cancer are increased. Radiation treatments also increase the risk of melanoma skin cancer and connective tissue cancer (sarcoma). The risks are generally greater with higher radiation doses or if the patient was given both chemotherapy and radiation. In recent years, radiation therapy for testicular cancer has changed. Lower doses of radiation are used, and preventive treatment to the mediastinum (the middle part of the chest which contains the heart and its vessels, the trachea, the esophagus, the thymus, and some lymph nodes) has been stopped. Long-term follow-up studies are needed to see if these changes have lowered the cancer risks.

Chemotherapy is linked with an 80% increased risk of solid tumor cancers — slightly less than what is seen after radiation. The risk of leukemia after treatment for testicular cancer is also increased. Most cases are linked to the chemotherapy drugs cisplatin and etoposide (VP-16, Etopophos, or Vepesid). Higher doses of these drugs have a higher risk of leukemia. Leukemia is normally a rare cancer, so although the risk of leukemia after testicular cancer is higher than average, very few patients develop leukemia from their treatment.

#### OVARIAN CANCER

The risk of second cancers in ovarian cancer survivors includes melanoma of the eye; cancers of the colon, rectum, breast, and bladder; and leukemia. Radiation therapy is linked with cancers of connective tissues, bladder, and possibly pancreas cancer. Chemotherapy is linked with an increased risk for leukemia. Reproductive and genetic factors that may have caused ovarian cancer in the first place may also add to the risk of breast and colorectal cancers and possibly ocular melanoma. Studies have shown that the risk of developing solid tumors was higher during all follow-up periods, including 10 to 14 years after ovarian cancer. Fifteen-year survivors had significant increases in cancer of the pancreas, bladder, and connective tissue.

#### BREAST CANCER

Many studies have shown that women with breast cancer are at a 3-to 4-fold increased risk of developing a new primary cancer in the opposite breast. Increased risk is also seen for cancers of the ovary, uterus, lung, colon, rectum, and connective tissue, as well as melanoma and leukemia. But for some of these cancers, such as cancer of the opposite breast, ovary, and uterus, the second cancer may be related to a common cancer-causing factor, such as a genetic factor or hormonal risk factor.

The most common second cancer seen in survivors of breast cancer is a new cancer in the other breast. The risk of a second breast cancer is high no matter what treatment is used for the first cancer. Even people who receive no radiation or chemotherapy have an increased risk of cancer in the

opposite breast. Still, depending on the patient's age when they were treated, radiation therapy can increase the risk even more. Radiation therapy does not seem to increase the risk of cancer in the opposite breast if the patient is past the age of 45 at the time of treatment. But in women who had radiation therapy before the age of 45, an increased risk is seen 10 years after treatment.

The risk of lung cancer is also increased in women who had radiation therapy for breast cancer. The higher lung cancer risk is first seen 10 years after radiation, and gets higher over time. The risk of lung cancer after radiation is even higher in women who smoke. Radiation therapy to the breast also increases the risk of sarcomas of blood vessels (angiosarcomas), connective tissue, and bone (osteosarcomas). These cancers are most often seen in the remaining breast area, chest wall, and the arm that had been treated with the radiation therapy. This risk remains high even 30 years after treatment.

Taking tamoxifen for 5 years not only makes it less likely that the first cancer will come back, it also helps to lower the risk of cancer in the opposite breast by 50%. This appears to be true for women who have been followed for 10 years after their first treatment. But tamoxifen increases the risk for endometrial cancer in 5- and 10-year survivors. Still, the benefits of treatment for breast cancer exceed the risk of a second cancer.

There is a small risk of developing leukemia after treatment for breast cancer. The risk is highest when both chemotherapy and radiation therapy are given, especially if the chemotherapy includes an alkylating agent (see the list of alkylating agents above). Cyclophosphamide (Cytoxan), an alkylating agent, has been used for over 30 years to treat breast cancer. It is a part of the regimen CMF [cyclophosphamide, methotrexate, and 5-FU], and is also included in the regimens AC [Adriamycin (doxorubicin) and cyclophosphamide] and FAC (adds 5-fluorouracil or 5-FU to the drugs in AC). Studies have shown that higher doses of cyclophosphamide (Cytoxan) increase the risk of developing AML. The dose of cyclophosphamide that is now used in standard CMF and AC is linked with a low risk of leukemia, but higher doses increase the leukemia risk. The risk also goes up with dose intensity (when a higher amount of drug is given over a shorter amount of time). Still, even with a risk of leukemia that is several times higher than what is seen normally, those who received 4 times the regular dose of cyclophosphamide had a risk of leukemia that was only about 1%.

#### CANCER OF THE CERVIX

Cervical cancer is often caused by infection with human papilloma virus (HPV). Survivors of cervical cancer have an increased risk for other HPV-related cancers, including cancers of the throat, anus, vulva, and vagina. Survivors of cervical cancer also have an increased risk of some cancers linked to smoking, such as lung cancer, bladder cancer, and pancreatic cancer. The risks of bladder and lung cancer are even higher in those women who were treated with radiation. Radiation for cervical cancer also increases

the risk of cancers of the colon, rectum, soft tissue, and stomach. Radiation is also linked to a higher risk of acute leukemia and non-Hodgkin lymphoma.

What symptoms should I look for?

- Easy bruising
- Paleness of the skin
- Excessive fatigue
- Bone pain
- Changes in moles
- Sores that do not heal
- Lumps
- Changes in bowel habits
- Blood in urine or stool

#### WHAT CAN I DO TO LOWER THE RISK OF GETTING A SECOND CANCER?

**Avoid cancer promoting habits.** Survivors should not smoke or chew tobacco and should avoid exposure to secondhand smoke when at all possible.

Because skin cancers are one of the most common second cancers, especially for those treated with radiation therapy, you should take extra care to protect your skin from sun exposure. This includes regularly using sunscreen with sun protection factor (SPF) of 15 or more, wearing protective clothing, avoiding outdoor activities from 10am to 2pm when the sun's rays are most intense, and not tanning.

**Drink alcohol only in moderation.** Heavy drinkers, especially those who use tobacco, have a high risk of cancer of the mouth, throat, and esophagus. The risk of breast cancer may be increased in women who drink alcohol.

Limiting the use of alcohol can reduce these cancer risks and decrease the chances of other alcohol-related problems, such as liver disease.

**Eat right.** A high intake of dietary fat has been linked to the risk of several common cancers. People who eat high-fat diets have a greater risk of getting colon cancer; this may also be true for breast and prostate cancers. To reduce all of these risks, daily fat intake should be limited to 30% or less of your total calories. Make sure to eat plenty of vegetables and fruits high in vitamins A and C such as dark green and deep yellow vegetables, citrus fruits and melons.

#### SUMMARY

The risk of second cancers must always be weighed against the benefits gained with treatment. The risks of treatments should always be compared carefully against the cost of not using such treatments. For many new cancer treatments, the long-term effects that cause second cancers are not yet

known. The need for ongoing follow-up of cancer survivors is important so that we can better understand the long-term effects of cancer treatment.

Works Cited

Adapted from the American Cancer Society

[www.cancer.org](http://www.cancer.org)

Adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

[www.survivorshipguidelines.org](http://www.survivorshipguidelines.org)