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# Future Risk for Survivors

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*Certain patients face greater possibility for a second cancer.*

Lori Sklar was diagnosed with aggressive stage 1 breast cancer in October 2003. Her doctors recommended a mastectomy and four months of chemotherapy. Everything looked good until April 2004. She had accompanied her husband Bill on a business trip to New Orleans but found herself exceedingly tired, quickly winded and bruising easily. When they returned home to Boca Raton, Florida, Lori immediately went to see her oncologist. He confirmed her suspicion of cancer: She had acute myeloid leukemia.

Before she started treatment for breast cancer, Lori and Bill were told the chemotherapy regimen of Adriamycin (doxorubicin), Taxol (paclitaxel) and Cytosan (cyclophosphamide)—a regimen that would best control her breast cancer—could, in rare cases, cause leukemia by damaging the DNA of bone marrow stem cells. But neither the doctors nor the Sklars dwelled on the risk. After all, the statistics were in their favor since only about one-tenth of 1 percent of breast cancer patients treated with chemotherapy and/or radiation develop acute myeloid leukemia. But statistics don't always count. She became that 0.1 percent.

Following her new diagnosis, Lori started back on chemotherapy—this time to treat leukemia. After numerous rounds of chemotherapy followed by brief periods of response and then relapses, Lori underwent a bone marrow transplant in the fall of 2005. She is now recuperating and devoting herself to community service, including her website designed for hereditary breast cancer survivors ([www.reachglobal.org](http://www.reachglobal.org)).

Lori's experience of a second cancer is not unique among cancer survivors. Indeed, survivors accounted for 16 percent of the new cancer diagnoses in 2003. Some chemotherapy drugs and radiation used to treat a first cancer can cause DNA damage and thus increase an individual's risk of developing a second cancer.



Lori Sklar, with her husband Bill, was diagnosed with leukemia less than one year after being treated for breast cancer. Photo courtesy of Lori Sklar.

While three large studies involving more than a million patients total indicate that adult cancer survivors have almost twice the risk of having a second cancer as healthy controls, it's more complicated than that. The total risk for the

population is misleading, say experts, because the actual risk of a second cancer differs among survivors and is influenced by numerous factors, including the type of primary cancer, age at diagnosis, type of treatment received, genetics and environmental influences. Additionally, several studies have found that people diagnosed with their first cancer after the age of 50 are not at greater risk for another cancer than people who have never had cancer, says Charles Sklar, MD, director of the Long Term Follow-Up Program at Memorial Sloan-Kettering Cancer Center in New York. (Dr. Sklar and Lori and Bill Sklar are not related.)

The causes of second cancers also vary from one survivor to the next. Some cases are related to treatment for their first cancer, sometimes referred to as secondary cancers. In other cases, a survivor may have a genetic predisposition that makes them more likely to develop malignancies than the general population. Finally, some of the cancers that survivors experience are sporadic cancers, of which the likelihood increases as a person ages, just as it does for people who have never had a cancer diagnosis.

### Young Survivors

The issue of second cancers has been better characterized in pediatric cancer survivors, in part because curative therapies for pediatric cancers have been around longer than for adult cancers, says Smita Bhatia, MD, a second cancers specialist and associate director of the City of Hope Comprehensive Cancer Center in California. Additionally, pediatric oncologists are keenly aware that their patients have a lot of growing cells and tissues that could be damaged by anticancer therapies.

In a study of 13,581 individuals who were diagnosed with their first cancer before age 21 and survived at least five years, about 3 percent developed a second cancer during a 20-year follow-up period. That rate is approximately six times higher than for the population at large, which sounds extraordinarily high, but only leads to 1.9 extra cancers per 1,000 individuals in the study. “The risk for the overall population of cancer survivors is not large,” says Dr. Bhatia.

As with adult cancers, the risk for pediatric survivors is not distributed equally. Females are at a higher risk than males, and patients diagnosed at a younger age are at higher risk than those diagnosed later. Survivors of pediatric soft-tissue sarcomas, Hodgkin’s disease and hereditary retinoblastoma are most likely to experience a second cancer. Though it is not yet obvious what predisposes sarcoma survivors to a second cancer, risk factors have been identified for Hodgkin’s disease survivors that explain some of the secondary cancers seen in this group.

In the case of hereditary retinoblastoma, the excess risk results from an interaction between an individual’s genetic makeup and environmental experiences, including radiation therapy. The retinoblastoma gene normally helps suppress tumor formation throughout the body, so individuals who carry a mutation in the gene frequently develop tumors in both eyes before age 5. Because they lack that tumor suppressor activity, an estimated 25 percent of these individuals will have a second cancer diagnosis within the next 50 years of life. If they receive radiation therapy for their original retinoblastoma tumors, that

risk doubles to 50 percent. Because researchers have found this link, Dr. Sklar says most oncologists no longer treat hereditary retinoblastoma with radiation.

When Steven Zachary (Zach) Sochor was 29 months old, he started complaining that his eye was “broken,” and his mother, Zoe Sochor could see him making an effort to focus. Zach was found to have one retinoblastoma tumor in each eye, indicating hereditary retinoblastoma. He was treated with six weeks of external beam radiation, which stopped the cancer in the left eye, but the cancer in his right eye continued to grow. In May of 1995, when Zach was just shy of his fifth birthday, the doctors removed Zach’s right eye.

Since that time, he has worn a prosthesis regularly and without complaint. But in 2004 he noticed his prosthesis no longer fit quite right. From April through June, the family and various doctors tried to figure out what was wrong, hoping initially that it was a bad flare-up of his springtime allergies. “An ill-fitting prosthesis is a symptom of second cancer,” says Zoe. “But even though you know that, it doesn’t come to the forefront of your mind right away—even though the possibility is with you all the time.”

Finally, one of the doctors saw a lump in Zach’s eye socket that hadn’t been there during a recent examination. The lump turned out to be a malignant fibrous histiocytoma that was growing toward Zach’s brain, a tumor most likely induced by the radiation used to treat Zach’s retinoblastoma 10 years earlier. After six heavy-duty rounds of chemotherapy, six weeks of radiation and a 14-hour surgery, Zach is in remission and doing regular ninth-grade stuff, including snowboarding. “I always wear my helmet and my goggles,” says Zach, who is well aware he needs to protect his one good eye. “Plus it looks cool because I have sweet goggles.”

## Why Second Cancers Happen

In both adult and pediatric survivors, most of the risk for treatment-related second cancers has been associated with radiation therapy and select chemotherapy agents. Thus far, there are two types of drugs implicated in causing second cancers: topoisomerase II inhibitors, such as VePesid (etoposide) and anthracyclines like Adriamycin, and alkylating agents, including Cytosan. Each of these treatments damage DNA in the tumor cells and can cause mutations in rapidly dividing cells in the body, leaving the patient at risk for new malignancies.

The chemotherapies are associated with leukemias and lymphomas, which frequently occur within one to 10 years after therapy. By contrast, radiation is the major risk factor for solid tumors, which almost always form within the radiation-exposed area. The delay between treatment and solid tumor development is longer than for blood cancers, with many solid tumors arising more than 10 years beyond therapy, and the risk continues to climb 15 years after exposure.

Researchers are beginning to understand how and when these therapies cause problems. For example, young girls and women under 30 who receive chest radiation for Hodgkin’s disease are more likely to have breast cancer later in life,

relative to women who never had such therapy. For this reason, physicians now avoid using radiation therapy in these patients.

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"This sort of information definitely feeds back into current treatment," says Dr. Sklar. "For cancers where the prognosis is very good and there are multiple agents that can be used for treatment, avoiding the ones with serious toxicities is clearly the way to go. Unfortunately for many malignancies, the outlook is not very good and the available drugs or modalities are limited." In those cases, the risks have to be tolerated.

One of the main questions facing researchers today is why some patients develop treatment-related tumors, while the majority do not. If scientists can determine what makes one person sensitive to the negative effects of therapy, they can avoid using that treatment for those individuals. In some cases, it seems risk is associated with genetic factors, while other cases point to environmental factors. The environmental ones can be controlled and already allow survivors to take steps toward prevention. For example, some researchers think that pediatric cancer survivors who smoke increase their risk of a second cancer, and survivors who received radiation therapy are at increased risk of skin cancer and sun exposure exacerbates the problem.

As researchers learn more about what causes second cancers, they are working to find ways to intervene. In the case of genetic syndromes they are looking for ways to preempt the problem, like using prophylactic mastectomies to reduce the risk of breast cancer in BRCA mutation carriers. And in the case of treatment-related disease, they are working to modify or reduce an individual's exposure. A good example of this has been the effort to narrow the radiation field and reduce radiation doses, which damage a smaller area of tissue and thereby reduce the risk of a new cancer.

The important thing for survivors, Dr. Bhatia says, is to know his or her risks based on what therapies they had and have regular follow-ups with a qualified physician and undergo recommended screenings, so if something does develop, it can be dealt with quickly. While it's important to use therapies that do not increase the risk of second cancers, doctors and patients agree that the bottom line is to cure the first cancer.

*Editor's Note: Lori Sklar passed away on December 30, 2006. CURE is proud to honor her memory.*