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From the editor

The Long-Term Follow-Up Study is 10 years old! This year marks the tenth anniversary of the Long-Term Follow-Up Study. Over the past decade study participants have generously sent in mountains of questionnaires, answered many phone surveys, and donated blood, tissue, and saliva samples. We want to thank you all very much, both survivors and members of the sibling comparison group, for staying with us all these years! As you know, the type of research we are doing takes many years to complete. We are just now really beginning to reap the results of our collaboration with you. The establishment of a DNA data bank from the specimens you have donated has been a major achievement. We know we are all different and we respond to illnesses and medicines in our own ways. We are now using this DNA data to study the genetic part of a person's response to treatment for cancer and similar illnesses. In this newsletter we feature two studies that used DNA gathered from the "Scope" mouthwash samples that many of our participants returned. These studies are quite preliminary, but they are examples of the types of questions that can be answered using this wonderful resource. If you did not receive a mouthwash kit or have misplaced it we would be happy to send you a kit so you can participate in this exciting part of the LTFU Study. Please call our toll-free study line: **1-800-775-2167**.

Bone tumor survivors are the major topic covered in this issue of the LTFU newsletter (*please see pages 2 and 3*). The ability to focus in on issues and concerns specific to single diagnoses is another important strength of the LTFU Study that has emerged from our 10-year collaboration with you.

Finishing up the Follow-Up 2002 survey. Thank you to everyone who returned the Follow-Up 2002 survey or responded over the phone. The majority of our participants completed the survey. We will soon be starting the process of looking at the information you have sent us and we'll report our findings in future issues of the newsletter. Please be aware that your participation is important to assure that our study results are accurate. We appreciate your time and effort in responding.

Upcoming survey. The next LTFU questionnaire has been finalized. We will be mailing it out to you after the first of the year. This time, we will only be asking you to update us about any major medical events you may have experienced. (Members of the sibling group will not receive this questionnaire because they responded to these questions on the previous survey.) We hope you'll find it quick and easy to complete. Thank you again for your help.

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Bone tumor survivors can face special challenges

by Dr. Melissa Hudson

The information shared by study participants continues to show that most survivors are generally doing well many years after completion of therapy. However, a small but important group of survivors report physical and emotional problems that may have negative effects in their everyday life. The goal of much of the research conducted by LTFU study investigators is to identify factors that are linked to higher risks of developing health problems with the hope that steps can be taken to reduce these risks. Because treatments vary according to the specific type of disease, study researchers are beginning to look more closely at the health of particular groups of survivors. Two recent studies have focused on survivors of pediatric bone tumors.

About 1,000 individuals who are currently participating in the LTFU Study were treated for tumors of the bone. Bone tumors, such as Ewing sarcoma and osteosarcoma, most often develop in the pelvis and legs; the second most common area where they occur is the arms and chest. In the past, surgery was the main treatment used for these tumors. However, surgery produced poor survival rates if the tumor could not be completely removed or if it had already spread to other parts of the body. Cure rates improved dramatically after 1970 with the use of more intensive treatments including combination chemotherapy, surgery, and radiation therapy. Now, information from survivors of childhood bone tumors participating in the LTFU Study are providing important insights about how treatment affects physical and social functioning in adulthood.

Since bone tumors predominantly occur in the pelvis and legs, these two initial studies have focused on those sites. Tumors that occur in the chest and arms are also known to have significant impacts and will be examined in the near future.

Psychological and social effects

An LTFU study that was recently published in the journal *Cancer*, looked at how bone tumor treatments affect education, employment, insurance and marriage in adults who had lower extremity bone tumors during childhood. In addition to treatment with large amounts of chemotherapy, these individuals had a major operation like an amputation or limb-sparing surgery and/or high doses of radiation. As a group, they are doing well overall. More than 97 percent have had a job and over 80 percent had worked in the past year. However, while almost 90 percent had health insurance, close to 30 percent reported having difficulty obtaining health insurance. Survivors were more likely to

report having insurance problems compared to individuals in the sibling comparison group. Survivors, especially males, were also less likely to be married than members of the comparison group. In addition, those who had an amputation when they were 12 years old or younger were more likely to be divorced. While results show that most survivors of lower extremity bone tumors appear to adapt well to the challenges of adulthood, a small group have difficulties in employment and marriage, as well as higher rates of health insurance problems and divorce. A report of this study can be found in *Cancer*, Vol. 97, 2003, pages 2554-64.

Effects of amputation vs limb-sparing surgery

A related study compared problems with function (everyday physical abilities) and quality of life of survivors of leg and pelvic osteosarcoma and Ewing sarcoma who were treated with either amputation or limb-sparing surgery. Limb-sparing surgery is an alternative to amputation. It

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is designed to save the affected limb while removing the tumor and usually involves replacing part of the limb with an implant. Many people assume

that survivors treated with amputation would have poorer physical function and quality of life compared to those who had limb-sparing surgeries. However, this was not the case. Function and quality of life of amputees were similar to those of survivors who had limb-sparing surgeries. Across both groups, over 90 percent of survivors considered themselves to be in good health; 95 percent had graduated from high school and almost 50 percent had graduated from college! The small group who showed higher levels of disability and poorer quality of life were more likely to report poor general health and to be older and female. This group was also less likely to graduate from high school.

Overall, it appears that survivors treated by amputation or by limb-sparing surgery are doing well. Continued follow-up is important to see if changes occur over time. Further study is also needed to help us understand why certain groups have more difficulty than others and how supports can be put in place to help alleviate their difficulties. A report of this research has been prepared and will be published in the *British Journal of Cancer*.



Dr. Raj Nagarajan

What should survivors and their doctors learn from these study results? Dr. Rajaram Nagarajan, assistant professor

of Pediatrics at the University of Minnesota, is the lead investigator of the bone tumor studies. According to Dr. Nagarajan, understanding risk factors for problems after treatment helps identify the patient who may need more attention and supportive services to achieve the best possible quality of life and function. “This is critical since the LTFU studies have noticed that the treatment of bone tumors may have a negative impact on educational status, employment, insurance access, marriage, and overall quality of life,” emphasizes Dr. Nagarajan. “Prosthetic fitting and function, mobility, chronic pain, and physical therapy are routinely addressed and used in the recovery period immediately after surgery. Long-term survivors deserve the same attention to assure that they maintain the best possible function.”

Recommendations

Some survivors need special arrangements at home, school or work to help with mobility and reduce the risk of injury. People treated with amputation should have the function and appearance of their prosthesis checked once a year. Those treated with limb-sparing surgery should be seen annually by an orthopedic surgeon to check the integrity and function of their endoprosthesis (bone graft and/or metal implant). A thorough musculoskeletal (muscles and bones) exam is important for both groups to check for other problems, like uneven limb-length, that may lead to chronic joint or back pain. Musculoskeletal problems that are not cared for may result in stiffening and wasting of muscles, tendons, and ligaments that lead to permanent tightening of the joint and to reduced mobility. The box below gives advice about how to keep the bones and muscles healthy after treatment for a bone tumor.

Life after bone cancer: Meet Laura Feldman

LTFU Study participant Laura Feldman of Knoxville, Tennessee, was diagnosed with osteosarcoma, a bone tumor, in her left leg at age 17, just after she graduated from high school. Laura was treated at St. Jude Research Hospital in Memphis. She went on a treatment protocol that was new at that time. She received chemotherapy followed by limb-sparing surgery in which a prosthesis was inserted into her leg. After the surgery she received additional chemo. “At the time, I was glad not to lose my leg,” Laura recalls. She had problems healing, however, (she needed a skin graft because of chafing burns from her cast) as well as problems with the engraftment of her internal prosthesis.

In 1990, when she was a student at the University of Tennessee, Laura made the decision to have her leg amputated above the knee. “I had the amputation over Christmas break. Getting the prosthetic leg was actually liberating for me because I was more mobile and in less pain,” she says.

Since then, Laura has faced plenty of surprises and challenges.

After high school she put college on hold for awhile because of her cancer treatment. But at the urging of her mother, she did take some math classes at a community college over the summer. There, a professor recognized her ability and

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Moving helps keep you healthy

CARDIOVASCULAR HEALTH

Keeping your heart healthy will make it easier to move around, even if you have difficulty moving or walking related to your previous bone tumor. Most stationary bikes will accommodate a standard prosthesis. However, riding a stationary bike even with one leg or with your arms has been shown to improve fitness in people who have had an amputation.

Swimming is also an excellent exercise. Persons with a prosthetic limb should remove it for swimming.

FLEXIBILITY AND RANGE OF MOTION

Try to limit the amount of time you keep your joints in a bent position because it shortens up the muscles around the joints. This may eventually reduce your ability to move your joint(s) through their full range of motion. **Move your shoulders, elbows, wrists, hips, knees and ankles through their full range of motion each day.** Hold the straightest position (your arm overhead or your leg fully extended while lying on your stomach) of the joint for a count of 30. When you stretch, you should feel a mild pulling sensation – no pain. Move slowly while you are stretching. Don’t forget to breathe.

STRENGTH

It is never too late to begin strengthening exercises. If you have been inactive, consult your physician or physical therapist before beginning an exercise program. **Exercise both your healthy limbs and those with impaired function.** Begin without weights on your limb and try to move it in all directions 5 times. Once you get to 20 repetitions, add weights (soup cans work well for arm motions). Increase the weight when 20 repetitions is no longer difficult.

Your current level of fitness, your general health, and the condition of the limb or body part that you had treated will all affect your ability to exercise.

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steered her toward an engineering program. She ended up with a master's degree in environmental engineering and holds a professional engineering license and currently works at the U.S. Department of Energy facilities in Oak Ridge, Tennessee, where she has handled many projects, including safety analysis and environmental clean-up.

Laura is married to Matt Feldman, whom she was dating when she had her amputation. They have two sons, Sam, seven, and Will, two. When she was pregnant with Sam she found out that none of her care providers had ever delivered a baby from an amputee. "They suggested I wear my prosthesis for the delivery, which I thought was a bad idea. We did not have to cross that bridge, due to an emergency C-section," she says. "With my second son I knew more what to expect."

Another surprise awaited Laura after Sam was born. "I limp a little but I have a pretty good gait," she says. "When my first son was not quite two years old he started limping. We did a lot of tests – what we finally found out was that he was just walking like mom. He had picked up on my gait!" Even though he was so young his parents were able to talk to him about it and he now walks normally.

"I feel like I have a pretty good attitude," says Laura. "But it can be incredibly frustrating. You feel pretty alone once you get away from where you had your treatment and get back into daily life. But you don't want to ask for help." And there are so many things to deal with – from finding parking to finding and keeping insurance coverage for maintaining a prosthetic limb. "I have great insurance. Everything has been covered for me so far but my company changes insurance providers a lot – and every time there's that fear. I've had the same leg for the last six years. If my prosthesis wasn't covered by insurance, fortunately, I'm in a situation where we would be able to deal with it. I know not everyone is, however."

Laura believes the key to coping with bone cancer survivorship is having a good support group, whether it's family, friends, or a community of other survivors. Through all the difficulties with a cancer diagnosis, surgery, treatment, and other complications along the way Laura had the total support of her family. She remembers that her mother, like the parents of so many kids with cancer, "completely put her life on hold" to go through the experience with her. "I have an incredible family. My parents, and Matt." Even her young boys know to be careful with mommy's special leg. "They can't just crash into me or play rough".

Despite all the difficulties she has had to deal with, Laura, with help from her family, is able to lead a full and "normal" life that includes work, children, church, PTA, and soccer.

"I think my kids think that all moms are like me," she says. "When I take my leg off at night I hop around and the kids hop right behind me."

"Scope" study results

Thank you to the many participants who have returned the mouthwash kits that they received. The "swish and spit" kits were used to collect cells from the lining of the mouth. Using DNA from these cells LTFU Study researchers have been investigating possible genetic factors that could be involved in a person's response to treatment for cancer and other serious illnesses. Two studies have recently been completed. These studies, like all our studies, contain no individual results. Rather, the experiences of all participants are examined together to show a trend.

The first study was led by Dr. Ann Mertens, project director of the LTFU. Her team looked at three genes that help protect against DNA-damaging agents. They wanted to see if normal variations in these genes are related to a person's chances of developing a secondary cancer after receiving radiation treatment for Hodgkin's disease (HD). We know that survivors of HD who were treated with radiation are at increased risk of developing a second cancer. All in all, the effects of these genes were small. For example, a certain gene variation seemed to slightly increase the risk of developing breast cancer after treatment for HD; this variation also appeared to very slightly decrease the risk of developing thyroid cancer. Results of this type are preliminary.

The study team notes that the risk of therapy-related second cancers is likely to be determined by interactions of many genes with treatment exposures, rather than just one or two. Additional gene variations must be tested and this study may then provide one piece of the puzzle. The results of this study were published in the journal *Cancer*, Sept. 15, 2004, vol. 101, pages 1463-1472.

The second study, led by Dr. Julie Ross of the University of Minnesota, looked at how variations in the leptin receptor gene relate to the risk of obesity in survivors of childhood acute lymphoblastic leukemia (ALL). Leptin is a protein produced by fat cells that helps regulate the amount of fat the body stores. Obese people are often resistant to leptin. Dr. Ross' group found that female survivors of ALL with one type of the leptin receptor gene were at increased risk of being obese. Their chances were increased if they had been treated with higher doses of cranial radiation (20Gy or more). This was not the case for the male survivors. These findings support the view that girls with this genetic variation, particularly those exposed to cranial radiation, have a reduced ability to make use of leptin to regulate body fat. The results of this study were published in the *Journal of Clinical Oncology*, September 1, 2004, vol 22, pages 3558-3562.