

Risks for, and Causes of, Leukemia

It's only human to wonder what causes disease. After a diagnosis, you may ask, "How in the world could this have happened? What caused me to get leukemia?" Nobody knows. There are many theories and ideas being promulgated about what causes leukemia, but there are no hard and fast answers out there that we can point to and say, "This is what caused the leukemia."

Who is at risk for leukemia

In 1993 about 10 Americans per 100,000 were newly diagnosed with leukemia. It is heartening that incidence rates of all leukemias dropped by 5.3 percent from 1973 to 1993. This drop was seen across genders and ethnic groups. Similarly, mortality rates dropped 6.2 percent during the same period. More effective methods for diagnosis and a much wider variety of treatment options have made this possible. Better understanding of possible causes and areas of concern also affected the statistics.

Although percentages have dropped, as the population has grown the number of people affected has risen slightly in the past few years. In 1999, an estimated 27,900 adults were diagnosed with leukemia. That's up from 23,100 in 1995, when 16,800 males and 13,400 females were diagnosed. According to 1999 statistics, AML has become the largest adult leukemia type, overtaking chronic lymphocytic leukemia in the numbers by about 2,300 individuals. More common use of blood tests has made early detection of these diseases easier and more efficient. To put the numbers in some perspective, in 1999 in the United States of America alone, about 1,221,800 new cases of all kinds of cancer are expected to be diagnosed, yet graphs of new leukemia diagnoses have remained pretty flat for the last five to eight years.

Leukemia rates vary by ethnic background, gender, and age. Caucasians are diagnosed with leukemia more often than African Americans, Hispanics, and Asians. Men are diagnosed more frequently than women. Leukemia diagnosis rates climb as people age. Out of 100,000 people in America, 10.3 were diagnosed with leukemia in the years 1992 through 1996. About 2 people per 100,000 were diagnosed below the age of 40,

and about 5.8 per 100,000 below age 65. At age 65 and up, 51.4 people per 100,000 were diagnosed with some form of this disease.

As a percentage of people diagnosed with leukemia, survival rates are rising. As of 1997, the one-year relative survival rate for patients with leukemia was 63 percent. Survival drops to 43 percent at five years after diagnosis, primarily due to the poor survival of patients with some types of leukemia, such as the acute myelocytic form. Nevertheless, there has been a dramatic improvement in survival statistics for patients with acute lymphocytic leukemia—from a five-year relative survival rate of 4 percent for people diagnosed in the early 1960s, to 38 percent in the mid-1970s, to 55 percent in the late 1980s.

Statistics say many things

The Physicians Data Query (PDQ) of the National Cancer Institute (NCI) gives ranges of life expectancy for people with varying cancers. Many patients read this information and panic. They may not know, or they forget, that each person is an individual and will react to the progress and treatments for this disease in different ways. Over and over again, people prove the percentages wrong. Medical treatment and research advances move far faster than demographic statisticians can keep current, so statistics lag behind actual practice. In other words, if you are in treatment in 2001 and are looking at 1997 survival rates, you are not only looking at an averaged rate (not your chances), but those figures are also discounting medical advances made between when survival was measured and the time you are reading the figures.

It is difficult to come up with reliable prognoses for leukemia. Patients, in the panic of first diagnosis, want to know, "How long do I have to live?" By the time they have lived with the disease for a while, many want to know, "How many months or years have I lived beyond the usual ranges?" Outliving the statistics becomes a personal goal for many patients at one point or another in their lives with leukemia.

Risks for, and Causes of, Leukemia

Do read the article by Stephen Jay Gould called *The Median Isn't the Message*. It can be found on the World Wide Web at <http://www.cancerguide.org>, Steve Dunn's very helpful Cancer Guide. The article explains how to look at the prognosis statistics and provides positive reinforcement about what may lie ahead.

Leukemia was first described only about 150 years ago. Since that time there have been substantial advances in diagnosis, tracking of cases, classification (although that is constantly evolving as diagnostic tools have become increasingly sophisticated), and treatment. The developmental, physical, environmental, and societal factors that may cause leukemia are not yet known. According to the present literature, it is most likely that the principal causes of leukemia have yet to be discovered.

Viral links to leukemia

Two viral diseases have been implicated in the development of leukemia. One is the Epstein-Barr virus (EBV); the other is the human T-cell lymphoma/leukemia virus (HTLV-1). While most people who get either of these viruses do not subsequently get leukemia, enough people do get it so that there is a definite link. There is also some evidence to implicate the human immunodeficiency virus (HIV) in causing leukemia.

The Epstein-Barr virus is a herpesvirus that can inhabit B-lymphocytes and nasopharyngeal cells. The HTLV-1 virus is closely associated with T-cell lymphocytic leukemia, found in Japan, Africa, and the Caribbean. Only a small fraction, no more than 4 percent, of those infected with this virus develop leukemia.

Both viruses leave residual traces in the cell markers. People who catch Epstein-Barr early in life are thought to be at increased risk of B-cell lymphoid tumors. EBV-infected B lymphocytes have an increased proliferation rate, increasing the likelihood of genetic error during DNA replication. Altered lymphoid cells with specific chromosomal transformations give rise to leukemic clones. These translocations rearrange elements of immunoglobulin genes resulting in B-cell ALL in children and adults. It is also implicated in CLL but not directly involved.

The following patient reconstructs a conversation she had with her doctor, in which she gleaned causative information without even asking for it.

When I was diagnosed with CLL 10 years or so ago, my doctor said to me, "Well you know, you test positive for having had the Epstein-Barr virus."

"That's nice," I replied. "What is Epstein-Barr, and what does that have to do with lymphocytic leukemia?"

"It's a B lymphocyte herpesvirus that starts out like a respiratory infection. But once you've had it, the traces stick around for life. You probably got it when you were a very young child."

Then he went on to tell me that it is associated with leukemia, lymphoma, and chronic fatigue syndrome and that most of his leukemia and lymphoma patients showed traces of it in their blood work.

I'm a fifty-year-old mother of three, and here we are discussing a childhood disease that I probably had before age ten. Was I supposed to believe this was a cause of my leukemia?

The doctor was very careful to explain that it was an indicator that is found in many patients. He made no claim that it was a cause of the disease. By the time he was finished talking, however, I was anxious to research other possible causes of the disease.

Speculative causes of leukemia

Most of the risk factors for the leukemias are poorly understood. Certain genetic disorders predispose individuals to leukemia. Certain viruses are closely allied to leukemia. There is much discussion of ionizing radiation and occupational and environmental chemical exposures, some known and some just thought to be responsible for development of leukemias.

Risks for, and Causes of, Leukemia

Ionizing radiation

Radiation is the best known and most studied risk for leukemia. Studies have been done of people exposed to radiation in war, on the job, or as part of medical treatment. CLL is one of the few leukemias that has not been linked with radiation exposure. The other three major leukemias were found during studies of ionizing radiation in survivors of the atomic bombing in Japan. Survivors developed leukemia at a minimum of two years and at an average period of ten years. People receiving high doses of radiotherapy for solid tumors have relative risks for leukemias as well. Further, the risk of subsequent leukemia is also increased in patients receiving radioactive iodine for thyroid cancer, radioactive phosphorus for polycythemia vera, and those receiving thallium dioxide as a radiographic contrast agent (rarely used today).

Nonionizing radiation

Nonionizing radiation, in the form of extremely-low-frequency electromagnetic field exposure induced by electricity has been suggested as a possible risk factor for leukemia. This suggested cause has been linked to adult ALL for those working in occupations where they have steady exposure. Power linemen, utilities workers, electronics workers and others are most often mentioned as possibly at risk. There have been studies showing an increased risk for these occupations, although results are not clear-cut. However, for electromagnetic exposure in the home, all but one study of the hazards to adults has been negative.

Occupational exposures

Exposures to certain known chemicals or certain occupations have been linked to increased risk of leukemia.

Various implications have been made about leukemias resulting from occupational or environmental exposure to benzene. Relative risks have been reported to be as low as 1.9 or as high as 10.0 among workers exposed to benzene. This means that, depending on the study, people exposed to benzene were from two to ten times as likely to be diagnosed with leukemia as were people who were not exposed to benzene. Workers in petroleum manufacturing, chemical manufacturing, rubber

manufacturing, and shoe manufacturing as well as printers and painters have been included in the categories at risk. AML is most strongly linked with these exposures, but there may also be a link to CML with benzene exposure. There also is a link to CLL. It must be noted that the industrial use of benzene has been outlawed in the US since the end of World War II; however, it is still used in some third world countries.

Other chemicals have also been linked with risks for leukemia. Fewer studies have been done, but styrene and butadiene have primarily been associated with lymphomas and with CLL. Hairdressers, garage and transport workers, rubber workers, and sawmill and wood products workers have all been exposed to some form of chemical that may be perceived as a leukemia risk factor.

Studies looking for an increased risk of leukemia in farmers have been suggestive but inconclusive. Some studies of farmers and farm workers have revealed elevated leukemia risks from 10 to 40 percent. Still others have shown no increase in risk for agricultural workers at all. Among farmers in those studies in which the results were positive for raised rates of leukemia, almost all types of leukemia have been found to be increased. Exposure to pesticides, herbicides, fertilizers, diesel fuel and exhaust, and infectious agents associated with livestock have all been listed as possible risk factors.

Bovine leukemia virus does produce transformed B-lymphocytes in the cow, so farm workers and veterinarians may be at some risk with this virus. Feline leukemia virus disease when present in cats has no relationship with human disease. Ironically, feline leukemia viral disease is a T-cell leukemia, while 95% of CLL is B-cell related.

Antineoplastic agents

Some people are exposed to chemotherapeutic agents destructive to bone marrow cells, primarily alkylating agents such as Leukeran (chlorambucil) and cytoxan (cyclophosphamide). Some people are given agents prescribed for other malignant and nonmalignant disorders (for example, rheumatoid arthritis and other autoimmune diseases). These agents increase the rela-

Risks for, and Causes of, Leukemia

tive risk of subsequent leukemia. AML has been reported to be increased consistently among patients treated with alkylating agents for many solid tumors and blood and lymphoproliferative malignancies.

Lifestyle risk factors

Lifestyle risk factors, shown to be important for many with solid tumors, have received little attention, or appear to play a very small part in the development of leukemia. Cigarette smoking is linked to leukemia. Several studies on the possible roles of diet and alcohol consumption on leukemia have shown nothing definitive.

Cigarette smoking has only been recognized as a potential cause of leukemia since 1986. Since then, more than 20 studies have been analyzed or re-examined to look into this assumption. Recent evaluations of the studies indicate the risk is greater for the myeloid leukemias, perhaps as high as 15 to 22 percent. Nevertheless, total leukemia incidence has not risen relative to the time during which the use of cigarettes and exposure to cigarette smoke climbed steadily. Lung and other smoking related cancers do have rising incidence rates that can directly be attributed to smoking. Therefore, it would appear that the attributable risk might have been overestimated for the leukemias. A few studies have shown increased risk for lymphoid leukemia among cigarette smokers, but most show a relationship to the myeloid types.

Immune suppression

Immune suppression can lead to leukemia or lymphoma transformations. Bone marrow transplantation, chemotherapy, and radiation aimed at controlling leukemia may also cause immunosuppression, which can also lead to transformations. Kidney transplantation and heart transplantation are associated with immunosuppressive drugs that have been implicated in secondary leukemias.

Other concerns

Invariably, with the diagnosis come questions that can't always be answered. Patients often feel that they are somehow responsible for the condition they have.

As a patient with CLL said after her diagnosis:

I immediately wanted to find out what caused leukemia. Could it have resulted from mononucleosis or radiation, both of which I had in college in 1949? It seemed very important to find a reason at the time, but having spent this past winter gathering all the information I could, from all the wonderful sharing people in my online support group, I found that I had a lot to be grateful for.

People looking for answers to the cause of leukemia might ask questions about what danger there might be to others in their families, what they might have done to prevent the disease, and what changes they can make to prevent recurrence or keep themselves healthy.

Familial predisposition

Inevitably, patients will ask if there is a familial predisposition to leukemia. Many times the answer is, "We still don't really know." As we learn more and more about the genetic composition of cells, we learn more about how leukemias arise, and so about hereditary connections or the lack of them.

Of all the major hematological malignancies, CLL shows the highest family influence, suggesting a genetic component to the cause of the disease. By definition, familial CLL occurs when the disease is present in parents or siblings. There have been reports of CLL involving two siblings in one generation and some reports of CLL in the same family in two generations. Reports of CLL in three succeeding generations are rare. The clinical path that the disease takes in such familial situations is extremely variable, and there are no consistencies. There is also the likelihood that CML, hairy cell, ALL, or non-Hodgkin's lymphoma may be found in families with CLL. Research into the question of heritability is ongoing in the US and in Great Britain.

It is becoming increasingly evident that familial leukemia can be associated with chromosome instability that is inherited. CLL, hairy cell leukemia, and AML M6 seem to have a greater tendency to run in families.

Risks for, and Causes of, Leukemia

Some researchers believe that the greatly increased incidence rates for leukemias in those over age 65 may be related to a general weakening of the immune system that comes with age. Research to come to some definitive conclusions about this needs to be done. Other researchers feel that the increased incidence rates in older individuals may be the result of the society in which we live and that genetic damage from substances in an industrialized society accumulate over time, becoming more apparent as we get older and less able to deal with them.

Reducing Risk

Many people also ask what they can do now, after a diagnosis, to help make a difference. Eating right and getting exercise are strongly recommended for good health for everyone. It's especially important for those who have been diagnosed with cancer. Patients often report a lack of appetite and weight loss associated with leukemia symptoms.

Many people receive a leukemia diagnosis and immediately look to make dietary changes in an attempt to slow the progress of the disease. Some blame themselves for eating incorrectly. Current nutritional theory strongly recommends a diet high in fruits and vegetables, whole grains, and cereals. It suggests you eat moderately of meats and dairy products and that you cut way back on sugars, fats, alcohol, and salt. However, healthy eating neither causes nor changes the progression of leukemia.

Some patients are anemic and really benefit from increased red meat or high protein in their diets. Some have diarrhea or mouth sores and should avoid foods containing high fiber, which aggravate those symptoms. Nutritional recommendations for leukemia patients may be different because they are designed to build your strength and help you withstand the effects of treatment. If you have leukemia and are undergoing treatment or are simply not feeling well, it is often difficult to get enough nutrients into your system to remain well nourished. A healthy pattern of eating is important so that your body works as well as it can. If you go into treatment having been eating a healthy diet, you'll have reserves to help you keep up your strength, prevent

body tissue from breaking down, rebuild tissue, and maintain your defenses against infection.

Eating well helps you cope with side effects of treatment, and in some cases treatment is actually more effective if the patient is well-nourished and eating sufficient calories and protein in his diet.

Be sure to check with your doctor before you eat grapefruit or drink grapefruit juice when you are under treatment. Grapefruit juice releases a compound at the cellular level that can expel medications from the body before they reach the blood stream.

Continuing to keep active and to exercise can be most beneficial. If you have been used to a high level of exercise and are fighting fatigue, it is smart to cut back but not eliminate kinds of exercise that have been part of your daily routine. If you have been sedentary, now is a good time to add moderate activity to your weekly routine so that you build strength to get you through treatment when that time comes. Proper professional help is recommended so that you don't try to do too much too soon.

Keeping active is not only good for body strength. It is known to assist in maintaining good mental health as well. There is real truth in the belief that if you are active and feel well, your emotional responses will be more normal and focused as well. Mind-body exercise programs such as yoga and tai chi have been shown to be very helpful in improving self-efficacy and long-term adherence to healthy behaviors as well as improve personal stress management skills. Mind-body exercise couples muscular activity with an internally directed focus, so that the participant enters a temporary self-contemplative mental state, resulting in a feeling of well being and stress relief.

This fact sheet was adapted from *Adult Leukemia* (forthcoming), by Barbara B. Lackritz © 2000 by Patient-Centered Guides. The content on which this fact sheet is based has been reviewed by several MDs and will receive further technical review prior to publication. For more information, call **(800) 998-9938** or check www.patientcenters.com for publication announcement.