

A microscopic view of several cancer cells, appearing as irregular, textured spheres with some internal structures visible. The cells are set against a dark blue background with a subtle grid pattern. The lighting is dramatic, highlighting the rough, crystalline surfaces of the cells.

# CANCER RISKS in PI Patients

Some PI patients are at higher risk of certain forms of cancer compared with the general population, but understanding risk factors and screening appropriately can help reduce risks.

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**A COMMONLY HELD** concept is that when the immune system malfunctions, “immunosurveillance” (the ability of the immune system to look for infections and cells developing into cancer) declines and, thereby, the risk increases for a developing cancer to go undetected.

Hence, an increased risk for cancer in patients with primary immunodeficiencies (PIs) seems logical. This article explores the risks for cancer in PI patients. (For greater depth on this subject, refer to the articles in the bibliography.)

## Types of PIs and Cancer Risks

Currently, there are more than 350 known PIs, many with now-defined genetic causes. Yet, fewer than 10 PIs account for nearly all cancer diagnoses. Unfortunately, the most common form of PI, common variable immunodeficiency (CVID), accounts for nearly one-quarter of cancer diagnoses.

PI can be divided into different categories. One classification is humoral and another is cellular. Humoral immunodeficiencies include complement deficiencies and antibody deficiencies. Cellular immunodeficiencies include phagocytic cells, B lymphocytes, T lymphocytes and NK cells. There are also overlaps between the categories. B lymphocyte deficiencies go along with antibody deficiencies, T and B lymphocyte-combined immunodeficiencies occur, and T and B lymphocyte immunodeficiencies may also have NK cell deficiencies. Cancer risk increases as cellular immunodeficiency increases, which is thought to be a consequence of reduced immunosurveillance. Thus, the overall rarer forms of combined immunodeficiencies may have among the highest risks for developing cancer.

The following are cancer risk findings reported from a study conducted by Resnick et al, looking at the demographics, immunologic parameters, medical complications and mortality statistics from 473 subjects with CVID who were followed over four decades in New York:

- Overall, some form of lymphoma is the most common cancer (approximately 49 percent of all cancers) in PI patients. In the study, lymphoma was diagnosed in approximately one in 12 (around 8 percent) CVID patients whose adjusted lifetime risk would be approximately one in 6 (about 16 percent). Compared to the expected rate in the general population of approximately one in 42 (2 to 3 percent), CVID patients have a five to eight times greater lifetime risk for developing some form of lymphoma.

In many cases, Epstein-Barr virus (EBV) infection of B lymphocytes is a driving force behind the development of lymphoma because immunosurveillance doesn't control EBV or its infected B lymphocytes. Any of the B lymphocyte and T lymphocyte immunodeficiencies increase risk for lymphoma. Indeed, it is considered that the greater the T lymphocyte immunodeficiency, the greater the risk for lymphoma. B lymphocytes reside in areas known as "Peyer's patches" in the intestinal wall. It is common for lymphoma to originate in Peyer's patches in the gastrointestinal (GI) tract. Thus, an inciting force may be the immune system interaction with organisms from inside the GI tract. Better

stated, a malfunctioning immunity that should be tolerized to normal organisms of the GI tract may be responding in an abnormal fashion, especially since it may be underresponding to actual pathogens. This overdrive of B lymphocytes in the intestinal wall may then allow for mutations, which in turn result in lymphoma. And, overdrive is worsened if EBV infection is present.

- The second most common cancer in CVID patients in the study was breast cancer. The adjusted risk for females was approximately one in 29 (about 3 to 4 percent), and the adjusted lifetime risks for females was approximately one in 15 (about 7 percent) compared with approximately one in eight (about 12 to 13 percent) for the general population. Because the genetic risk factors for breast cancer (such as the inheritance of specific mutations in BRCA1 and BRCA2 genes) have not been well studied in PI patients, it is unknown how these may affect the risks.

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- Some form of GI cancer occurred in approximately one in 79 (about 1 to 2 percent) of CVID patients in the study. Adjusted for lifetime risks, it occurs in approximately one in 40 (about 3 percent), and the incidence can be as high as approximately one in 23 (about 4 to 5 percent) in the general population.

- Melanoma was found in approximately one in 158 (about 0.6 percent) of CVID patients in the study. And, the adjusted lifetime risk was approximately one in 79 (about 1 to 2 percent), whereas the lifetime incidence in the general population may be as high as approximately one in 38 (about 2 to 3 percent).

- Approximately one in 237 (about 0.4 percent) of CVID patients developed lung cancer. Adjusted for lifetime risk, it was approximately one in 119 (about 0.8 percent). The lifetime risk in the general population is reported to be approximately one in 16 (about 6 percent).

Therefore, in CVID patients, risks for certain forms of cancer may be no greater than the general population. In contrast, higher risks for lymphoma are found, with a lifetime adjusted risk five to eight times greater than the general population. What has not been explored is whether the rates correspond to known genetic risk factors.

Other forms of PI rarer than CVID have an even higher risk for cancer. Some of these have a more severe T lymphocyte deficit, which results in poorer immunosurveillance, so that developing cancer cells go undetected. Still others such as ataxia-telangiectasia (AT) and Nijmegen breakage syndrome have abnormalities that hinder their ability to repair damaged DNA. For example, if DNA is damaged by X-rays, it cannot be appropriately repaired, allowing mutations that result in cancer.

Based on data, the risk for developing some form of cancer in CVID patients may be no greater than the general population, except for the five-to-eight-times increase in lifetime risks for the development of lymphoma.

Patients with AT are at risk for essentially any form of cancer, but GI tract cancer followed by breast cancer are the most common forms. Indeed, the cancer risks may be approximately six times that of the general population. Unfortunately, relatives of patients who may be carrying the genes responsible for disease are at an overall higher risk to develop cancer. Patients with other forms of DNA repair abnormalities have similar profiles.

As specific mutations responsible for causing different types of PI are found, there will be a better understanding of the genetic risk factors specific for cancer development in these patients.

## What Do the Incidence or Occurrence Rates of Cancer in PI Really Mean?

Based on data, the risk for developing some form of cancer in CVID patients may be no greater than the general population, except for the five-to-eight-times increase in lifetime risks for the development of lymphoma. And, risks may be even higher for those with poorer T lymphocyte function. In forms of PI in which DNA repair is affected, the rates may be approximately six times the general population for any form of cancer.

What is missing, though, is information about other risk factors. We now know of many specific genetic risk factors for the development of cancer in the general population. For example, patients diagnosed with lymphoma will frequently have a panel of specific genes analyzed because they can have bearing on prognosis, specific interventions and therapies. Further, in conditions with DNA repair abnormalities, cancer risk is greater regardless of whether an immunodeficiency is present. Until we have determined the presence or lack of additional genetic risk factors, it remains difficult to fully attribute the development of cancer to only having the presence of an immunodeficiency (with lymphoma the exception).

## What Can Be Done to Ameliorate the Risk of Developing Cancer?

Tobacco smoke exposure remains one of the greatest risk factors for developing many forms of cancer. Stopping smoking and avoiding exposure to cigarette smoke can be very helpful. Alcohol intake promotes GI cancer. Drinking in moderation or not imbibing in alcohol reduces these risks. Infection of the stomach with helicobacter pylori bacteria increases the risk of stomach cancer. But, undergoing treatment may reduce the risk. Unfortunately, other infectious agents may not be so readily avoided or treated. Once an EBV infection has occurred, it remains within the person's B lymphocytes, along with the risk for developing lymphoma. Therefore, knowing whether one has EBV can be a starting point for awareness about the potential risk of developing lymphoma and for maintaining a higher vigilance for disease development.

Avoiding as best as possible events that result in radiation exposure can reduce risks for damaging DNA, which reduces cancer potential. For those with known DNA repair abnormalities, minimizing exposure to X-rays is imperative. In addition, minimizing flying at high altitudes (estimated to be equivalent to a chest X-ray exposure of radiation, or approximately one two-hundredths of the acceptable annual exposure to radiation

with each flight) can reduce some radiation exposure.

Drinking clean water that is free from impurities that promote cancer (trichloroethylene, benzene, etc.) can also decrease cancer risk. Using a water filter containing activated charcoal may be necessary to remove such items. Lastly, eating a diet with many natural antioxidants may be helpful.

## What Can Be Done to Evaluate for Cancer?

Any changes in fatigue (energy level), temperature, achiness, lymph nodes, stool or stooling patterns, rashes, headaches, etc., could represent changes associated with cancer. An obvious problem is these signs may represent inflammation, which can be caused by an infection or autoimmunity. Therefore, appropriate judgment must be used in evaluating clinical features for distinguishing the source of the inflammation, infections, autoimmunity and/or cancer.

Blood tests may be helpful for some. Changes in white blood count, platelet count and hemoglobin/hematocrit can be useful screening tests. The serum LDH and uric acid levels may go up with lymphoma. Thus, some simple blood tests can be useful in screening for the presence of cancer.

Since GI cancer and lymphoma of the GI tract may represent nearly 60 percent of cancers found in PI patients, annual endoscopies may be quite worthwhile, especially once a patient has reached 40 years of age. Some have advocated an initial PET-CT scan as a baseline, which is repeated when there is suspicion of cancer since it does a relatively good job of cancer detection. However, caution is always necessary about the potential radiation exposure.

Routine breast and cervical examinations in women remain important screening tools.

For those with DNA repair abnormalities, using alternative testing such as magnetic resonance imaging or ultrasound can reduce radiation exposure.

Family history of cancer may be a very useful indicator of risks, since gene mutations associated with these may be different from those causing the PI. For example, a family history of breast cancer may be a good indication to check for BRCA1/BRCA2 mutations and to treat as appropriate.

As more gene mutations are identified with risks for specific cancers, these too may be evaluated. One major dilemma remains, however, that while the risks may be greater for development of cancer from specific gene mutations, there is no guarantee cancer will develop. The tests merely identify risk. For some individuals, knowing a risk is present can be psychologically difficult. Thus, individuals should be

screened for cancer genetics only after appropriate counseling and acknowledgment that they can psychologically deal with the results.

## Summary

In general, the risk for cancer in PI patients varies from the general population depending on the type of cancer and the type of PI. Overall, some form of lymphoma is the most commonly diagnosed in PI patients, with the risk in CVID patients five to eight times that of the general population over a lifetime.

Altering lifestyle issues can be helpful for reducing risks. Identifying family risks with specific gene mutations may be quite useful for assessing an individual's risk. Any inflammatory illness should be reasonably assessed. While infection would be most highly considered, risk for cancer should not be ignored. Simple blood tests obtained at appropriate intervals may be helpful for screening. Annual endoscopies beginning at age 40 years are reasonable for assessing the GI tract. Some would recommend a baseline PET-CT scan useful as a reference for future evaluations. Other general screening, breast examination, Pap smears, etc., should be routinely performed. And, testing for gene mutations as they become identified with risks for specific cancers may be useful, but only in patients who can psychologically handle the information.

Finally, the most important thing is for PI patients to have a good working relationship with the physicians providing their care. For their part, physicians should listen to patients' concerns and evaluate them with appropriate measures. ■

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