M aureen Lengel has enough on her mind. There’s her demanding job with a school district in suburban Pittsburgh. Add to that a few home-remodeling projects and a head-spinning family and social life, with season tickets to Steelers games, a subscription to Broadway shows, and frequent out-of-state visits to friends and relatives.

Oh yes, and then there’s the rheumatoid arthritis (RA) the 52-year-old has been living with since her teens, as well as the hip replacements and other surgeries she’s endured throughout the years as a result of the condition. The last thing this woman needs is having to worry about an even scarier health problem – cancer. But worry is there, lurking in the back of her mind.

“I know that people with RA have a higher risk of developing cancer,” says Lengel, who keeps up on the latest news related to her disease by reading, sharing and discussing information with her doctor. The worry first set in for Lengel in the mid-1980s, when she realized that the methotrexate she was taking for her RA was the very same drug her friend’s mother was receiving for breast cancer.

“Whether it’s the disease itself or the drugs people take for it that increase the risk – I’ve seen articles on both sides of the story,” she says. “Some say RA drugs may not raise cancer risk, but other articles link cancer – specifically, lymphoma – to one of the drugs that I’m...
CANCER AND RA:
same system, opposite effects

"RA IS NOT CANCER – LET’S BE CLEAR ABOUT
THAT – but RA has some features that resemble
cancer, so treatment we normally would think
of as oncology (cancer-killers) have application
to RA," says Gary S. Furst, MD, chief of the
Division of Rheumatology, Allergy & Immunology
at the University of California, San Diego. Kinship
at the cellular level makes such treatment crossovers possible, says Dr. Furst.
The two diseases have a faulty immune system in common,
says rheumatologist Daniel E. Furst, MD, of the University
of California, Los Angeles. "Cancer occurs when the body’s
normal immune response to cancer cells—which appear in us
all the time—fails. The immune system doesn’t catch something
that’s abnormal. In the autoimmune diseases—such as RA, lupus, Sjögren’s syndrome, psoriatic arthritis, myositis,
sarcoidosis and scleroderma—the immune system overreacts
to the normal, turning against itself,” says Dr. Furst.
It’s true that those autoimmune diseases have been linked
to an increased risk of cancer—lupus with lung or blood
cancer; Sjögren’s syndrome with lymphoma; psoriatic arthritis
with skin cancer; myositis with all types of cancer; sarcoidosis
with skin, liver, lung and lymphoma; and scleroderma
with lung cancer. So why has RA’s link to lymphoma
been studied the most intensively? One reason is that many
of the medications suspected of increasing the lymphoma
risk are approved to treat RA, but not all of the other auto-
immune diseases. Another is that RA involves a cellular process
akin to tumor growth.

In RA, the delicate lining that surrounds and protects a joint,
known as the synovium, becomes inflamed, making the
joint swollen and painful. As the disease progresses, the
cells that make up the synovium go through a process much
like what happens in cancerous tumors: Normal cells multi-
ply unchecked, and invade and destroy healthy tissue.
To complicate matters, says Dr. Furst, many drugs used to
treat RA suppress the immune system, meaning the immune
cells that search the body for cells gone bad aren’t able to do
their job. “If a drug suppresses not only the abnormality that’s
causing the disease, but also immune surveillance, one could
get cancer from the therapy,” he says.
That’s the theory. But what about the evidence? It’s been accumulating
for some time. The first hints surfaced in 1978, when researchers in Finland
matched hospital records of patients treated for RA with patients treated
for cancer and saw an overlap. That study, as well as other studies of RA
patients from around the world, showed a higher incidence of lymphoma—
in particular, non-Hodgkin’s lymphoma—in people with RA, com-
pared with people without RA.
By current estimates, the lymphoma risk for people with RA is two to
four times greater than for people without RA, when adjusted for age and
gender. That may sound huge, but when you consider the rarity of
non-Hodgkin’s lymphoma—about 90 cases per 100,000 people in the
age group affected by RA, compared with 213 cases for breast cancer and
150 cases for prostate cancer—even the elevated risk is still relatively low
(less than 0.1 percent per year).
**SHARED CAUSES, SHARED TREATMENTS**

**THERE IS A HOPEFUL SPIN ON THE COMPLICATED CONNECTION BETWEEN CANCER AND RHEUMATOID ARTHRITIS (RA).** Cancer researchers have been exploring whether anti-inflammatory drugs may play a big role in cancer as it does in autoimmune diseases, such as RA.

“It’s clear now that there’s cross talk between inflammation, immune activation and cancer. Many of the same pathways and molecules can go awry in parallel,” says Gary S. Firestein, MD, chief of the Division of Rheumatology, Allergy & Immunology at the University of California, San Diego. “That’s encouraging, because when you really start to understand the mechanism of one particular disease, a broad shadow is cast on others.”

As more shared chemicals and pathways are uncovered, the number of possible targets for treating both increases. Here are two of the latest finds:

**TARGET: B Cells.** The biologic agent rituximab (Rituxan) was approved by the FDA in 1997 for treating aggressive lymphomas. In 2006, it received FDA approval for treating RA. Rituximab zeroes in on B cells, which are a type of white blood cell that proliferates out of control in certain types of lymphoma and is also important in promoting RA, says Mary Chester Wasko, MD, a rheumatologist at the University of Pittsburgh Medical Center. As part of the normal immune system, B cells kill foreign invaders indirectly by triggering production of antibodies. In RA, B cells flock to the affected joints, secrete chemicals that encourage inflammation and produce autoantibodies.

**TARGET: NF kappa B (NF-kB).** At the University of California, San Diego, immunologist Michael Karin, PhD, is studying NF-kB, a protein that has been called the “master switch” of inflammation. Karin’s research suggests that NF-kB may be the “smoking gun” connecting inflammation and cancer. “Inflammatory cells don’t undergo any genetic changes in cancer and don’t become cancerous themselves, but they are major players in tumor development,” says Karin.

Karin’s group has found that activation of NF-kB prompts production of growth factors, which, in turn, stimulates the multiplication of cells that will become cancerous. When the activity of these growth factors, which, in turn, stimulates the multiplication of cells that will become cancerous, is blocked, this prevents the development of cancerous tumors.

Might the drugs that block TNF’s pro-inflammatory properties also hamper its tumor-fighting tendencies? That’s been the concern ever since TNF inhibitors, such as adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade), came on the scene during the past decade. But because they’ve been around for so long, relatively short time, many studies looking at lymphoma risk haven’t been done. So far, “the evidence is mixed,” says Dr. Wasko. “Some studies point to a slight increase in risk of lymphoma in RA patients who receive TNF inhibitors, but it’s not a consistent finding.”

It’s possible that TNF-inhibiting drugs have contradictory effects — both reduce cancer risk in some situations and lowering it in others. That’s a plausible scenario, given the mercurial nature of the protein they target: The NF-kB-driven cancer risk could depend upon your ethnic background, your exposure to toxins in the environment or multiple other factors,” says Dr. Wasko. “And the type of cancer you’re talking about — the effect on lymphoma risk could be different from the effect on colon or lung cancer risk.”

Frederick Wolfe, MD, director of the National Data Bank for Rheumatic Diseases, in Wichita, Kan., points out another factor. “If you have severe RA, you’re more likely to be prescribed a biologic, but you’re also more likely to get lymphoma — because of the severity of your disease — whether or not you get the biologic,” he notes. “It’s difficult to disentangle the effect.”

To tangle matters even more, lymphomas are relatively rare, so researchers must study large numbers of RA patients in order to find enough lymphoma cases from which to draw meaningful conclusions. But RA itself, although the second most common arthritis diagnosis, is fairly rare, occurring in only 1 percent of the general population.

Keeping those caveats in mind, consider the results of recent studies, which shift the blame away from treatments and suggest that keeping RA in check should be your biggest concern.

**NOW: less worry, more aggression**

IN RESEARCH PUBLISHED IN THE JOURNAL ARTHRITIS & RHEUMATISM IN 2006, INVESTIGATORS AT HARVARD MEDICAL SCHOOL AND THE UNIVERSITY OF BRITISH COLUMBIA, VANCOUVER, POOLED MEDICAL DATABASES from Pennsylvania, New Jersey and British Columbia to compare cancer rates between patients using the older disease-modifying anti-rheumatic drug (DMARD) methotrexate and those using a newer biologic drug, such as a TNF-inhibitor. The conclusion? Users of biologic agents probably are no more likely than users of methotrexate to develop cancer. Similarly, a study of 19,562 patients led by Dr. Wolfe and his colleague, Kaleb Michaud, showed no evidence for an increase in lymphoma incidence in those on TNF inhibiting drugs.

In another investigation, Swedish researchers mined a national registry of nearly 75,000 RA patients, finding a dramatic association between lymphoma and disease activity, which is determined by currently swollen or tender joints, increased levels of inflammatory markers and X-ray evidence of erosion in at least one joint.

Compared with patients who had low RA activity, those with medium disease activity showed an eightfold increase in the likelihood of developing lymphoma. For the 1 percent who had high activity, the probability took a staggering 70-fold jump, leading the authors to conclude that suppressing RA disease activity with aggressive treat ment actually may reduce, rather than raise, the odds of developing lymphomas.

As for other cancers, Dr. Wolfe and Michaud studied 13,000 patients in the National Data Bank for Rheumatic Diseases, looking specifically at links between treatment with a biologic agent and cancer risk. They found that biologic therapy doubled the odds of developing skin cancers, including melanoma, but did not put patients at greater risk for lymphoma, or breast, lung, colon or any other cancer.

“These increased risks are extremely small,” Dr. Wolfe emphasizes. “Melanoma is serious but not common; most other skin cancers are not serious. I don’t think anyone should be concerned.”

Weighing all the evidence, Dr. Furst offers this advice: “Rheumatoid arthritis is a very serious disease, and, over all, the therapeutic benefits of the drugs used to treat it far outweigh their downsides. The risk from not doing anything to contain the disease is much greater.”