THE WALL STREET JOURNAL

Probing Surgery's Link To Cancer Recurrence

Some Researchers Say Removing A Tumor Can Trigger a Process That Leads to New Growth

By: Amy Dockser Marcus Staff Reporter of THE WALL STREET JOURNAL
Updated Sept. 13, 2005 11:59 p.m. ET

Doctors have long noted that the rate of recurrence for women with breast cancer is highest during the first two years after surgery to remove the tumor. Now a group of researchers say they have found a reason why: the surgery itself.

In a paper published today by the quarterly International Journal of Surgery on its Web site, the researchers argue that taking out the tumor triggers the release of certain substances in the body, perhaps as part of the wound-healing process or in response to the absence of the tumor. They believe that these substances, in turn, enable cancer cells that had been lying dormant in other parts of the body to undergo angiogenesis -- the process by which the body forms new blood vessels -- which also feeds the tumors' growth. This can cause the women to relapse early, the researchers concluded.

The researchers' findings are based on their study of a database of 1,173 breast-cancer patients treated in Italy. They didn't conduct examinations or blood tests on the subjects. Rather they offer the theory of "surgery-induced angiogenesis" as the best explanation for a statistical cluster of recurrences in the group. They say the cases recurred too early to be explained by another mechanism, so the researchers concluded they were related to the women's surgeries.

Relapse Patterns

In a database of 1,173 breast-cancer patients treated with surgery from 1964-1980:

- In total, 520 relapsed.
- Women of all ages whose cancer had spread to the lymph nodes were at higher risk of early relapse.
- In premenopausal women whose cancer had spread to lymph nodes, 20% relapsed within 10 months of surgery.
- This relapse rate was twice as high as that of women after menopause whose cancer had spread to the nodes.

There is support for this idea in animal and human studies that link surgery to remove tumors, including lung and colon cancer, with cancer recurrence. For instance, in a 2002 paper published in the journal Lancet, colon-cancer patients who had traditional surgery had a significantly higher rate of relapse than patients who had a minimally invasive laparoscopic procedure.

And the study's lead author, Michael Retsky, a lecturer in surgery at Children's Hospital Boston and Harvard Medical School, says the theory of surgery-induced angiogenesis may have implications for treatment of a variety of cancers. Cancer drugs that try to stop tumors from being able to form new blood vessels, such as Avastin, are being increasingly used as part of therapy. And other "anti-angiogenic" agents are being studied in animals and humans, focusing new attention on how to best use these drugs to improve survival.

The paper's authors don't advocate that women with breast cancer forgo surgery. Most women with breast cancer have surgery -- either mastectomy or lumpectomy -- to remove the tumor, and this has long been part of the standard treatment.

"Surgical therapy cures a large majority of women with early-stage breast cancers and I don't want patients to run away from the operating room," says Susan E. Clare, a breast-cancer surgeon at Indiana University School of Medicine in Indianapolis, who wasn't involved in this study.

Women typically undergo chemotherapy or radiation in addition to surgery to try to cut the risk of the cancer coming back. But the study suggests that this may not be enough, and that doctors might want to study the idea of giving certain women anti-angiogenic drugs in the days before and after surgery.

Dr. Retsky and his colleagues looked specifically at breast cancer because it involved a large, deep database of patients, he said. The research has led him to believe that "over half of all relapses in breast cancer are accelerated by

surgery."

It isn't yet known which women might be most at risk for this sort of recurrence. But in studying the relapse patterns of the 1,173 women, who were treated at the Milan Cancer Institute in Italy only with surgery and then followed for 16-20 years, the researchers determined that younger women are the hardest hit by surgery-induced angiogenesis. According to the analysis, 20% of premenopausal women whose cancer had spread to their lymph nodes at the time of diagnosis relapsed within the first 10 months after surgery. This relapse rate was twice as high as that of women after menopause whose cancer had spread to the lymph nodes, indicating that surgery-induced angiogenesis may be regulated in some way by hormones.

The study also contended that this phenomenon might help explain the so-called mammography paradox for women ages 40-49 that has come up in some breast-cancer-screening studies. In some trials, women ages 40-49 who were invited to be screened died of breast cancer in greater numbers than women who weren't part of the group asked to be screened. Dr. Retsky, and his co-authors Romano Demicheli and William J.M. Hrushesky, theorize that if the women underwent mammography and had their cancers discovered earlier, they then would be treated by surgery and be at higher risk of being affected by surgery-induced angiogenesis.

The paradox theory itself is hotly disputed, with some scientists contending that it doesn't exist. "The number of cases in the early years of the screening trials are too small to permit accurate analysis," says Daniel B. Kopans, a professor at Harvard Medical School and the director of breast imaging at Massachusetts General Hospital in Boston.

The study comes at a time of increasing interest in finding ways to prevent recurrence. Other researchers also believe that angiogenesis plays a role in the process of recurrence. Michael S. O'Reilly, an assistant professor of radiation oncology and cancer biology at M.D. Anderson Cancer Center in Houston, says that animal data suggest that surgery-induced angiogenesis exists, and could be a factor in early relapse. But he said that it still wasn't clear whether the phenomenon worked the same way in every cancer, how to identify at-risk patients, or even whether surgery-induced angiogenesis was the only explanation. "It may explain the phenomenon in some patients but not all of them," Dr. O'Reilly says.

A national breast-cancer trial sponsored by the American College of Surgeons Oncology Group is examining whether treatment that alters hormone levels around the time of surgery will improve outcome and prevent recurrence. "We know that endocrine manipulations have strong effects on tumor blood vessels," says Matthew J. Ellis, director of medical oncology at Washington University School of Medicine in St. Louis, and the principal investigator of the trial.

The question of whether surgery spurs the growth of previously undetectable cancer cells has been around for decades, in part because animal data indicated a connection. Some research suggests that it is the removal of the primary tumor that acts as the trigger, with lab work in animals showing that some metastasized cancer cells don't grow on their own until a primary tumor is removed. The primary tumor may inhibit the growth of blood vessels in cancer cells elsewhere in the body, and cutting out the tumor alters that process. Researchers compared the situation in the body to a huge stew, with the removal of the tumor upsetting the balance of the different ingredients.

Another theory on how surgery jump-starts angiogenesis in a tumor involves the wound-healing process. In the 2002 Lancet study on patients with advanced colon cancer some doctors speculated that in the more-extensive surgery, a larger wound was made than with the laparoscopic surgery -- and more substances and proteins involved in healing the body were released into the blood as a result. These "growth factors" also may spur the angiogenesis process in tumors.

Harikrishna Nakshatri, a colleague of Dr. Clare in the department of surgery at Indiana University School of Medicine, developed a mouse with breast cancer that would spread to the lung only after the removal of the primary tumor. Earlier this year, blood samples from 12 mice were taken before and after the tumor was removed. Then, Dr. Clare and colleagues at the Indiana Centers for Applied Protein Sciences identified proteins that surged or decreased after surgery. Some substances dropped precipitously, suggesting that they might have played a role in stopping cancer cells from previously growing. Others that are involved in helping the body to heal wounds surged.

The next step, Dr. Clare says, is to see whether the same proteins they are seeing in mice are present also in women. "If it turns out to be true in women, we can then try to find therapies to block it," she says.