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Hormone Hazards

A new study finds even short-term use of a menopausal therapy may increase the risk of breast cancer.

By Barbara Kantrowitz
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Just 10 years ago doctors routinely recommended estrogen for women at menopause, because they believed it would lower the risk of heart disease as well as relieve symptoms, such as hot flashes. Women who had not had hysterectomies (in which the uterus is removed) also took progesterone to prevent an estrogen-fueled thickening of the uterine lining, which increases the risk of uterine cancer. (Women who have had their uteruses and ovaries removed, as a result of cancer or fibroids or other health issues, take only estrogen.) But in 2002 a major federal study, the Women's Health Initiative (WHI), was halted early because researchers found that the combination of estrogen and progesterone actually increased the risk of heart attack, stroke and blood clots. Even scarier for many women was the increased risk of breast cancer after taking estrogen and progesterone, especially after five years. Within weeks of the widely publicized announcement of these findings, millions of women threw out their pills. Since then many scientists have been looking more closely at the WHI results and conducting their own research on the effects of estrogen therapy. This week researchers from the Fred Hutchinson Cancer Research Center in Seattle are reporting that taking estrogen and progesterone for three or more years during or after menopause may result in a fourfold increase in the risk of getting lobular breast cancer, the second-most common type of the disease. In the study, published in the January issue of *Cancer Epidemiology, Biomarkers and Prevention*, researchers looked at 1,500 postmenopausal women; 1,044 had breast cancer, while 469 without cancer were a control group used for comparison. NEWSWEEK's Barbara Kantrowitz talked to the lead author of the study, Dr. Christopher Li. Excerpts:

NEWSWEEK: Many doctors currently tell patients that taking estrogen therapy for fewer than five years to relieve menopausal symptoms is reasonably safe. Do your results mean there's no safe length of time to take it?

Dr. Christopher Li: I think you have to look at the findings in context. There are different types of breast cancer. If we look at it by histology [the microscopic structure of the tissue], the most common type is ductal carcinoma. That accounts for about 70 percent of all cancers. The second-most common type is the lobular type, and that's now about 20 percent of all cancers. In this study we found that women who used the combined therapy, the estrogen plus progesterone, for three to five years had a fourfold increased risk of the lobular type. But they had no elevation in their risk of the most common type, the ductal type. That short duration of use may impact risk of the rare type of breast cancer but probably is not having any real impact on the most common type of breast cancer. In the study we also looked at use of unopposed estrogen, which is also still commonly used. There was no effect, even among women who used [only] estrogen for 10 years or longer, for any type of breast cancer, whether it was ductal or lobular. So I think women who are using that regimen could actually feel somewhat reassured. The WHI trials essentially found the same thing, that there was no elevation in risk of breast cancer for women using unopposed therapy. It is women who are using the combined therapy who really have to worry about breast cancer risk.

How concerned should women be who use the combined therapy?

The lobular cancer is challenging clinically in that it's harder to detect and treat. But at the same time it actually has a somewhat better survival rate than the ductal carcinoma. That is really because the lobular cancers are more hormonally responsive. They're more likely to be estrogen-receptor positive, so therefore they are much more amenable to some of the targeted therapies we have available, like hormonal therapies and aromatase inhibitors. It is, in a sense, a better type of breast cancer to get than the ductal type because it has a better survival rate and it is treatable. But of course it is still going to cause the same amount of anxiety and worry that any breast cancer would induce in women.

There's no way a woman starting estrogen therapy can know whether she is more likely to get one or the other kind of breast cancer.

Right. We don't know that.

So can we say who would be a good candidate for estrogen therapy and who would not be, in light of your study?

It ultimately is an individual decision. We can't really stratify and say one group of women is going to be more likely to develop breast cancer than another. We're not at the point where we can do that. One of the real problems with breast cancer is that we have a lot of risk factors that we have identified, but none of them really seem to add together in any simple mathematical way. We're stuck with all these different risk factors. A lot of them are not even modifiable, such as family history or reproductive history. Those are things women can't really change once they are postmenopausal. So I think it's a tough decision, and women have to weigh the risks and benefits. Breast cancer is certainly one of the risks. But with the WHI trials there were all sorts of other risks associated with combined therapy, and I don't think our study really changes the overall situation, which is that women should obviously talk to their doctors about this and they should use the lowest dose of hormones possible and use them for the shortest time possible. Quality-of-life issues are certainly going to be important and maybe even more important to some women than these risks of disease. It ultimately comes down to a woman's individual choice.

Since it is only the combined therapy that appears to increase risk, could progesterone be the problem?

I certainly think that progesterone is playing a very important role because of the total lack of effect on women who use unopposed estrogen. That is something that we are also trying to understand better. What is it about the progesterone that creates risk, particularly of the lobular subtype? On this study we collected all of the tumor tissues, so we're running different tests on the tumors to try and see what is correlated with hormone therapy, what markers may be associated with that. That's what we're actively working on, but we don't have the answers quite yet.

Women who use unopposed estrogen generally have had their ovaries removed or have other health issues. How does that affect the difference in risk?

Women who have had a hysterectomy, particularly an oophorectomy [in which the ovaries and sometimes the fallopian tubes are removed], will have a lower risk of breast cancer regardless of whether or not they take hormones. That is because breast cancer risk is driven by hormones produced by the ovaries. The sooner that ovarian production of hormones stops—and it would typically occur earlier in a woman who had her ovaries removed—the lower the lifetime risk of breast cancer.

Why are epidemiological studies like yours an important tool for following this and understanding risk?

The advantage of this type of study is really that we can collect very detailed information from women and we can also get tumor tissue blocks. The WHI was a big study, but it had certain limitations because it was so big. It was more expensive. They didn't collect any tumor tissue blocks in that study, so this is the first study to confirm what the actual histology was by a centralized histology review.

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Study: The Pill protects against cancer Scientists say birth control pill protects against ovarian cancer for decades

AP

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Women on the birth control pill are protected from ovarian cancer, even decades after they stop taking it, scientists said. British researchers found that women taking the pill for 15 years halved their chances of developing ovarian cancer, and that the risk remained low more than 30 years later, though protection weakened over time. The findings were published Friday in *The Lancet*.

"Not only does the pill prevent pregnancy, but in the long term, you actually get less cancer as well," said Valerie Beral, the study's lead author and director of the Cancer Research UK Epidemiology Unit at Oxford University. "It's a nice bonus." The study was paid for by Cancer Research UK and Britain's Medical Research Council.

Beral and colleagues analyzed data from 45 studies worldwide, covering 23,257 women with ovarian cancer, of whom 31 percent were on the pill. They also looked at 87,303 women without ovarian cancer, of whom 37 percent were on the pill.

In both groups, the women on the pill took it for about five years. The researchers found that in rich countries, women taking oral contraceptives for a decade were less likely to develop ovarian cancer. Without the pill, about 12 women per 1,000 are expected to get ovarian cancer before age 75. But that figure dropped to 8 women per 1,000 in those on the pill.

The experts estimated that use of the pill so far has prevented about 200,000 cases of ovarian cancer and 100,000 deaths from the disease. Based on current levels of oral contraceptive usage, they guessed that 30,000 cases could be avoided every year.

"To be able to save thousands of women's lives every year by using contraceptives is remarkable," said Dr. Beth Karlan, director of the Women's Cancer Research Institute at Cedars Sinai in California and an official with the American Society of Clinical Oncology. Karlan was not connected to the *Lancet* study.

In the West, ovarian cancer is one of the most common types of cancer in women. Older women are most at risk and survival rates are generally poor.

While the pill protects against ovarian cancer, it slightly increases the chances of breast and cervical cancer. But those risks disappear after women stop taking oral contraceptives. And

the pill also provides long-term protection against endometrial cancer, which affects the lining of the uterus.

Scientists don't know why the pill increases some cancer risks while decreasing others. "It may have something to do with the hormones in the contraceptives," said Dr. Debbie Saslow, director of breast and gynecologic cancer at the American Cancer Society. "Hormones such as estrogen can be growth-promoting in some body parts and have the opposite effect in other body parts," she said.

But because there is no early test for ovarian cancer, which is often diagnosed late with a bad prognosis, doctors say that the pill's protective effects against ovarian cancer outweigh the small increased risks of breast and cervical cancer _ unless women already have a history of those cancers.

"This is the first medication that we know of to cut ovarian cancer risk," Beral said. Other measures to protect against ovarian cancer are probably not things women would do unless they had more compelling reasons: having children or getting their tubes tied.

Still, most doctors do not suggest that women take the pill exclusively for its anticancer properties. The pill comes with side effects including risks of blood clots, migraines, and high blood pressure. Those risks are particularly elevated in women in their late 30s and in smokers.

In an editorial in *The Lancet*, experts called for better access to oral contraceptives, arguing that the drugs should now be available over the counter.

As the pill becomes more common in developing countries, experts estimate that ovarian cancer incidence will fall worldwide. In 2002, the United Nations estimated that 120 million women globally were on the pill, two-thirds of whom were in developing countries.

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