What Risk Hormones?

Conflicting studies reveal problems in pinning down breast cancer risks

By LISA SEACHRIST

Women contemplating postmenopausal hormone therapy have a right to be confused. Scientists report one week that taking hormones raises the likelihood of developing breast cancer. A few weeks later, another study indicates that they don't.

The controversy surrounding whether hormone replacement therapy (HRT) makes women more susceptible to breast cancer leaves them trying to decide for themselves whether the benefits of therapy outweigh their individual risks—which may depend on factors such as reproductive and family history. Amid the current scientific uncertainty, it's like betting all your money on a horse without knowing the odds for the race.

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Estrogen-only preparations of postmenopausal HRT undoubtedly offer substantial protection against heart disease and osteoporosis. In fact, comparing the use of estrogen-only HRT to no therapy shows that "HRT benefits outweigh the risks in terms of basic deaths from any disease," says Louise Brinton of the National Cancer Institute in Bethesda, Md.

But that protection may come at a price: Endometrial cancer is a side effect of estrogen-only therapy. What's more, estrogen-only HRT appears to increase the risk of breast cancer, especially with long-term use.

Results of a recent study indicate that adding progestin (synthetic progesterone) to estrogen protects against endometrial cancer without eliminating estrogen's beneficial cardiac effects. Scientists then wondered whether the addition of progestin would ameliorate or amplify estrogen's effect on the breast. Harvard University researchers led by Walter Willett seemed to have answered that question when they reported in the June 15 NEW ENGLAND JOURNAL OF MEDICINE that long-term use of HRT increases the risk of developing breast cancer, regardless of formulation (SN: 6/17/95, p.375).

Yet just 4 weeks later, a team led by Janet L. Stanford at the Fred Hutchinson Cancer Research Center in Seattle reported in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION that women who took the estrogen-plus-progestin formulation did not face an increased risk of breast cancer.

These conflicting reports left women even more confused about the prudence of taking HRT, whether for the rest of their lives or just a short time. For the scientific community, the wide discrepancy between the reports illustrates the difficulty of assessing moderate risk factors associated with disease and the perils of comparing very different epidemiological studies.

Unlike the case of lung cancer, which strikes smokers 10 to 20 times more often than nonsmokers, pinning down risk factors for developing breast cancer hasn't been easy. With the exception of the rare and not able *BRCA1* and *BRCA2* genes, which lead to breast cancer for 85 out of every 100 carriers, no one risk factor proclaims dire consequences.

Brinton maintains that "at best we can only explain 50 percent of all cases of breast cancer with any [identifiable] risk factors." This fact has led Willett to note that "simply being a woman in America places you at risk."

Approximately one out of every eight women in the United States will develop breast cancer during her lifetime (SN: 7/31/93, p.77). The American Cancer Society estimates that in 1995, doctors will diagnose 182,000 U.S. women and 1,400 U.S. men with breast cancer. "Quite obviously there is something different about being a women…that puts you at risk for breast cancer," says Barbara Hulka of the University of North Carolina at Chapel Hill School of Public Health.

The most obvious difference between men and women is the sex hormones coursing through their bodies. Estrogen and progesterone, the primary female hormones, stimulate breast cells to grow and divide. Studies in animals show that the two hormones spur the growth of breast cancers. And studies have found that women whose ovaries were removed early in life have markedly reduced rates of breast cancer, presumably because they lack ovarian estrogen and progesterone.

Further evidence of estrogen's involvement in breast cancer lies in the fact that early menarche and late menopause—in other words, an extended period of estrogen production—also increase risk. The known effects of estrogen and lack of estrogen on breast tissue make it plausible that extra estrogens of any kind will dramatically increase the risk of breast cancer.

"The fact of the matter is that it is surprising how little taking hormones increases the risk for breast cancer," says Hulka. While not all studies show increased breast cancer risk from either oral contraceptives or HRT, the ones that do typically gauge that risk as 1.3 to 1.7 times the "normal" chance—a number that pales in comparison to the risks seen with the *BRCA1* and *BRCA2* genes.

The Harvard team found comparably small elevations of risk in its study in June; the Hutchinson group failed to find a correlation in July. However, the two studies employed very different methods.

The Harvard group analyzed data from the Nurses Health Study, begun in 1976, in which 122,000 initially healthy women filled out detailed questionnaires about their health and health practices, including use of hormones. The team looked at only the 70,000 women who had reached menopause by 1992.

Scientists classify the Nurses Health Study as a prospective study, because all participants were in good health at the outset and researchers could watch the emergence of illnesses over time. Of the 70,000 women, roughly a third used HRT, and a third of those used a formulation that included progestin.

Using any form of HRT for more than 5 years gave women 1.3 to 1.4 times the

usual risk of developing breast cancer, the Harvard team found. Taking hormones continuously from age 55 onward would give a woman a 3 percent chance of getting breast cancer between the ages of 60 and 65, whereas a woman who chose not to receive HRT would have less than a 2 percent chance. Progestin neither increased nor decreased the risks found with estrogen therapy alone.

The Nurses Health Study found the greatest risk with current or recent HRT use. "We found that risk diminished rapidly once women stopped taking hormones," says Willett.

The phenomenon of risks that seem to dissipate over time emerges from many other analyses of exposures in the Nurses Health Study and may be a result of the way researchers gather their data, notes NCI's Brinton.

"Many people thought that the Nurses Health Study answered the question about progestin and breast cancer," says Stanford. "But that just isn't the case."

The Hutchinson group evaluated hormone use among 537 postmenopausal breast cancer patients and 492 postmenopausal controls selected at random. During personal interviews, researchers showed the women pictures of various hormone pills in order to determine exactly which HRT formulations the women used.

Because the study started with women who suffered breast cancer and compared them to healthy women of the same age, it is classified as a case-controlled retrospective study. The group found that 57.6 percent of the women with breast cancer had used HRT at some point in their lives, compared to 61 percent of the controls. As to combined estrogen-progestin HRT, 21.5 percent of women with breast cancer and 21.3 percent of controls had used such a formulation at some point.

Therefore, "it can't be said that HRT results in modest increases in breast cancer risk," says Stanford, who maintains that the evidence implicating HRT in breast cancer is equivocal.

Not all epidemiologists agree with Stanford's assessment. Ingemar Persson of the University Hospital in Uppsala, Sweden, points out that the Hutchinson group's study had so few long-term HRT users that only factors which increased risk by 2.5 times or more would show up reliably.

"What bothers me [about this study] is the fact that other known risk factors, like age at first birth, are lower than what would be expected," says Brinton. "And several large studies show a moderate increase with [HRT] use."

Hulka doesn't dispute the findings, but she points to the fact that Stanford's study was of the case-controlled type. The researchers in that group are "experts at doing case-controlled studies," says Hulka. "But I question whether it is possible to get fully accurate information from these types of studies, given how sophisticated the populace is becoming."

Hulka refers to the fact that an increasing number of people asked by researchers to participate in case-controlled studies refuse. Because there may be something different about those who respond and those who refuse, scientists can't be sure that their controls are representative of the population at large.

Another problem with case-controlled studies, although not likely with the Seattle study, is that U.S. women have heard so much about risks for breast cancer that those who have the disease are likely to overreport risks, while those without it may underreport.

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A full understanding of hormonal influences on breast cancer will take more than impeccably designed studies. Many hormone-related risk factors for breast cancer appear to "switch over" as a woman approaches menopause. For example, postmenopausal obese women have a greater chance of suffering breast cancer because their fatty tissue produces a form of estrogen. But premenopausal obese women enjoy significantly less risk of early breast cancer than their lean counterparts.

"It's just illustrative of how complicated breast cancer is with these effects crossing over, which is pretty unusual in epidemiology," says Willett.

Obesity isn't the only factor that crosses over. A woman who gives birth in her late teens or early twenties increases her risk of early breast cancer. Over time, that risk falls, becoming significantly smaller after menopause. The protective effect of pregnancy even seems to switch over in the premenopausal years: Women who have children after age 30 have greater, rather than less, overall risk of breast cancer.

"We simply don't understand much at all about the biology of breast cancer," says Brinton. "We need to associate molecular findings to the epidemiologic data to really pin down what is happening."

Meanwhile, women have to make choices about using HRT. Brinton points out that many studies have demonstrated HRT's survival advantage, but she observes also that many women are terrified of breast cancer. "It is a disease that really affects a woman's sexuality and the quality of a woman's life," she notes. She maintains that other factors, such as exercising, staying lean, and eating a healthful diet, can prevent heart disease and osteoporosis.

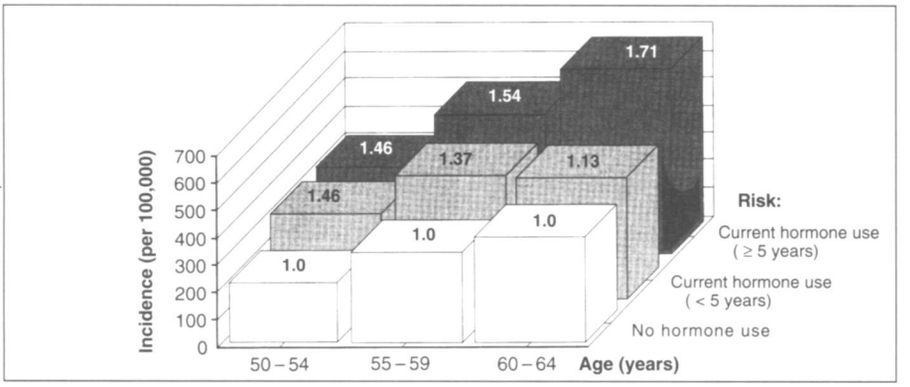
In broad terms, the women who are most likely to get breast cancer—educated, health-conscious, middle-class women who have put off childbirth—are the least likely to need lifelong HRT to prevent heart disease, Hulka points out.

But that doesn't mean these researchers disapprove of HRT. As Stanford points out, "there is no good reason to deny a woman suffering from vicious hot flashes and night sweats relief."

The case for long-term HRT isn't as clear cut. For the time being, women will have to make their decisions using current knowledge. But several large studies around the world may resolve the dilemma soon. The Women's Health Initiative, designed to examine the cardiovascular benefit of combined HRT, may deliver important breast cancer information as a by-product. The results should be in by early next century.

Some researchers are looking to treatments that will protect the breast as well as the heart. Says Willett, "I am hopeful that by the time the current generation of young women approaches menopause, we will have alternatives for them." □

Adapted from: Brinton/NEJM



Incidence and risk of breast cancer among postmenopausal women in the Nurses Health Study. Risk for women taking HRT is relative to women in their age group who have never received HRT.