EPIDEMIOLOGY

Search for a Killer: Focus Shifts From Fat to Hormones

For all the time and money invested in breast cancer studies over the past two decades, epidemiologists have made little headway in explaining the long, relentless increase in the incidence of this disease over the past 50 years. For a woman living in North America, the lifetime odds of getting breast cancer now stand at 1 in 8, double the risk of 1940. Indeed, the mystery of what lies behind the inexorable rise in risk over the past half-century seems to have deepened and grown more complex. And, to millions of women confronted by the bleak statistics and wondering how they can reduce their own chances of getting breast cancer, the mystery is unsettling.

Not all the news is grim. Researchers believe that most of the surge in breast cancer cases in the past few years is due to better detection: More intensive screening and better technologies picked up many new cases in the late 1980s that might not otherwise have been diagnosed until the early 1990s, when the tumors would have been more advanced and less treatable. And mortality rates have held almost steady over the past 20 years, even though the number of new cases has grown. Even so, breast cancer is by far the most common cancer among women and, after lung cancer, the most lethal: It kills around 46,000 U.S. women each year. The search for the culprit behind these figures is therefore intense—and urgent.

In a minority of cases, the rough location of the culprit is clear: It is lurking in the genes. Researchers have shown that a woman with a family history of breast cancer has one of the highest risks of getting the disease herself (see table). But epidemiologists have also shown beyond doubt that something other than inherited vulnerability—something in the environment—is driving cancer rates upward. They cannot say, however, what those causal factors are for more than 60% of the breast cancers they observe. Many theories have been offered recently to explain this mystery, but none has been accepted as definitive. Indeed, perhaps the biggest news is negative: A popular theory among cancer epidemiologists in the 1980s—that eating fatty foods during adulthood greatly increases breast cancer risk—seems to have bombed out, and with it may have gone one of the best hopes for stemming the rise in breast cancer through changes in lifestyle. The National Institutes of Health (NIH) is, however, funding a major study to probe further the link between diet and breast cancer. And it is launching a slew of epidemiological research on other risk factors such as exposure to toxic chemicals—especially pesticide residues—use of birth control pills, alcohol consumption, and even exposure to electromagnetic fields.

Most researchers believe that these studies will not reveal significant new risk factors, however, and they are now refocusing attention on an old suspect: hormones, especially estrogen. But there could be a sobering message coming out of this research: Increasing exposure to hormones may be partly the result of a declining age of first menstruation—something that may itself reflect improved nutrition—and a trend toward later childbirth and menopause. And if that's true, there may not be an easy way to reduce one of the major risks of breast cancer. As a result, some researchers are looking into pharmacological methods—as well as sources of estrogen in the diet—as a way of preventing and treating the disease.

A rising tide

Driving all of this interest and political attention are the grim statistics on breast cancer incidence. Ever since 1940, when Connecticut became the first U.S. state to keep good records on the number of new cases diagnosed, breast cancer rates have been increasing steadily by about 1% a year. Although it is this underlying, insidious trend that has epidemiologists baffled, much of the public concern has been caused by a more recent phenomenon—a sharp jump in the number of cases reported just in the past few years.

During the mid-1980s, the incidence shot up—some would say to "epidemic" proportions—reaching a growth rate of 4% a year by 1987. Statisticians at the National Cancer Institute (NCI) insist, however, that it isn't right to call this an epidemic. NCI analysts Barry Miller, Eric Feuer, and Benjamin Hankey say the recent increase is the predictable result of a rise in the use of x-ray machines capable of detecting small tumors. If so, this "epidemic" is a one-time bulge in reported new cases, indicating that a whole cohort of tumors was found at an earlier stage of development. If they are correct, the growth rate should return to the historical—but still unsettling—1% by the mid-1990s (see charts).

Feuer calculates that about three-quarters of the rise in the 1980s was due to the expanding use of mammography machines. He has tracked doctors' purchase orders and shown that since 1984

Risk Factors for Breast Cancer in Females

Factor	High risk	Low risk	Magnitude of differential
Age	Old	Young	•••
Country of birth	North America Northern Europe	Asia, Africa	••
Socioeconomic class	Upper	Lower	••
Marital status	Never married	Ever married	•
Place of residence	Urban	Rural	•
Place of residence	Northern U.S.	Southern U.S.	•
Race	White	Black	•
Age at first full-term pregnancy	Older than 30	Younger than 20	••
Oophorectomy	No	Yes	••
Body build, postmenopausal	Obese	Thin	••
Age at menarche	Early	Late	•
Age at menopause	Late	Early	•
Family history of premenopausal bilateral breast cancer	Yes	No	•••
History of cancer in one breast	Yes	No	•••
History of fibrocystic disease	Yes	No	••
Any first-degree relative with breast cancer	Yes	No	••
History of primary cancer in ovary or endometrium	Yes	No	••
Radiation to chest	Large doses	Minimal exposure	••

Key to magnitude of risk differential ••• = relative risk of greater than 4.0; •• = relative risk of between 2.0-4.0; • = relative risk of between 1.1 and 1.9.

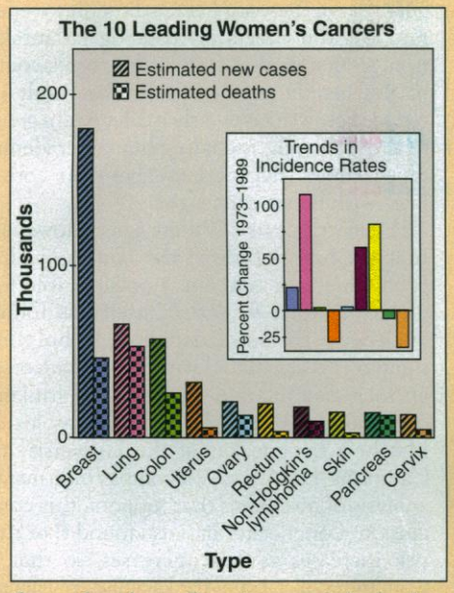
SOURCE: ADAPTED FROM KELSEY AND GAMMON, *CANCER* 20, 146 (1991).

Risk of Developing Breast Cancer

By age 25:	one in 19,608
By age 30:	one in 2,525
By age 35:	one in 622
By age 40:	one in 217
By age 45:	one in 93
By age 50:	one in 50
By age 55:	one in 33
By age 60:	one in 24
By age 65:	one in 17
By age 70:	one in 14
By age 75:	one in 11
By age 80:	one in 10
By age 85:	one in 9
Ever:	one in 8

NATIONAL CANCER INSTITUTE

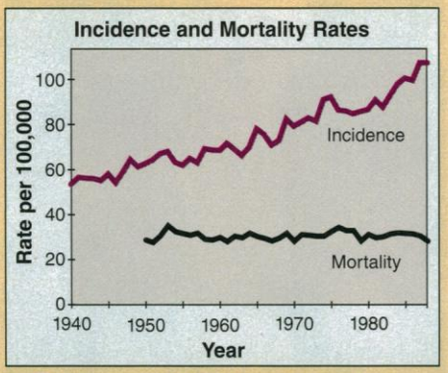
A Statistical Portrait of Breast Cancer



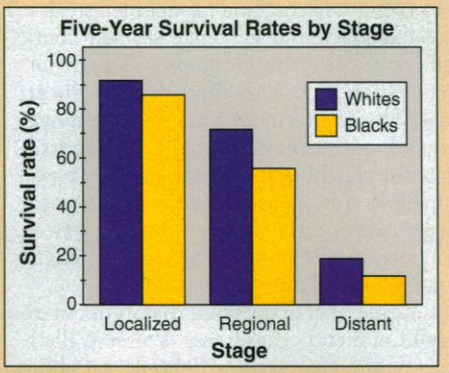
Cause for alarm. Breast cancer is by far the leading cause of cancer among women and the second biggest killer, after lung cancer. The incidence rate increased by 21% between 1973 and 1989 (inset), while that for lung cancer shot up by more than 100%. (Trends chart combines colon and rectal cancer.)

Early detection. Most of the sharp increase in incidence in the 1980s is due to detection of cancers while they are in situ (before they have invaded other breast tissue) or at Stage I. The incidence of more advanced cancers (Stage II and beyond) at the time of diagnosis has barely changed.

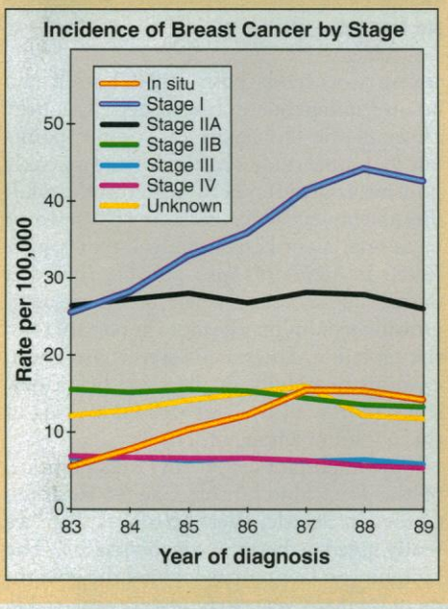
[SOURCES: CLOCKWISE FROM ABOVE: AMERICAN CANCER SOCIETY AND *(INSET)* NATIONAL CANCER INSTITUTE (NCI); NCI DATA, *NEW ENGLAND JOURNAL OF MEDICINE* **327**, 320 (1992); NCI; KESSLER *ET AL.*, *PREVENTIVE MEDICINE* **20**, 170 (1991); NCI]

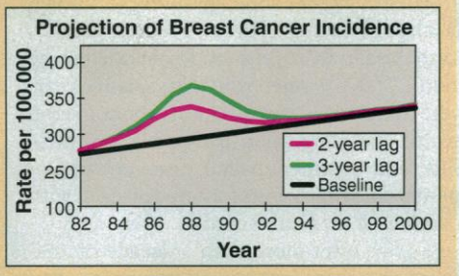


Steady increase. Data from Connecticut, which has the earliest reliable breast cancer records in the United States, show a 1% annual increase in incidence over half a century, while mortality rates have held constant. Similar trends are now evident nationwide.



Earlier the better. Survival rates are highest if the cancer has not spread to the lymph nodes when it is first detected. (Regional means evidence of spread to the lymph nodes, chest wall, or skin; distant means that tumors have been detected in other organs.)





Decade-long bulge? More intensive screening and better detection methods picked up cancers in the 1980s that would not otherwise have been diagnosed until later. A model developed by researchers at the National Cancer Institute indicates that this caused a temporary surge in the incidence rate, which should return to the long-term 1% annual increase in the 1990s. The model seems to be holding up through 1989, the latest year for which accurate figures are available. (Top line assumes detection was advanced by 3 years on average; middle line, 2 years.)

the rapid diffusion of this technology paralleled the rise in new cases of breast cancer. In addition, Miller and Feuer have shown that most of the big jump during the 1980s may reflect the increased detection of small tumors. For example, Feuer points out that the fastest growing elements of the "epidemic" are the discovery of the very earliest tumors (the "in situ" variety that have not yet invaded surrounding breast tissue) and the smallest ones (less than 2 cm in diameter). The incidence of large tumors (more than 3 cm) has actually declined since 1982. More important, NCI statisticians note that the incidence of new cases declined slightly in 1988 and 1989—the last year for which accurate records are available—which is consistent with the claim that intensive screening in the mid-1980s caught breast cancer cases that otherwise would have been diagnosed later. And yet, this analysis isn't satisfying because there's a lot it doesn't explain—like the death rate.

If the mammography boom sent case numbers upward in the 1980s, says Feuer, "we should start to see some declines in mortality" very soon, as women are treated and cured at an earlier stage. "But we haven't seen much movement as yet," Feuer notes. Deaths from breast cancer have remained steady at 27 per 100,000 women for decades. Says Feuer: "We are anxiously awaiting positive declines in mortality." There's a lag between diagnosis of cancer and death, and Feuer thinks it may take as long as 5 years for the benefits of mammography to show up in a declining death rate. Thus, 1992 and 1993 will be critical test years for the NCI theory.

The NCI experts concede, however, that their analysis applies only to recent trends—only to 3% of the 4% rise in breast cancer incidence. It does not explain why incidence has been increasing steadily since Connecticut began tracking the trends a half-century ago. And it does not explain why this underlying trend is expected to continue in the years ahead.

High-fat, high-risk?

The hunt for environmental causes of breast cancer has kept scientists well employed since the 1960s. Fourteen years ago, epidemiologists seemed ready to nab one of the chief villains behind the decades-long rise in incidence. They were on the verge—they thought—of discovering why women in North America and Europe have a risk of

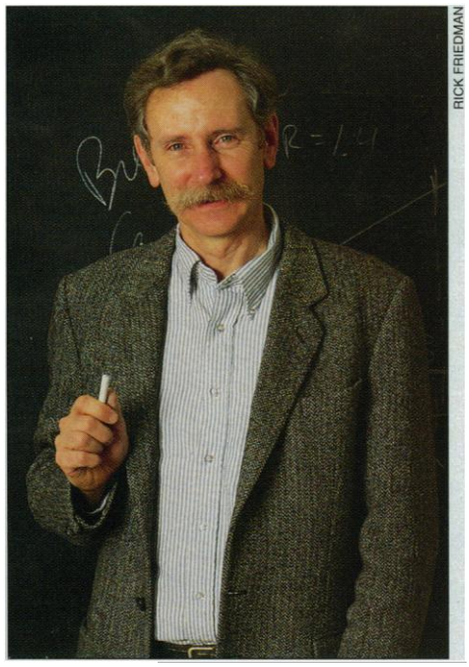
getting the disease that is five times higher than that faced by women in Asia and less industrialized areas. The leading suspect was the fatty American diet: burgers, french fries, potato chips, bacon, and fat-marbled steaks. The circumstantial evidence seemed compelling because the geography of high fat diets matches up with that of high cancer rates. This is true even when women move from a low-risk environment like Japan to a high-risk area like North America. The newcomers to a high-risk zone show increased breast cancer rates in a generation or two, demonstrating that something in the environment stimulates the disease.

One member of the posse that went out in pursuit of dietary causes was Walter Willett of Harvard University's School of Public Health. In 1978, he says, he was determined to "nail down" once and for all the case against the high-fat diet. Willett was one of many in this field, but he had a major advantage: access to data from the largest and best-controlled survey ever done on this topic, known as the Harvard Nurses Health Study. Launched in 1976, the study included more than 120,000 women who in successive years were asked to answer questions about overall health, smoking, diet, use of birth control pills, and postmenopausal estrogen supplements. Epidemiologists followed up each with a review of medical records.

Today, after more than a decade of analyzing the responses to questionnaires and comparing them with medical histories, Willett concludes that the evidence for the fat hypothesis just isn't there. Not only can he find no association between fat in the adult diet and breast cancer, but he believes that women on an extreme high-fat diet (nearly 50% energy intake as fat) are at little or no more risk than those who adhere to an extremely lean diet (less than 29% fat). This result is all the more credible because Willett did find a clear association between fatty diets and colon cancer, suggesting that the data on fat consumption are at least reliable enough to pick up this effect. But the fat/breast cancer hypothesis—widely taken as gospel in the 1980s—seems to have lost its punch.

The Nurses Health Study was not the first to raise questions, says Louise Brinton, an environmental epidemiologist at NCI. In the late 1980s, she and her colleagues at NCI ran a large prospective study that led to conclusions similar to Willett's. But the results made few headlines—perhaps because no one wanted to hear the message that a promising avenue of research was turning into a blind alley, and perhaps because it swam against the "medically politically correct" idea that fat is bad. But that view is gaining acceptance today, largely because Willett is so emphatic and his data are hard to fault.

This doesn't mean the debate has ended. On the contrary, the dietary fat theory has strong proponents both in NCI itself and among independent researchers. Geoffrey Howe of the University of Toronto points out that some studies have detected a weakly positive association between fat in the adult diet and breast cancer, including Howe's own meta-analysis of 12 case control studies, published in 1990. It's also possible that diet during adolescence, when breast tissue is growing rapidly, may be more important than the adult diet. This potential risk hasn't been examined carefully in the past, but a new study sponsored by NCI will be looking at this question, among others.


RICK FRIEDMAN

No fat factor. Walter Willett.

The important lesson, says Ross Prentice, of the Fred Hutchinson Cancer Research Center in Seattle, Washington, is that "we really need a better type of study." The Hutchinson Center has lobbied the government for many years to fund a clinical trial in which women would be randomly assigned either to a low-fat or normal diet group and tracked for a period long enough to detect a difference in cancer rates. NIH recently agreed to fund such a study as part of its Women's Health Initiative, selecting the Hutchinson Center as the coordinator. Many clinicians and epidemiologists doubt that even this more aggressive approach will produce any definitive results on breast cancer, however. One reason for skepticism: Studies that did find fat intake to have an effect on breast cancer found the increased risk to be quite small—around 35%. Furthermore, as Willett points out, the multiple goals of the study—women will be asked to eat certain vegetables as well as cut back on fat—could muddy the results.

One diet hypothesis that hasn't been examined carefully is the possibility that ultra low-fat diets (20% or less) could have a beneficial effect not provided by low-fat diets. Experiments with lab animals show that severely restricting fat intake reduces the incidence of mammary tumors. But Willett argues that in these studies it's difficult to separate out the effects of reducing fat intake from reducing calorie intake. He thinks some of the benefit may really be the result of reduced growth rates early in life. And a great deal of research, including human epidemiology, shows that total energy intake correlates with breast cancer risk.

Even critics like Willett agree, however, that the null finding of the Nurses Health Study does not rule out a possible role for dietary factors. Willett himself has found evidence in the nurses data that alcohol consumption is associated with breast cancer—an increased relative risk for daily drinkers over nondrinkers of 40%. Epidemiologist Matthew Longnecker of the University of California, Los Angeles, is completing a meta-analysis of 36 studies that supports this conclusion. Longnecker has also found that the risk increases as dose increases, so that a woman having three drinks a day appears to have almost twice the risk of one who has two drinks a day. But Longnecker warns that the data are not in uniform agreement. And even if alcohol proves to be risky, it won't be an important factor for most women. And Willett concludes: "I fundamentally think we are not going to be able to find any lifestyle factor that we are going to be able to modify easily—or even with difficulty—that will have a large impact on risk...."

An old suspect returns

With the high-fat thesis in decline, epidemiologists are retracing their steps, as Willett says, and "we've come back to what we already knew" long ago. What they knew was that the timing of and exposure to two natural hormones—estrogen and progesterone—play a large part in determining breast cancer risk. This insight, gained over many decades, was crystallized in studies published in the 1970s by another Harvard epidemiologist, Brian MacMahon. This work identified a woman's age of first menstruation (menarche), the age of menopause, and the age of first childbirth as critical risk points. Early menarche and late menopause independently increase the likelihood of having breast cancer, while an early first child (in the teens or early twenties) reduces it. A woman who gives birth before age 20 has half or less the risk of one who waits until after age 30.

The thread that runs through these findings is the body's natural pattern of hormone production. Beginning at menarche and continuing until menopause, a woman experiences a sharply rising and falling exposure, first to estrogen, and then to progesterone, in a repeating 4-week ovulation cycle. This cycling stops during pregnancy, when hormones

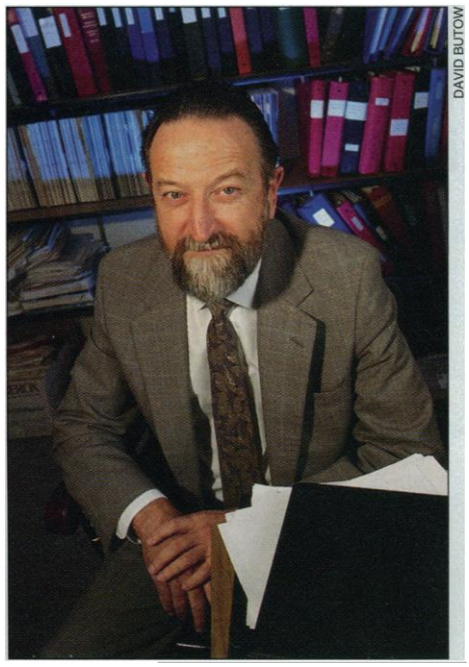
climb to high but steady levels. Because estrogen stimulates cells in the breast tissue, it has long been thought that a woman's total exposure to estrogen may be a key indicator of breast cancer risk, and that hormonal factors may explain some of the puzzling international disparities in risk. Recent research suggests that cell proliferation itself may increase the risk of cancer—by increasing the number of mutant (cancer) cells—and it has led some scientists to focus on estrogen and progesterone exposure as the most important environmental risk for most women.

An ardent proponent of this view is Malcolm Pike, a former Oxford University statistician now doing epidemiological and clinical research at the University of Southern California (USC) School of Medicine. Pike was puzzling over the studies of breast cancer several years ago, he explains, when his 15-year-old daughter took him to task, saying, "It isn't enough to study it, Daddy. You've got to do something." Today, he and his colleagues at USC are running a clinical trial. Their goal: to lower the breast cancer risks for 14 women patients by using synthetic drugs to directly reduce their natural estrogen exposure.

The idea behind the experiment—based on both old and new data—is that estrogen exposure should be kept to a minimum. It was known long ago, for example, that women who have their ovaries removed early in life, and are therefore exposed to vastly less estrogen than other women, rarely have breast cancer. This reduction in risk associated with late menarche and early menopause is probably due to the fact that one delays exposure to estrogen and the other ends it earlier. In addition, a recently published study by Anders Ekbom of the University of Uppsala, Sweden, indicates that even prebirth exposure to estrogen can affect a person's chances of getting breast cancer. Ekbom found that the offspring of women who suffered during pregnancy from a syndrome called pre-eclampsia (associated with low estrogen) were significantly less likely to have breast cancer than normal controls.

Studies of obesity have come up with related, though complex, results. Young women who are overweight have a slightly lower risk of breast cancer than others, but women who are overweight after menopause have a slightly higher risk. Why? The logical answer, according to Pike and his USC colleagues Brian Henderson, Ronald Ross, and Darcy Spicer, is that since it's known that young obese women tend to ovulate less frequently, they have lower estrogen levels and are probably at less risk for that reason. Yet body fat itself produces estrogen, so that after menopause, when hormones generated by the ovulatory cycle decline, excess body fat may grow more important.

These innate biological facts, and not fat consumption, Willett suggests, may be the keys to the different risk levels found in the United States and in nations like China. And the differences are provocative. For reasons not fully understood, Chinese women reach menarche on average at age 17, while U.S. women do so at 12.8 years. But 200 years ago, North American women were like the Chinese, reaching menarche at 17. Could the long-term shrinkage of childhood in the United States, the increased exposure to estrogen, and the rising breast cancer rates all be related? And could they all be the result of improved nutrition? Yes, they very well could, say Willett, Pike, and other epidemiologists.


DAVID BUTOW

Focus on hormones. Malcolm Pike.

Many new studies on hormones, in Pike's view, tend to support the estrogen-risk theory. For example, Graham Colditz, a colleague of Willett's at Harvard who also relies on the Nurses Health Study data, has come up with evidence of hormone-related effects based on the use of synthetic drugs—for example, those used in estrogen replacement therapy (ERT) for postmenopausal women. The data show that current users of ERT pills (which supply estrogen artificially) have a slightly higher relative risk for breast cancer (40% greater) than women who have never used such pills. The risk drops off rapidly after use of ERT ceases. Studies of birth control pills have produced conflicting data, but the consensus appears to be that pill users have a modest relative risk of getting breast cancer (50%) while they are on the pill, but that it drops away once they quit.

Pregnancy reveals the full complexity of the role played by estrogen and progesterone in governing cell behavior. According to Pike, laboratory studies have shown that when such hormones are given to animals at moderate levels, they stimulate tissue growth. But when given at high doses (as in pregnancy), they actually cause cells to differentiate into new forms—and that breast tissue becomes more resistant to the stimulative effects of estrogen. It has taken a while to figure out what's going on during pregnancy, says Pike, but this is how it seems to work: Early pregnancy transforms breast cells so that fewer are susceptible to the harmful effects of estrogen. This lowers a woman's lifetime risk of breast cancer. Yet recent epidemiological research shows that pregnancy also slightly increases risk over a short period for some women. This may be the result of the initial, stimulative effect of rising estrogen levels on undifferentiated cells. This effect fades with the passage of time.

Pike and colleagues are so confident that this interpretation is right that they have begun "anti-estrogen therapy" for women who have a high risk of breast cancer—injecting a peptide that stops hormone production by the ovary. They then add back a small amount of synthetic hormone by pill to keep the women healthy. It's a drastic approach whose long-term effects are unknown and which perhaps few women would choose to follow.

Although it is still experimental, the underlying concept of blocking the effects of estrogen in healthy women has received partial endorsement in a much larger trial funded by NCI. This trial will focus on tamoxifen, a nonsteroid that binds to and blocks estrogen receptors, so that a woman's own estrogen cannot stimulate growth in the tumor cells. Interest in tamoxifen arose from experimental cancer therapy, which showed that the drug improved the prospects for women who had already been diagnosed with breast cancer. The new project, however, will give tamoxifen to women who have never had cancer but are likely to benefit from preventive therapy because they have very high risks of getting cancer.

To the extent it's possible to see a trend emerging in the 1990s, this anti-estrogen strategy appears to be the leading contender. As Willett says, even vastly superior epidemiological studies of environmental risk factors are likely to "leave us with an unresolved problem," because the environmental aspects of life that promote breast cancer are not readily changeable. He tends to agree with Pike that, "in the end, I think we're going to have to go to some pharmacological fix." There may be some reluctance to support such experiments, because people feel they are "unnatural." But, he observes, "our whole lifestyle is unnatural."

For now, women have little choice but to rely on intensive screening to detect tumors quickly, and to hope that biologists studying the molecular changes that turn healthy breast cells into cancers will come up with better indicators of the earliest stages of the disease—and, that, before long, they will find methods of preventing breast cancer.

–Eliot Marshall