The Birth of a Breast Cancer

Do adult diseases start in the womb?

By KATHLEEN FACKELMANN

Epidemiologist Dimitrios Trichopoulos, puzzling over why women develop breast cancer, focused on various factors before homing in on a chemical that appeared to operate in a surprising environment many years earlier.

That chemical is the natural hormone estrogen, which may have set the stage for cancer while the women were still in the womb, says Trichopoulos of the Harvard School of Public Health in Boston.

Invasive breast cancer strikes about 180,000 women in the United States each year. It is the most common cancer among U.S. women. Known risk factors, such as a family history of the disease, early menarche, or a first live birth after age 30, account for only a small portion of cases. What's behind the high frequency of this disease in the U.S. population?

Over the years, scientists have blamed and exonerated many factors, including a high-fat diet and abortion, but none has proved the central villain in the story of breast cancer.

New research is drawing attention to the beginning of a woman's life. Trichopoulos and others now believe that some factor within the uterus programs fetal cells for the development of cancer decades later.

"It is a provocative hypothesis—one that needs to be explored further," comments Louise A. Brinton, chief of the environmental epidemiology branch of the National Cancer Institute in Bethesda, Md.

Breast cancer is not the only disease scientists think may be linked to the intrauterine environment. A spate of recent reports suggests that conditions in the womb may play a role in the risk of prostate cancer, heart disease, diabetes, high blood pressure, and other chronic diseases. Such ailments don't appear until the fifth, sixth, or even seventh decade of life.

In the 1980s, Trichopoulos had been trying to figure out why, despite advances in treatment, breast cancer continued to cut a wide swath among U.S. women.

He knew that cells, including mammary cells, face the highest risk of cancer before they become specialized for a specific function. Once a breast cell is specialized for, say, milk production, it is relatively resistant to cancer. Yet some breast cells remain largely immature until puberty or even a woman's first pregnancy. While other researchers looked for the genesis of breast cancer in the teenage years or during a first pregnancy, Trichopoulos went back even further—to the immature breast cells of the fetus.

Trichopoulos also knew that the female sex hormone estrogen fuels the growth of breast cells. Rapidly dividing cells are at greater risk of genetic error, which can lead to cancer. Indeed, some researchers believe that postmenopausal women who take estrogen alone, rather than a combination of hormones, face a higher-than-average risk of breast cancer.

Putting these two ideas together in the April 21, 1990 LANCET, Trichopoulos suggested that high concentrations of estrogen circulating in a mother's womb may increase her daughter's subsequent risk of getting breast cancer.

"If it turns out to be right, it will be an important advance, " Trichopoulos says. "We feel confident that something is happening during the perinatal period."

He is the first to admit that many questions remain about estrogen's role in the womb. Moreover, the hormone is just one of many players that could influence the mammary cells of the fetus, he says.

The first empirical data supporting his theory hit the press 2 years after he proposed it. In the Oct. 24, 1992 LANCET, Trichopoulos, Anders Ekbom, Hans-Olov Adami, both at Uppsala University in Sweden, and their colleagues reported that women who had weighed 8 pounds or more at birth had a 30 percent greater risk of breast cancer later in life (SN: 10/31/92, p. 293).

Other research has suggested that women with higher-than-average concentrations of estrogen in their blood during pregnancy give birth to heavier babies. Because the Swedish study was small, the link between breast cancer and weight at birth could have been due to chance.

To follow up on that intriguing lead, Trichopoulos, Karin B. Michels, also at the Harvard School of Public Health, and their colleagues decided to mine the information being collected in the Nurses' Health Study I and II. In these studies, established in 1976 and 1986, respectively, researchers ask U.S. registered nurses once every 2 years a series of questions related to breast cancer risk. They also note each time that one of the nurses receives a diagnosis of breast cancer.

Trichopoulos knew from his earlier work that a newborn's weight might foretell breast cancer risk. To explore this statistic further, his team decided to contact each nurse's mother. Some of the mothers had died or developed dementia by the time their daughters got breast cancer, but the researchers did manage to find more than 2,000 women who told them how much their daughters weighed at birth.

To check the mothers' recall, the team verified as many weights as possible by studying birth certificates. Their findings confirmed that the mothers remembered accurately.

The researchers found that being scrawny at birth was protective—at least as far as breast cancer is concerned. The risk of this cancer for women who had weighed 5.5 pounds or less at birth was less than half of the risk faced by women who had tipped the delivery scales at more than 8 pounds.

Even when the researchers accounted for several established risk factors, the protective effect of low birthweight remained. They detailed their findings in the Dec. 7, 1996 LANCET.

"This is the first paper to show a statistically significant association with birthweight," comments Lars Vatten at the University Medical Centre in Trondheim, Norway. Vatten wrote an editorial in the same issue.

The finding that skinny babies are shielded from breast cancer is consistent with the theory that estrogen underlies the cancer risk. However, Michels cautions, "there is no proof" of a link between estrogen exposure in the womb and breast cancer risk.

Vatten's editorial says it would be pre-

mature to jump to any conclusions about what's causing that risk. "These compelling results suggest that prenatal life is another window through which the nature of breast cancer should be seen," he says.

More evidence on the dawn of breast cancer comes from a study in the Jan. 1 JOURNAL OF THE NATIONAL CANCER INSTITUTE. Trichopoulos, along with Ekbom, Adami, and other colleagues, had an advantage in conducting the study in Sweden. They could look at pregnancy data on women who had given birth at five hospitals from 1874 through 1961.

The researchers sent abstractors out to page through dusty volumes of notes handwritten by Swedish midwives, who had recorded problems during pregnancy and labor as well as the weight of newborns.

Data like these avoid a common research problem—the selective memory of participants who have already learned of an illness, Adami says.

The researchers obtained birth records for 1,068 women who had developed breast cancer. They compared those women to 2,727 women of the same age who did not get this cancer.

Statistical analysis revealed a sharply reduced risk of breast cancer among women whose mothers had developed a pregnancy-induced high blood pressure called toxemia. Such women showed nearly a 60 percent decrease in breast cancer risk. (Trichopoulos' team had reported a 75 percent reduction in risk associated with toxemia in its 1992 report.)

Research suggests that toxemia of pregnancy results in low concentrations of estrogen. The disorder involves many perturbations in hormone balance, however, and remains poorly understood, Adami points out. An unknown factor could provide the shield against breast cancer.

The team did discover that women who had suffered from jaundice as newborns later had an increased incidence of breast cancer. Jaundice occurs when a newborn's immature liver can't keep up with the production of bilirubin, the orange pigment in bile. A few studies have found that jaundiced babies have high concentrations of estrogen in their bloodstream—hence the breast cancer risk, or so the theory goes.

The Swedish study also found that women who were born prematurely (before the 33rd week of gestation) faced an increased threat of breast cancer later in life. Earlier research had suggested that extremely premature infants may have been exposed to high estrogen concentrations in the uterus.

"We have now recognized that the intrauterine environment plays a role [in breast cancer]," Trichopoulos says. Researchers don't know whether estrogen is the culprit, though. Insulinlike growth factor, another substance that spurs cells to divide, has also been mentioned as a risk for breast cancer.

"Estrogen is a natural suspect," Ekbom says. "Is it the exposure of interest? We don't know."

Even proponents of this theory admit that the mechanism behind it remains pure speculation. It could be that high concentrations of estrogen mutate DNA in the mammary cells of the fetus, but the damage doesn't result in an outright tumor until many years later.

Alternatively, high concentrations of estrogen in the womb could prime breast cells to react excessively to the changes of puberty, resulting in cancer.

Hormones circulating in the womb may ready some fetal cells for the development of breast cancer decades later.

The traditional risk factors for breast cancer are often viewed as virtually immutable. A woman can't do anything about her family history, for example. Although women who bear many children at a young age have a lower risk of breast cancer than those who never have children or those who have a small family later in life, women are unlikely to change their family planning choices to lower their risk of breast cancer.

At first glance, the new research might seem to add to this dismal outlook by indicating that the risk of getting breast cancer is fixed at birth.

Researchers disagree with this view. "We know that breast cancer is a multifactorial disease," Brinton says. "Lots of things can influence your risk."

Women can focus on lifestyle factors, she says. Those who stay fit and limit their consumption of alcoholic beverages may gain some protection against breast cancer, according to Brinton. Public health officials recommend monthly self-examination of the breasts for all women and annual mammograms for women over 50; the need for yearly mammograms between ages 40 and 49 remains controversial.

For public health researchers, the appeal of an intrauterine risk factor is that it exerts its effect over a relatively short period of time. If unusually high concentrations of estrogen are found to underlie breast cancer risk, researchers could focus on finding ways that pregnant women could reduce the hormone in their bloodstream. The beauty of such an approach is that it would require intervention for just the 9 months of pregnancy—a time when most women are motivated to give their baby a healthy start, Adami says.

Additional studies may help elucidate the mechanisms of breast cancer. In the next 5 years, an animal model of the human intrauterine environment during pregnancy will probably be developed, Ekbom says. Researchers could administer high doses of estrogen to such an animal. If its offspring develop mammary tumors, it would add credence to the idea that estrogen is the culprit in the development of breast cancer, he says.

Such research may help scientists understand what causes other cancers as well. Ekbom, Adami, Trichopoulos, and their colleagues have studied cancer of the prostate, a walnut-sized gland that surrounds the male urethra. Prostate cancer kills more than 41,000 men in the United States each year, yet researchers have very few clues to its origins.

They do know that hormones fuel the growth of prostate tumors. In the Aug. 10, 1996 BRITISH MEDICAL JOURNAL, the trio discovered that men whose mothers had suffered from toxemia during pregnancy had a reduced risk of getting prostate cancer. The team also noted a trend toward hefty male babies having a greater risk of prostate cancer later in life.

Both of those findings hint that some factor in the womb may prime prostate cells for cancer in the future. Is that factor estrogen? "We generally believe that prostate [cancer] is related to hormones, but the role of estrogen in prostate cancer is unclear," Adami says.

Researchers have uncovered intrauterine ties to other diseases as well. For example, a report in the Dec. 15, 1996 CIRCULATION suggests that weight at birth can influence the risk of developing several adult diseases. High birthweight correlates with an increased risk of obesity. Low birthweight has been linked to high risk of hypertension and diabetes. A study in the Nov. 30, 1996 LANCET shows high birthweight associated with lower risk of heart disease.

Taken together, such findings suggest that life in the womb may contain glimmerings of diseases that appear to strike in middle age and beyond. Many researchers now hope that the factors operating during pregnancy can be altered.

For breast cancer, that hope is something to hold onto in a field littered with grim statistics. "We do not have many other options in terms of preventing breast cancer," Adami says. □