

# Motherhood and Cancer

## Can hormones protect against breast and other cancers?

By KATHY A. FACKELMANN

**M**alcolm C. Pike proposes an unorthodox theory of breast cancer. "The cause of most female cancers in this country at the current time is incessant ovulation," Pike told researchers attending a conference on cancer prevention held in Boston this September.

Pike blames the epidemic rates of breast and other female cancers on a fact of modern life: The average American woman starts menstruating at age 12 and typically gives birth to one or two infants. Pike estimates she will ovulate a whopping 450 times during her lifetime. By contrast, a woman who lived 200 years ago would have started menstruating at age 17 and would have delivered and breast-fed about eight babies. That history suggests our foremothers ovulated fewer than 150 times during their lives.

What does a woman's reproductive history have to do with breast cancer and other malignancies afflicting women? Plenty, according to Pike. He argues that pregnancy and lactation provide a crucial resting period for the ovaries, the female sex glands that produce not only eggs, but also several powerful hormones, including estrogen and progesterone.

Each month, a woman's body readies itself for pregnancy. The ovaries secrete estrogen and progesterone, which tell the breast cells to begin dividing in preparation for milk production. In years past, women went through this cycle less frequently because they were more often either pregnant or breast-feeding. Today, more women are chronically exposed to powerful hormones that tell breast and other body cells to proliferate—a fact that may increase the risk of breast cancer

and other cancers as well.

Nobody's suggesting that women go back to delivering scores of children. Indeed, Pike believes that technology can confer the breast cancer protection that multiple pregnancies provided in the past.

At the Boston conference, which was sponsored by the General Motors Cancer Research Foundation and the Harvard School of Public Health, Pike presented preliminary results of a hormonal regimen designed to stave off breast cancer and to protect against cancers of the endometrium, ovaries, and cervix. So far, Pike and his team at the University of Southern California School of Medicine in Los Angeles have given the experimental treatment to 14 women who are at high risk of developing breast cancer.

At the same meeting, Walter C. Willett of the Harvard School of Public Health presented data from the ongoing Nurses' Health Study, which includes a prospective study of diet, lifestyle, and breast cancer risk factors in more than 89,000 nurses. Contrary to widely accepted theory, the findings suggest that dietary intake of fat and fiber do not play a major role in the development of breast cancer. Willett's group published their report in the Oct. 21 *JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION* (SN: 10/24/92, p.276).

"Basically, we have a disease [breast cancer] that is out of control," Willett

says, noting that one of every eight women in the United States will suffer breast cancer at some time during her life. The Nurses' Health Study findings dashed hopes that a relatively simple dietary intervention could significantly reduce a woman's risk of breast cancer, Willett says. Thus, he believes Pike's approach, although controversial, deserves attention.

"I think there's very little question that [Pike's] approach can reduce breast cancer. Whether it can be done in a way that will ultimately be safe and acceptable remains to be seen," Willett told *SCIENCE NEWS*.

**P**ike and his colleagues began their quest to prevent breast cancer with the knowledge that oral contraceptives help protect women from ovarian cancer. Indeed, a review article that culled data from 20 studies published between 1970 and 1991 demonstrates that women who use oral contraceptives for five years or more show



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nearly 50 percent reduction in their risk of ovarian cancer. That article appears in the October OBSTETRICS AND GYNECOLOGY.

Birth control pills typically consist of synthetic estrogens and progesterone. They prevent conception by suppressing ovulation, the monthly release of an egg from an ovary. When an egg pops out, it disrupts the surface of the ovary, stimulating ovarian cells to divide and repair the surface. By stopping ovulation, the pill discourages that cell proliferation and thus helps lower a woman's chance of developing ovarian cancer, Pike notes.

However, the pill's protective effects vanish when it comes to the breast. Scientists know that estrogen and progesterone together spur breast cells to divide. In fact, Pike argues that oral contraceptives may slightly increase the risk of breast cancer, a contention disputed by a number of other researchers.

Pike and his colleagues took on the tricky task of trying to reduce that risk and prevent pregnancy at the same time. They knew they had to stop ovulation, but they couldn't rely on breast-stimulating hormones, such as estrogen and progesterone. They therefore turned to a synthetic version of another naturally produced substance, called gonadotropin-releasing hormone agonist. This drug prevents ovulation and thus reduces the production of estrogen and progesterone.

The hormone agonist gave the Los Angeles researchers an effective means of blocking ovulation, but it went too far: It reduced the ovarian production of estrogen and progesterone to levels that could cause other health problems, such as bone loss. In an attempt to counter such ill effects, Pike and his colleagues designed a regimen that added back small amounts of estrogen and a synthetic progesterone-like drug.

The 14 women who volunteered for the pilot trial take a complex brew of hormones. They receive a monthly injection of gonadotropin-releasing hormone agonist and a low-dose estrogen pill for 24 out of 28 days in each cycle. Every fourth month, they also receive a synthetic progesterone pill for 13 days, adds Pike's colleague Darcy Spicer, who is also at the University of Southern California School of Medicine.

Although the regimen is difficult to follow, the recruits say the method provides them with some unexpected benefits. For example, the women get a menstrual period once every four months. That means they experience any premenstrual symptoms such as cramps, bloating, or mood changes only three times a year, Pike says.

**D**espite the researchers' attempts to minimize side effects, the women using this experimental birth control method do suffer bone loss. For comparison purposes, Pike's team has carefully monitored seven women who are not using contraceptives of any sort. Compared with women in this control group, women in the experimental group are losing about 2 percent of their bone density per year. "And that's too much," Pike says, adding that the study has revealed no other side effects.

To address the problem of bone loss, the researchers are now adding another bone-stimulating hormone to the treatment.

On average, the women have been on the regimen for about a year, Pike notes. The study is a pilot trial designed to make sure the regimen is safe, not to prove that the method can reduce a woman's risk of breast cancer, he cautions. However, scientists know that when surgeons remove a woman's ovaries, her risk of breast cancer is reduced. In effect, the hormonal soup is a reversible form of such surgery.

The researchers suspect that the treatment will cut a woman's risk of breast cancer dramatically. "We estimate that

the regimen could reduce lifelong breast cancer risk by 30 percent if used for five years and by about 50 percent if used for 10 years," Pike says. However, he and Spicer admit that much larger, long-term studies are needed. If the pilot trial proves the regimen does no harm, they plan to embark on a large-scale study of women at high risk of breast cancer.

In the future, Pike believes, the breast-cancer-detering effects of this regimen may also benefit women who do not run a high risk of developing the disease. Spicer agrees, noting that women in the general population who take oral contraceptives may very well switch to the new method if it proves safe and if researchers can make it easier to use.

Pike suggests an even more radical idea. Scientists have long noticed that many women who get pregnant in their teens seem to have a built-in defense against breast cancer later in life. They believe that the hormonal changes during and after such an early pregnancy may alter a woman's breast tissue, shielding it from malignancies. Pike speculates that physicians might someday reduce a young woman's lifelong breast cancer risk by giving her a hormonal regimen of

## *Pregnancy protection for brain cancer?*

Reproductive cancers aren't the only cancers with ties to motherhood. According to a surprising new report, women who have given birth appear to have greater protection against brain cancer than women who have not.

This is the first time scientists have discovered a link between a woman's reproductive history and brain cancer, says epidemiologist Kenneth P. Cantor of the National Cancer Institute in Bethesda, Md. He presented his data in September at the annual meeting of the American College of Epidemiology, held in Bethesda.

Cantor and his colleagues weren't even looking at the question of hormones and pregnancy. In fact, their original study was designed to look for a link between drinking water and cancers at various body sites. However, the information collected during the study offered them the chance to examine other potential risk factors for cancer, including that of parity, or number of childbirths.

The team focused on 1,075 women who had been diagnosed with cancer of the brain, colon, rectum, pancreas, or kidney and 833 cancer-free women who served as a control group. The researchers mailed a survey form to each woman in the study, asking questions about childbearing history.

After adjustments for age and other factors related to the development of cancer, statistical analysis revealed that women who had given birth were slightly less than half as likely to develop brain cancer as women who had never given birth. Although the number of pregnancies did not influence the risk of brain cancer, the researchers noted that women who had delivered a child before age 20 were less likely to develop brain cancer than older mothers.

Cantor says his group's research confirmed other findings suggesting that motherhood protects against colon cancer as well. However, their data revealed no significant link between parity and cancers of the rectum, pancreas, or kidney, he told SCIENCE NEWS.

The new findings, although preliminary, suggest that sex hormones play a role in shielding mothers from brain cancer, Cantor says. He notes that brain tissue contains receptors for certain sex hormones that fluctuate dramatically during and after a pregnancy.

The association between brain cancer and parity needs further confirmation, Cantor cautions, adding that his group's analysis was not really designed to study the role of hormones in the development of cancer.

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contraceptives designed to mimic a first pregnancy.

**T**he Los Angeles researchers have a long way to go before they can answer the scientific, practical, and ethical questions raised by their speculations, warns Robert N. Hoover of the National Cancer Institute in Bethesda, Md.

That caution is echoed by Helene Smith of the Geraldine Brush Cancer Research Institute in San Francisco.

She especially takes issue with the concept of a hormonally induced pseudo-pregnancy for teenage women. "Nobody is real comfortable with the idea of taking healthy young women and doing something drastic to them," she says. Such an approach might trigger morning sickness and other unpleasant side effects associated with pregnancy, she notes. "I wouldn't be willing to do that to my 13-year-old daughter, would you?"

For the high-risk adult woman, however, the risk-benefit equation might look quite different, Smith acknowledges. Pike's cancer-protection method might appeal to such women, who have very few means of reducing their chances of developing this deadly disease, she says.

Other scientists doubt the approach will ever win widespread acceptance. Women are unlikely to put up with such a complex regimen, says Gabriel Bialy, chief of the contraceptive development branch of the National Institute of Child Health and Human Development in Bethesda, Md. Doctors often have trouble getting their patients to follow relatively simple drug regimens, yet Pike's method involves a once-a-month injection as well as several different types of pills taken at various times, he says. Indeed, Pike plans to simplify the regimen, perhaps by delivering all the drugs together in a single injection.

Furthermore, Bialy says, the birth control method would rack up quite a bill. The complexity of the method, together with its cost, would make large-scale clinical trials difficult, if not impossible, he says. "The hypothesis, while reasonable on the surface, is terribly difficult to support with actual data," he contends.

Everyone agrees that women will have to wait a long time for research findings to catch up with the theory. Even if the researchers can generate enough support to kick off a large clinical trial, it will take at least a decade to gather enough information to evaluate the regimen's prowess against breast cancer.

No doubt about it: The approach is radical. Yet breast cancer is too important a disease for scientists to ignore this intriguing lead, says Willett.

"The problem is so serious," he argues, "that we should pursue anything that is at all promising." □

*Continued from p.297*

can also monitor the motion of stars at the core of certain more distant neighbors, such as NGC 3115, because the black holes believed to reside there rank among the biggest of the current candidates.

In the mid-1980s, while studying the far more luminous core of another galaxy, NGC 1068, Dressler stumbled onto evidence that nondescript Andromeda might harbor a black hole. Although NGC 1068 seemed like a prime candidate for containing a compact object, Dressler's observations turned the tables on his prediction.

"I took the spectrum of [Andromeda] merely as a calibration, to make sure I knew what the center of a galaxy looks like where there *wasn't* a black hole," recalls Dressler. "I didn't see anything special in NGC 1068, but I saw this amazingly rapid rotation of stars [at the core of Andromeda]." In a separate study, Kormendy also found evidence that a supermassive black hole could best explain the motion of stars at Andromeda's core. Dressler and Kormendy say they consider the core of Andromeda the most likely candidate for a black hole.

According to Kormendy, the galaxy NGC 3115 ranks second in the black hole sweepstakes. Located some 30 million light-years from Earth, this neighboring galaxy has a dense cluster of stars — within a few hundred light-years of the center — that rotates rapidly about the core. Observations with the Canada-France-Hawaii telescope atop Mauna Kea show that the motion is so fast that the mass of the visible stars can't explain it — not by a long shot.

Although the apparent runner-up as far as kinematic evidence goes, NGC 3115 appears to be the heavyweight champ among the leading black hole contenders, with a mass more than a billion times that of the sun. Kormendy and Douglas O. Richstone of the University of Michigan at Ann Arbor reported their work in the July 10 *ASTROPHYSICAL JOURNAL*.

Andromeda's tiny satellite M32 garners third place among galaxies most likely to contain a black hole, Kormendy suggests. Again, the discovery was made by serendipity. John L. Tonry of the Massachusetts Institute of Technology examined the general character of this small spherical galaxy, believed to be the remnant of a larger galaxy that was stripped of material by the gravitational tug of Andromeda.

His 1987 study revealed stars moving so rapidly that the mass of visible stars estimated to lie at the galaxy's core couldn't explain their motion. In addition to the spectroscopic evidence, recent Hubble images have revealed that the core of M32 emits an unusually high intensity of starlight, indicating that the tiny galaxy may harbor a black hole about

3 million times the mass of the sun (SN: 4/18/92, p.245).

Dressler notes that, aside from Andromeda's large central bulge, the galaxy appears "kind of common, kind of dull." Thus, "if Andromeda, the closest spiral galaxy to us . . . has a black hole, then it does imply that a black hole is probably in every galaxy with a big spheroidal bulge," including the Milky Way (see sidebar, p.296).

Dressler suggests that some of these bulging galaxies — those with the most massive cores — once shone with the blinding light of quasars, the most brilliant objects observed. Other galaxies, such as Andromeda, lacked the extraordinary brilliance associated with quasars but did possess highly luminous cores. In either case, when the central fireworks burned out, they left behind the superdense bodies that gave them their energy. He estimates that up to half the galaxies in the universe may harbor supermassive black holes.

Ironically, he adds, researchers shy away from galaxies with highly energetic cores, some of the most likely places to look for supermassive black holes. Instead, they prefer to hunt their quarry among some of the *least* active galaxies — provided the galaxies have a central bulge. Galaxies with quiet cores, notes Dressler, don't spew out jets of material that can outshine starlight and confound measurements of stellar motion.

**I**f Andromeda, its satellite, and NGC 3115 rank among the likeliest candidates for housing black holes, what would it take for astronomers to obtain compelling proof?

Because the radius of a supermassive black hole is no bigger than the solar system, the ability to watch stars begin to fall toward such an object — even in a nearby galaxy — would require a telescope a million times sharper than now exists, Kormendy notes. Lacking such an instrument, astronomers had looked to Hubble to gather more convincing proof. Indeed, Dressler notes, Andromeda and its satellite were prime targets for spectroscopic studies with Hubble.

"We thought we'd actually go in and nail them [as having central black holes], getting that extra factor of 10 in resolution that would eliminate any other contrived explanation," Dressler says.

Such studies will probably have to wait until astronauts correct Hubble's optics late next year. But over the next several years, Kormendy says, ground-based telescopes atop such choice viewing sites as Hawaii's Mauna Kea may nearly match a repaired Hubble.

Until then, contends Alexei V. Filippenko of the University of California, Berkeley, "extragalactic black holes will remain like Darth Vader, cloaked in a shroud of circumstantial evidence." □