What All Women Dread

Women fear breast cancer more than any other disease. Although miracle cures may not be in sight, there are a number of innovative research approaches

Ursula Goldmann-Posch discovered the lump in her breast in early summer. It was a small, hard knot directly over her heart. We do not have any breast cancer in the family, the journalist thought. And everything was fine in her last routine control. So she went to her physician, had an ultrasound examination and also a mammogram. A histological test confirmed the presence of a carcinoma slightly less than three centimeters in size. In the hours after the diagnosis she sensed a deathly inner silence. “Never in my life have I felt so helpless – like a lamb being led to the slaughtering block,” she said.

PHOTO: FOCUS

Breast cancer is the most common type of cancer among women in North America and Europe. Every year about one million new cases will be diagnosed. Of all kinds of tumors, breast cancer is the most common cause of death in women between the ages of 45 and 55.

After the initial shock subsided, Goldmann-Posch was determined to fight against the disease. "I'm not the type to bury my head in the sand like an ostrich," she said. "I started looking into all the latest developments in breast cancer research." She had to face the fact that there still is no miracle weapon to cure the disease. But researchers are making more and more progress in the fight against cancer. They are testing active substances with which physicians hope to overcome one major problem: the various tricks cancer cells use to resist chemotherapy.

After surgery, chemotherapy is still one of the most important weapons against cancer. This weapon is often rendered ineffective because the tumor cells become insensitive to the chemotherapeutics in the course of the treatment. Physicians especially dread multidrug resistance, in which many popular medicines fail to work. This may soon change. Researchers at Schering AG are currently testing a new active substance that will once again make resistant cancer cells susceptible to cytostatic agents.

The molecule with the name MS-209 blocks a mechanism that plays a central role in producing resistances: the P-glycoprotein (PGP) pump. It is located in the cell membrane and consists of one protein molecule, the PGP. The molecule functions like a waste collection system for the cell: it pumps out toxins that have entered the cell and thus makes the chemotherapy ineffective. An excessive amount of these PGP molecules is found on the surface of many cancer cells.

The new active substance called MS-209 blocks this detoxification process. It occu-

pies the binding part of the pump and thus prevents the medication from being washed out of the cell. "The efficacy of MS-209 has already been proved on cell lines and in animal models," explains Dr. Barbara Putz, an expert for Clinical Development at Schering AG. "After administering the active substance together with a chemotherapeutic agent, the originally resistant tumors once again responded to treatment," reports the scientist.

Schering AG's researchers in Japan are now testing the active substance on patients. "We are treating 227 women with metastatic breast cancer, in which the tumor cells show an excess of PGP proteins," explains Wakao Sato, who is supervising the study. One group of women is having the standard chemotherapy, while the second group is receiving MS-209 as well. Whether the new active substance actually meets the high expectations will remain to be seen until after the study has been concluded. With the help of such novel approaches, researchers hope to be able to better adapt the chemotherapy to the tumor of the patient.

In another field, immunotherapy, experts have made progress in developing individually adapted breast cancer treatment. One outstanding example of this approach is the active substance trastuzumab that has been used with success for years in treating metastatic breast cancer. The genetically engineered antibody binds to certain proteins on the surface of the tumor cells called Her2 receptors. There can be ten to one hundred times more Her2 proteins on cancer cells than on normal body cells. If the receptors are blocked by the antibody, the cancer stops growing – at least temporarily. Therapy with trastuzumab attacks only those tumors whose cells carry too many Her2 receptors on their surface, which is the case in about one quarter of all affected women.

"I was not prepared for cancer, but it wasn't prepared for me either."
Ursula Goldmann-Posch, Journalist, Augsburg

Cancer researchers are not only setting their hopes on new drugs. Well-proven medicines can also have surprising potential. Take, for example, Schering AG's active substance, clodronate, which belongs to the bisphosphonate family. These compounds have been used in breast cancer patients with bone metastases for nearly 20 years. They reduce the accompanying symptoms of the metastases, such as the increased brittleness of the bones. New studies now show that clodronate may be able to inhibit the formation of metastases.

In the field of immunotherapy experts have made progress in developing individual treatment

Bone metastases occur in about one in five breast cancer patients. The presence of cancer cells in the bones results in a loss of bone substance. Consequently, patients suffer from painful bones, and the risk of fracture also increases. Bone resorption can also lead to a dangerous excess of calcium in the blood. "Clodronate reduces the symptoms," says Christian Lardot, International Marketing Manager at Schering Oy in Finland, a subsidiary of Schering AG. Studies also show that the active substance can apparently delay further growth of the metastases. "Clodronate can not only improve the patients' quality of life, it can also have a favorable effect on survival time," stresses the expert.

A large-scale study now shows that taking clodronate can also benefit women without metastases. A total of 1,069 women suffering from breast cancer without metastases participated in the study, coordinated by the Royal Marsden Hospital, Sutton, England. Half of them were treated preventively with clodronate for two years; the other half received a placebo. "Only 12 of the women who were treated with clodronate developed bone metastases during the trial period; in the placebo group this figure was 28," says Professor Trevor J. Powles, who supervised the study.

Another study conducted earlier by the cancer researcher Professor Ingo J. Diel at the University of Heidelberg showed similar results. Here, too,

PHOTOS: M. SANDMANN/SCHERING AG; FOCUS

fewer metastases developed in the bones and other organs of patients treated with clodronate compared with the women in the control group. The women in the clodronate group also lived longer. This was particularly true in the case of women who already had cancer cells in their bone marrow and thus have a higher risk of a relapse. Additional studies will investigate this potential.

In the meantime, Ursula Goldmann-Posch has learned to live with her cancer – "increasingly without fear," she adds. She has since written a book to help deal with the emotions caused by the disease. "The Lump over My Heart," was published four years after she was diagnosed with cancer. She uses her newly gained inner strength to help other women. "More women die from breast cancer in Germany than in other European countries, which is also due to the deplorable state of affairs in the German medical system," comments Goldmann-Posch. Clinical research in Germany lags behind that in other countries because, among other reasons, the government does not invest enough money in patient studies. "Most research funds for clinical cancer studies come from the often unjustly blamed pharmaceutical industry," says the journalist.

Goldmann-Posch also criticizes that research results take such a long time to be put into practice. In addition, many physicians and clinics are not very willing to cooperate, says the 54-year-old. "They are all researching and treating patients on their own – very often to the disadvantage of patients." To promote the development of patient-friendly research, the journalist together with other women and committed scientists founded the "mamazone" and "PA.T.H." initiatives in Germany.

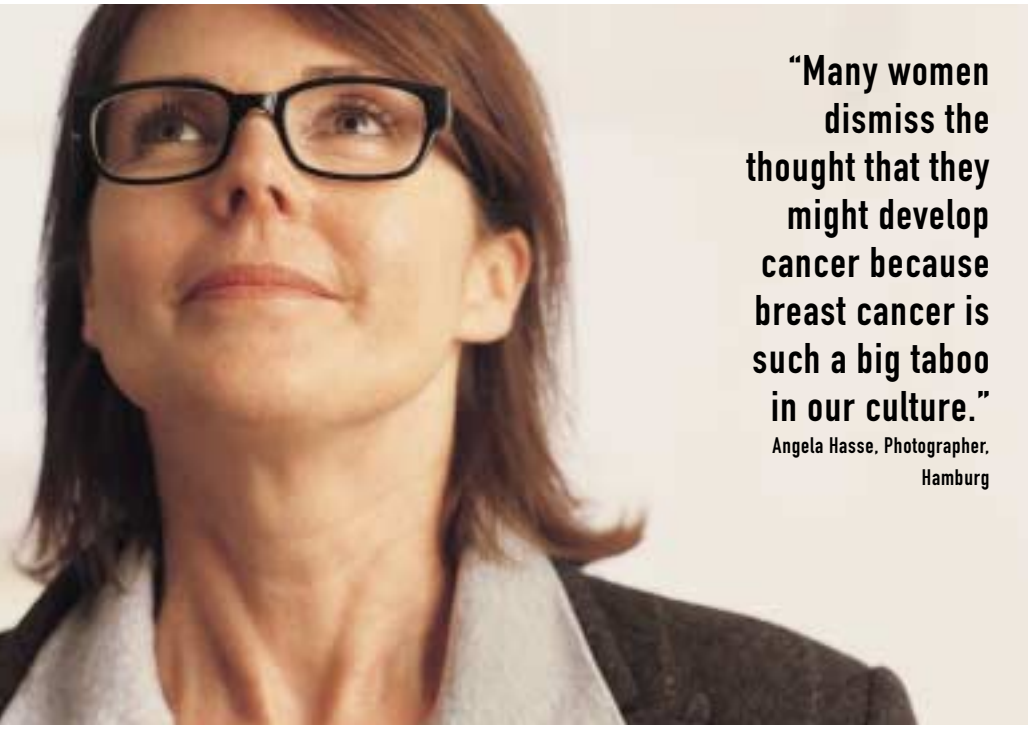
Excessive alcohol or certain gene mutations have been proved to increase the risk of breast cancer

Women with breast cancer in the United States have achieved a lot more than their fellow sufferers in Germany by publicly lobbying politicians and scientists. The sum that the U.S. government invests in breast cancer research increased in the 1990s from 90 to 700 million dollars. In the meantime it is common practice for patients to have a say in the planning of clinical trials. "This is due, in particular, to the commitment of patient organizations like the National Breast Cancer Coalition," stresses the New York journalist Laney Katz Becker. The journalist has also had personal experience with breast cancer. The mother of two children was 38 years old when she was diagnosed with cancer. "I never thought that I would be affected," says the now 45-year-old. "I don't smoke or drink, I eat plenty of broccoli and exercise regularly." But leading a healthy life is clearly not enough to protect yourself against breast cancer, says Becker.

Of course, the risk of cancer can be reduced by a healthy life. And vice versa, women who drink excessive amounts of alcohol have a clearly higher incidence of breast cancer. Researchers know that there are other causes of the disease. For example, some women have a genetic predisposition because of a mutation of their BRCA1 or BRCA2 genes. In these cases, the disease has often already affected close relatives. But this does not mean that all carriers of these genes will inevitably develop the disease.

The female sexual hormones – and especially estrogen – can also influence the risk. Women who began to menstruate before the age of 12 and enter menopause later in life have a higher incidence of breast cancer – presumably because they have been exposed longer to the ups and downs of the sexual hormones of the menstrual cycle. For similar reasons, women who have children after the age of 30 or who remain childless face a higher risk of breast cancer.

Physicians have long made use of estrogen dependence for the therapy of breast cancer. In the case of hormone-sensitive breast tumors, they prescribe so-called antiestrogens, preparations such as tamoxifene, which block the effect of estrogen in the body. However,



"Many women dismiss the thought that they might develop cancer because breast cancer is such a big taboo in our culture."

Angela Hasse, Photographer, Hamburg

these medications have side effects. They increase, for example, the risk of uterine cancer. Researchers at Schering AG are, therefore, testing new active substances that will take effect more selectively and persistently than conventional antiestrogens. "The estrogen-receptor destabilizers are especially promising," reports Dr. Jens Hoffmann, a researcher in Experimental Oncology at Schering AG. Substances that block the effect of the sexual hormone progesterone are also being tested, says Hoffmann.

Like Ursula Goldmann-Posch, Laney Katz Becker also found writing about her illness to be very liberating and comforting. In her novel "Dear Stranger, Dearest Friend" Becker tells the story of two women with breast cancer who meet through a self-help group on the Net. The reader only discovers that the author herself had had breast cancer in the epilogue. "I wanted to write a novel and not the autobiography of a survivor of breast cancer," says Becker. "It is the only way to reach healthy women who are not affected by breast cancer."

With her book of photographs entitled "Nine Women and I," Angela Hasse also wants to reach healthy women. The photographer from Hamburg was lucky: she too underwent surgery because of suspected cancer. But the lump discovered in her breast turned out to be harmless. Nonetheless, she will never forget the time she spent waiting for the diagnosis. "Four long weeks of fear and a feeling of helplessness," describes the 49-year-old. The subject totally consumed her. Then one day she had the idea to produce a book about women affected by breast cancer. One thing is very important for Hasse: she wants to encourage more women to go to their physician to enable early diagnosis.

"Leading a healthy life is not enough to protect yourself against breast cancer."
Laney Katz Becker, Journalist, New York

"Many women dismiss the thought that they might develop cancer because breast cancer is such a big taboo in our culture," says Hasse. With her book of photographs she would like to show that even after breast cancer surgery, women can feel good about their bodies and enjoy their femininity. "Illness is just as much a part of our life as eroticism," it says provokingly in the commentary to the photos of the women. "I was very impressed by the power and love of life these women radiated during the interviews for the book," says Hasse.

If a tumor is recognized in time, the chances of being able to cure the patients are 90 percent

At the same time the photographer wants to draw attention to the possibilities offered by early diagnostic methods such as mammography and ultrasound examinations. "If a tumor is recognized in time, the chances of curing the patient's disease are 90 percent," it says in the epilogue to the book. And with a mammogram it is possible to detect tumors at a stage when they still cannot be felt by hand. Women over the age of 40, in particular, benefit from having regular mammograms – if they are performed as part of highly professional screening programs. Eight international studies over recent decades have come to this conclusion. One important example showing the benefits of screenings is the Netherlands, where breast cancer deaths dropped by 30 percent after a quality-controlled screening was introduced in 1990. The Dutch mass examinations fulfilled the strict European Mammography Screening Guidelines: every mammogram is taken at one of the certified breast centers and evaluated by two specially trained physicians.

Despite all these successes, mammography still has some drawbacks. It is estimated that 15 percent of all malignant changes are not recognized. On the other hand, false alarms because of an inaccurately positive diagnosis are also common. In addition, this method does not provide reliable results for younger women because the X-rays do not sufficiently penetrate the dense network of glands in the mammary tissue.

Sonography (ultrasound) and magnetic resonance imaging (MRI) with a contrast agent are the most important examinations to supplement X-ray mammography. MRI is

PHOTOS: M.KENTZ, FOCUS

a highly sensitive method that up to now has primarily been used when mammograms or ultrasound images have produced unclear results. But it is also useful to help rule out additional tumors after a carcinoma has been identified, for example before surgery. Due to its high sensitivity, MRI is also suitable for early recognition examinations in women who have a particularly high hereditary risk for breast cancer.

A new process called optical mammography is currently being tested at the Robert Rössle Clinic in Berlin together with researchers from Schering AG. In this method the breast is examined using so-called near-infrared light. This term refers to light produced by a laser with wavelengths of between 700 and 900 nanometers, i.e. in the range between visible light and infrared light. "Light of this type penetrates up to 8 centimeters into body tissue," explains Dr. Volker Hoffmann, a radiologist working in the Diagnostics and Radiopharmaceuticals business area of Schering AG.

After passing through the tissue, the rays are collected by countless light-sensitive detectors, digitalized and processed in a computer. "In this way it is also possible to produce three-dimensional images," says Hoffmann.

Optical mammography has two crucial advantages compared with X-ray mammography. First, it is fully harmless for the patients and can thus be repeated as often as desired. Second, near-infrared light is able to penetrate the glandular density of mammary tissue, which means this method can be used on younger women. Optical mammography is thus being researched worldwide with great interest. "But studies with patients so far have been disappointing. It has only been possible to detect relatively large tumors," reports Hoffmann. The reason for this is the poor resolution of the images because of the strong diffusion of the near-infrared light in the tissue.

A vision for the future: molecular imaging will identify tumors at the earliest possible stage

Researchers at Schering AG hope to solve this problem by using so-called fluorescent dyes, which are injected into the patient before the examination. Hoffmann: "We assume that the dye will be distributed throughout the entire breast but will be eliminated from tumor tissue much slower than from healthy tissue." The difference can be utilized for diagnostics. If the near-infrared light strikes the dye left primarily in the tumor, the molecules of the dye will send out fluorescent light. "In the images the tumor will shine brightly against the dark healthy tissue," explains Hoffmann. Schering AG's researchers have since succeeded in further developing a promising substance for the dye.

"Animal experiments and tests with human tissue samples show that the use of the novel dye considerably improves the quality of the method," reports Dr. Kai Licha, who is working on the development of the fluorescent dyes at Schering AG. According to the scientists, even small tumors were easily detected in the images. In a study now launched, the new substance will be used in an optical mammography system produced by the U.S. company Imaging Diagnostic Systems. Researchers at the Robert Rössle Clinic are testing optical mammography on around 70 patients in this study, whereby the method will also be compared with X-ray mammography and ultrasound examinations. "We want to determine in which fields optical mammography can supplement diagnostic methods already available," explains Dr. Thomas Moesta, who is supervising the study at the clinic. For example, this technology could be used to clarify suspicious findings from mammography or ultrasound examinations. "We may be able to spare many women from having to undergo unnecessary biopsies," says Moesta, who expects to have the first results from this study by the end of 2003.

But many researchers see the biggest potential for optical imaging in molecular imaging – imaging with target-specific contrast agents. "In this method a fluorescent dye is coupled to a target-searching molecule, for instance an antibody," explains Dr. Michael Schirner, who works in Diagnostics & Radiopharmaceuticals at Schering AG. The antibodies bind only to very specific molecules – for example the proteins located on the surface of cancer cells. "With the help of molecular imaging, it may be possible one day to diagnose tumors at the earliest stage possible," says the researcher enthusiastically and adds, "Diagnosing cancer at an early stage is the best way to cure it."

Ursula Goldmann-Posch does not know whether she is totally cured as yet, but she has not had a relapse so far. For the moment, the German journalist has concluded a kind of standstill agreement with her cancer. "I was not prepared for cancer, but it wasn't prepared for me either."

Franziska Beckmann

Quick links

Patients' Tumorbank of Hope (PA.T.H.)
www.pa-t-h.org

National Cancer Institute (NCI)
www.cancernet.nci.nih.gov

American Cancer Society
www.cancer.org

National Breast Cancer Coalition
www.natlbcc.org