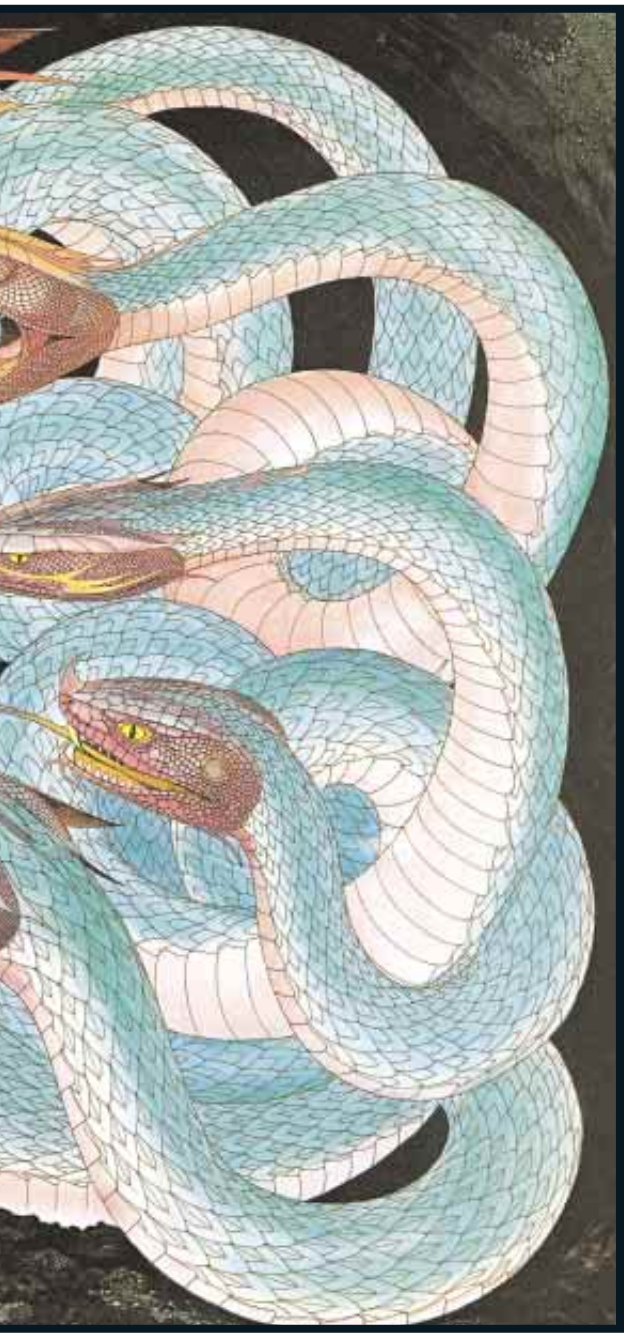
stopping C

EARLY INTERVENTION MAY PREVENT CANCER FROM BECOMING INEVITABLE WITH AGE

HERCULEAN TASK: Fighting cancer can be like trying to kill the Hydra, which grew back two heads when one was severed.

GIOVANNI CASELLI, REPRINTED BY PERMISSION OF EUROBOOK LTD.

ancer before it starts



BY KEN HOWARD

To a degree, we are all ticking time bombs. As we eat, sleep, think and work, our cells divide again and again. Randomly over time, occasional bad copies are created. Meanwhile external insults such as tobacco smoke trigger other mutations. Most of the sinister cells are too crippled to survive, but some do. And sometimes they undergo further aberrations. When enough mutations have occurred, the result can be cancer.

"We are all walking around with millions of premalignant cells," explains Robert A. Weinberg, professor of biology at the Massachusetts Institute of Technology's Whitehead Institute. "If we live long enough, we'll all come down with one form of cancer or another."

After decades of research, scientists are getting a more complete picture of cancer. Most cancers do not suddenly spring up and run wild. They develop over many years, as a result of biochemical and genetic changes that push healthy cells into a precancerous state and later into cancer. This greater understanding is now prompting researchers to find drugs that can intervene early in the process, rather than be resigned to battling cells that have already become malignant.

In the short term, this "chemoprevention" strategy will probably involve chemical compounds that retard the proliferation of cancer cells in patients who have had cancer surgery, chemotherapy or radiation, buying them more years of life. In the longer term, it is hoped that these agents can slow, stop or even reverse precancerous cells from developing into the full-blown disease. Ultimately, drugs would prevent normal cells from even starting down the path to malignancy.

At the same time, researchers are trying to develop cellular imaging tests that would indicate mutations early in the precancer stage, giving far more advance notice of potential trouble than do current screening tests such as PSAs, which indicate the likelihood of prostate cancer. If such early indicators proved reliable, they could be used throughout life, and at the first signs of trouble a chemoprevention strategy could be set in motion.

Because the road to cancer often takes place over 20 years or more, it is a disease skewed toward old age. Cancer is rare among children. The median age of a U.S. cancer patient is 70, according to the National Cancer Institute. The odds of getting cancer after age 60 are 16 times greater than before age 40, according to the National Cancer Institute.

Although we all carry around mutated cells, it fortunately takes a number of mutations acting in concert to create problems. Michael B. Sporn, professor of pharmacology and medicine at Dartmouth Medical School,

the progression toward cancerous cells

Cells don't "switch" from normal to cancerous. Over time, biochemical and genetic changes may cause cells to advance gradually in a process of carcinogenesis from normal

TOMO NARASHIMA

suggests we think of our body "as a knit sweater with 100 fibers going along the *x* axis and 100 fibers along the *y* axis. If you have one tear, you still have a functional sweater. But if you get enough tears, it's no longer a functional unit. The nature of carcinogenesis is one of increasing disorganization."

The number of tears any individual sustains in a lifetime depends on an overwhelming number of variables, from inherited genes to diet, environment and lifestyle. But the time lag between the early stages of the process that leads to cancer, called carcinogenesis, and full-blown cancer gives scientists a window of opportunity to stop or at least slow the process before cancer emerges. Recent trials indicate that certain chemicals can indeed interrupt the steady progression from normal to carcinogenic cells.

Don't Wait

Cancer chemoprevention research is 10 to 15 years behind cancer treatment research, but the field is evolving, says David S. Alberts, director for cancer prevention at the Arizona Cancer Center in Tucson. "We have a lot of work to do, but it makes more sense to treat precancerous lesions than to wait for people to develop cancer."

The idea of prevention was demonstrated in practice in 1998, when a historic study with a drug called tamoxifen demonstrated that agents could be introduced into patients to prevent cancer from occurring. The Breast Cancer Prevention Trial (BCPT) of 13,388 women at increased risk for breast cancer showed a 49 percent reduction in breast cancer risk for women taking tamoxifen versus a placebo. The result was so dramatic that researchers identified those subjects taking the placebo before the trial ended, so they could begin taking the drug.

"The study proves for the first time that you can decrease women's chances of getting breast cancer by taking a pill," says Therese B. Bevers, medical director of the M. D. Anderson Cancer Prevention Center in Houston. Soon after the results were announced, the Food and Drug Administration approved tamoxifen as the first drug that can be prescribed to reduce the risk of a cancer.

Tamoxifen is far from perfect, however. The trial linked it with an increased risk for endometrial cancer and pulmonary embolisms. Over the next 10 years, tamoxifen will be compared with another drug, raloxifene, which is used for treating osteoporosis. During an osteoporosis trial, it was observed that women on raloxifene had a 76 percent decrease in risk for invasive breast cancer, but there was no corresponding increase in risk for endometrial cancer. The Study of Tamoxifen and Raloxifene (STAR) has already begun to enroll 22,000 postmenopausal women and will follow their progress over five years.

The trial may offer clinical corroboration in humans of cancer prevention seen in animal studies. Tamoxifen and raloxifene are known as selective estrogen receptor modulators (SERMs)—chemicals that block estrogen reception in some tissues while mimicking the hormone's effect in others. Animal studies have shown that the use of two SERM agents with different mechanisms of action—in these cases, fenretinide and tamoxifen—can suppress cells' advancement from precancer to cancer.

Developing a Preventive Arsenal

Discovering a prevention pill for any one cancer will nonetheless prove difficult. In breast cancer, for instance, a variety of mechanisms are implicated, and there are various types of breast cancer that respond differently to hormones such as estrogen. "Cancer is not one disease but hundreds of diseases," emphasizes Steven K. Clinton, program leader for cancer prevention and control at the Ohio State University Comprehensive Cancer Center.

Many cancers, however, harm similar tissues in the body, such as the epithelial tissue that lines all internal organs. "Over half of cancer deaths in adults are epithelial, including cancers of the lung, breast, prostate and colon," says Dartmouth's Sporn. "From what we know, you have to have a lot of mutations—a series of multiple hits—to lead to cancer." Because the hits accumulate with age, intervening early could prevent our cellular sweater from sustaining too many tears as we get older and older.

The approach, then, in designing drugs to thwart carcinogenesis is to take aim at various points in the process where mutations may occur. One target is drugs that limit the damage from substances that can cause cell mutations, such as tobacco smoke, environmental pollutants

to precancerous to cancerous. Today's treatments attack only the last stages. The goal is to detect this growth earlier and intervene.

Invasive carcinoma **Metastasis**

and anything toxic we may eat—from nitrosamines in bacon to pesticide residue in fruits and vegetables. Another target is to stop random genetic miscopies from going further down the road toward cancer. A third target is to intercept "free radicals"—errant oxygen molecules released during normal cellular metabolism that can damage cells and possibly trigger genetic mutations. Antioxidants currently under study include selenium, beta-carotene and vitamin E.

Some unusual cases of cancer may provide opportunities to test the chemoprevention strategy. For example, people with the inherited disease familial adenomatous polyposis (FAP)—about 1 percent of colon cancer patients—are at very high risk for colon cancer. They are born with a mutation in their *Apc* gene, a tumor-suppressant gene whose main job is to prevent cancer cells from multiplying uncontrollably. It leads to "lots of polyps in the colon, and 100 percent of the patients then develop colorectal cancer at a young age," explains Waun Ki Hong, professor of medicine at the M. D. Anderson Cancer Center. The current standard of care is prophylactic removal of the colon. But recent understanding of the carcinogenesis of colon cancer indicates possible additional forms of treatment. Preliminary data suggest that two anti-inflammatory drugs, sulindac and celecoxib (Celebrex), may reduce the number of polyps in FAP patients enrolled in clinical trials. But the long-term efficacy is uncertain. Clinical trial data on sulindac indicate that polyps regress while such drugs are administered but may recur afterward, according to Robert J. Mayer, director of the center for gastrointestinal oncology at the Dana-Farber Cancer Institute in Boston.

It is still unknown whether Celebrex would reduce cancer in the general population, and even if it did, the drug may have potentially adverse side effects, perhaps on other organs. Investigators have already begun to look at a broader group of patients, those with sporadic adenoma polyps, of whom 30 percent will have additional polyps after three years. If the drug is deemed beneficial and safe after a three-year trial, researchers might move to larger populations at less of a risk.

Future Prevention Trials

The design of trials for larger populations will be aided by better understanding of specific carcinogenesis pathways. Work on the Human Genome Project may contribute through the identification of genes that may fos-

reduce your risk of cancer

Most cancers stem from an accumulation of genetic faults and exposure to environmental hazards and carcinogens over time. Preventive strategies, such as not smoking and good diet, can reduce cancer risk, but don't be lured by fads or pills that can purportedly "prevent" or "cure" cancer. "There are a lot of people who promote substances in health food stores and supermarkets," says Steven K. Clinton, program leader for cancer prevention and control at the Ohio State University Comprehensive Cancer Center. "These people are entrepreneurs and not scientists. They are selling $50 bags of garbage."

For those of us who'd like to do something reputable to perhaps increase our odds of escaping cancer, here is the accepted medical wisdom, according to "7 Ways to Prevent Cancer," by the Harvard Center for Cancer Prevention at the Harvard School of Public Health.

You can further improve your cancer defenses by knowing your family's history of cancer and getting recommended screening tests at appropriate ages [*see box on next page*].

1. Eat a healthy diet. Make fruits and vegetables part of every meal. Opt for chicken, fish or beans instead of red meat. Choose foods like pasta, brown rice and whole wheat bread. *Lowers risk of cancers of the prostate, breast, lung, colon, rectum, stomach and pancreas.*

2. Get at least 30 minutes of physical activity every day. Many activities count: walking, jogging, dancing. Any activity is better than none. *Lowers risk of colon cancer and may lower risk of breast cancer.*

3. Drink no more than one alcoholic drink a day. One drink is a glass of wine, a bottle of beer or a shot of liquor. *Lowers risk of cancers of the breast, colon, rectum, mouth, throat and esophagus.*

4. Maintain a healthy weight. *Lowers risk of cancers of the colon, rectum, uterus and breast.*

5. Don't smoke. This includes cigarettes, pipes, cigars and chewing tobacco. *Lowers risk of cancers of the lung, throat, pancreas, kidney, bladder, cervix, prostate, colon and rectum.*

6. Protect yourself from sunburn. Stay out of direct sunlight between 10 A.M. and 4 P.M., the peak burning hours. Use hats, long-sleeved shirts, and sunscreens rated SPF 15 or higher. Do not use sunlamps or tanning booths. *Lowers risk of skin cancer.*

7. Follow safe sex practices. *Some sexually transmitted infections are linked to cancers of the cervix, vagina, anus and liver.* —*K.H.*

early cancer detection

The American Cancer Society recommends the following tests to maximize early detection of cancer, thereby improving the chances for effective treatment.

GENERAL

A cancer-related checkup is recommended every three years for people aged 20 to 40, every year for ages 40 and older. Depending on age, the exam might check for cancers of the thyroid, oral cavity, skin, lymph nodes, testes and ovaries.

BREAST

Women aged 20 to 39 should have a clinical breast exam (CBE) every three years. Women aged 40 and older should have an annual mammogram and an annual CBE. All women should perform monthly breast self-examination.

COLON AND RECTUM

Beginning at age 50, men and women should follow one of the schedules below:

- Fecal occult blood test every year and a flexible sigmoidoscopy every five years.
- Colonoscopy every 10 years.
- Double-contrast barium enema every five to 10 years.

A digital rectal exam should be done at the same time as sigmoidoscopy, colonoscopy or barium enema.

PROSTATE

Beginning at age 50, men with a life expectancy of at least 10 years should have an annual prostate-specific antigen (PSA) blood test and a digital rectal exam. Men in high-risk groups (two or more affected first-degree relatives) and black men should begin at a younger age, such as 45.

UTERUS

Cervix: All women aged 18 and older (or younger if sexually active) should have an annual Pap test and pelvic exam. After three or more consecutive successful results, the Pap test can be performed less frequently, after discussion with a doctor.
Endometrium: Women at high risk of uterine cancer should have a sample of endometrial tissue examined when menopause begins.

SOURCE: "Cancer Facts & Figures 2000," American Cancer Society

ter initiation of tumors. Epidemiological studies may also uncover precancerous associations. One example is the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), begun in 1985 by the National Cancer Institute. The trial failed to demonstrate that beta-carotene prevented lung cancer for the Finnish smokers enrolled, but analysis did show that the men in the vitamin E (alpha-tocopherol) arm of the study experienced 34 percent fewer cases of prostate cancer and 16 percent fewer cases of colorectal cancer.

Discovery of biomarkers that are associated with precancerous lesions could also become an important tool in prevention studies. Myriad markers have been proposed, but none have yet been validated. "We have nothing like LDL [the bad cholesterol] levels that are linked to heart disease," says Peter Greenwald, director of the division of cancer prevention at the National Cancer Institute. Finding a marker would improve research efficiency and save money. The markers would also provide a basis for evaluation of the general population for risk factors, helping doctors decide who might be a candidate for a particular chemopreventive agent.

Other technologies to evaluate risk factors are also being developed. Currently there are only a few screening tests (such as the Pap smear for uterine cancer) that are able to detect precancerous cells, allowing intervention before progression to fully expressed cancer. If more tests were developed, it would still be difficult to access organs such as the prostate, liver or breast as easily as the cervix to get cell samples. And doctors can't biopsy the entire population. Even if they could, the results wouldn't support the effort: the likelihood of actually hitting the specific spot in an organ where cancer may be developing would be too small.

The grand solution would be the equivalent of x-rays on the gene level, so that an entire organ could be evaluated noninvasively. Unlike traditional medical imaging, which is based on macroscopic information such as bone mass and blood flow, this "molecular imaging" could peer into cells at the microscopic gene level, explains Ralph Weissleder, director of the Center for Molecular Imaging Research at Massachusetts General Hospital. Researchers must understand more about molecular changes in precancerous cells, however, before imaging schemes can be devised. Weissleder estimates that practical use of this tool "is decades away."

What should people do until better imaging technology, biomarkers and preventive drugs arrive? Wait for more data from the dozens of chemoprevention trials being supported by the National Cancer Institute. And keep eating your fruits and vegetables.

KEN HOWARD, *a journalist based in New York City, is making sure that he eats plenty of grapefruit and carrots.*

Further Information

Prevention of Cancer in the Next Millennium. Report of the Chemoprevention Working Group to the American Association for Cancer Research in *Cancer Research,* Vol. 59, pages 4743–4758; October 1, 1999. (For reprints, call 215-440-9300.)

Harvard Center for Cancer Prevention (www.hsph.harvard.edu/cancer).

National Cancer Institute's CancerNet (http://cancernet.nci.nih.gov/).