

## CANCER

Cancer is caused in all or almost all instances by *mutation* or *abnormal activation* of cellular genes that control cell growth and cell mitosis. The abnormal genes are called *oncogenes*. As many as 100 different oncogenes have been discovered. Also present in all cells are *antioncogenes*, which suppress the activation of specific oncogenes. Therefore, loss or inactivation of antioncogenes can allow activation of oncogenes and lead to cancer.

Only a minute fraction of the cells that mutate in the body ever lead to cancer. There are several reasons for this.

First, most mutated cells have less survival capability than normal cells and therefore simply die.

Second, only a few of the mutated cells that do survive become cancerous because even most mutated cells still have the normal feedback controls that prevent excessive growth.

Third, those cells that are potentially cancerous are often, if not usually, destroyed by the body's immune system before they grow into a cancer. This occurs in the following way: Most mutated cells form abnormal proteins within their cell bodies because of their altered genes, and these proteins then stimulate the body's immune system, causing it to form antibodies or sensitized lymphocytes against the cancerous cells, in this way destroying them. In support of this is the fact that in people whose immune systems have been suppressed, such as those who are taking immunosuppressant drugs after transplantation of a kidney or a heart, the probability of developing a cancer is multiplied as much as five-fold.

Fourth, usually several different activated oncogenes are required all at the same time to cause a cancer. For instance, one such gene might promote rapid reproduction of a cell line, but no cancer occurs because there is not a simultaneous mutant gene required to form the needed blood vessels.

But what is it that causes the altered genes? When one realizes that many trillions of new cells are formed each year in the human being, this question should probably better be asked in the following form: Why is it that all of us do not develop literally millions or billions of mutant cancerous cells? The answer is the incredible precision with which DNA chromosomal strands are replicated in each cell before mitosis takes place and also because the proofreading process cuts and repairs any abnormal DNA strand before the mitotic process is allowed to proceed. Yet, despite all these inherited cellular precautions, probably one newly formed cell in every few million still has significant mutant characteristics.

Thus, chance alone is all that is required for mutations to take place, so we may suppose that a large number of cancers are merely the result of an unlucky occurrence.

Yet the probability of mutations can be increased many-fold when a person is exposed to certain chemical, physical, or biological factors. Some of these are the following.

1. It is well known that *ionizing radiation*, such as x-rays, gamma rays, and particle radiations from radioactive substances, and even ultraviolet light can predispose to cancer. Ions formed in tissue cells under the influence of such radiation are highly reactive and can rupture DNA strands, thus causing many mutations.

2. *Chemical substances* of certain types also have a high propensity for causing mutations. Historically, it was long ago discovered that various aniline dye derivatives are likely to cause cancer, so that workers in chemical plants producing such substances, if unprotected, have a special predisposition to cancer. Chemical substances that can cause mutation are called *carcinogens*. The carcinogens that cause by far the greatest number of deaths in our present-day society are those in cigarette smoke. They cause about one quarter of all cancer deaths.

3. *Physical irritants* can also lead to cancer, such as continued abrasion of the linings of the intestinal tract by some types of food. The damage to the tissues leads to rapid mitotic replacement of the cells. The more rapid the mitosis, the greater the chance for mutation.

4. In many families, there is a strong *hereditary tendency to cancer*. This results from the fact that most cancers require not one mutation but two or more mutations before cancer occurs. In those families that are particularly predisposed to cancer, it is presumed that one or more of the genes are already mutated in the inherited genome. Therefore, far fewer additional mutations must take place in such a person before a cancer begins to grow.

5. In laboratory animals, certain types of viruses can cause some kinds of cancer, including leukemia. This occasionally results by either of two ways. First, in the case of DNA viruses, the DNA strand of the virus can insert itself directly into one of the chromosomes and thereby cause the mutation that leads to cancer. In the case of RNA viruses, some of these carry with them an enzyme called *reverse transcriptase* that causes DNA to be transcribed from the RNA. Then the transcribed DNA inserts itself into the animal cell genome, thus leading to cancer.

**INVASIVE CHARACTERISTIC OF THE CANCER CELL.** The major differences between the cancer cell and the normal cell are: (1) The cancer cell does not respect usual cellular growth limits; the reason for this is that the cells presumably do not require all the same growth factors that are necessary to cause growth of normal cells. (2) Cancer cells are far less adhesive to one another than are normal cells. Therefore, they have a tendency to wander through the tissues, to enter the blood stream, and to be transported all through the body, where they form *nidi* for numerous new cancerous growths. (3) Some cancers also produce *angiogenic factors* that cause many new blood vessels to grow into the cancer, thus supplying the nutrients required for cancer growth.

**WHY DO CANCER CELLS KILL?** The answer to this question usually is simple. Cancer tissue competes with normal tissues for nutrients. Because cancer cells continue to proliferate indefinitely, their number multiplying day by day, one can readily understand that the cancer cells will soon demand essentially all the nutrition available to the body or to an essential part of the body. As a result, normal tissues gradually suffer nutritive death.

## PERSONAL HEALTH

# How Cancer Rose to the Top of the Charts

By JANE E. BRODY

An amazing statistic emerged just weeks ago that seems to have gotten somewhat lost in the news about the weather, the Inauguration and the aftermath of the tsunami. Heart disease is no longer the leading killer of Americans under age 85. Cancer is.

In fact, cancer deaths surpassed heart disease in people under 85 as far back as 1999. But until the American Cancer Society compiled its annual statistical report for this year, no one had looked before at deaths among people in this very large age group, which accounts for 98.4 percent of the population.

In 2002, the latest data fully available, 476,009 Americans younger than 85 died of cancer, while 450,637 died of heart disease. Cancer is the leading cause of death among women 40 through 79 and among men 60 through 79.

For the entire American population (that is, including the 1.6 percent who die after their 85th birthdays), heart disease remains the leading cause of death and cancer is the second, accounting for about one death in four.

## What the Numbers Mean

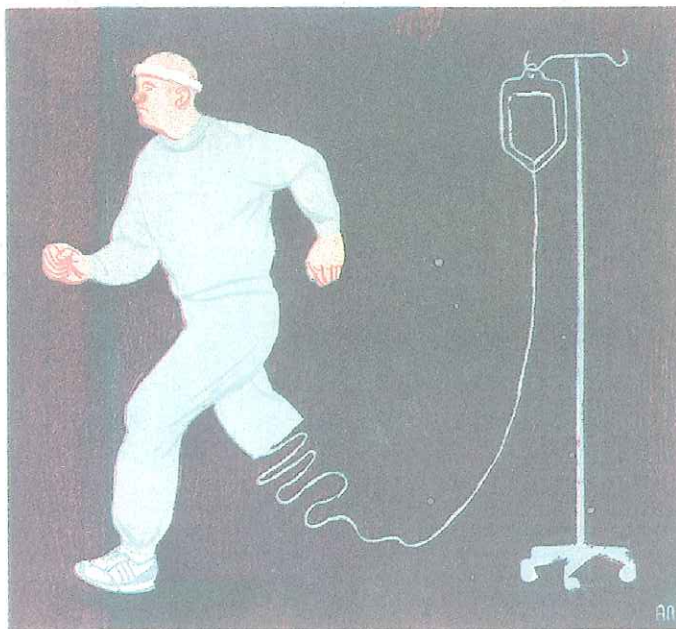
The fact is that if the leading cause of death falls sharply, as cardiac deaths have, the second leading cause, cancer, will eventually replace it in the hierarchy of mortality.

But the story behind the newly announced statistics can help dispel many mistaken notions about cancer. It may even prompt some people, especially the young, to make life-enhancing changes that may enable them to live cancer-free beyond the age of 85.

Many people have remarked to me in recent years that "everyone" seems to have cancer, and they envision an expanding epidemic of the disease that people in this country fear most. But the facts are different: cancer death rates, too, have been falling, though not for as long or as fast as those for heart disease.

Heart disease long claimed far more lives than cancer, both for the overall population and especially among people over 40. In fact, heart disease is still the leading killer for some segments of the population, including men 40 through 59 and both men and women 75 through 84.

But over all, cardiac deaths have been on a rather sharp decline since



Alex Nabaum

1975, whereas a fall in deaths from several leading types of cancer — like breast cancer in women and lung and prostate cancer in men — has been more gradual and did not become notable until 1990 or later.

The reasons for this disparity in mortality rates are not hard to find, and they attest to fundamental differences between the two diseases.

By far the main reason for the steep decline in cardiac deaths has been the reduction in cigarette smoking, especially among middle-aged men. Smoking is a leading cause of sudden cardiac death, and quitting smoking nearly eliminates this risk within a smoke-free year or two.

The relationship between smoking and cancer is quite different. Smoking can damage the genetic material in cells in many organs of the body. The damage is cumulative and irreversible, and evidence of it can take decades to emerge as a cancer — of the lung, larynx, mouth, bladder, pancreas, even the breast, among other organs. A person may quit smoking, but a nascent cancer will not disappear.

Another leading reason for the reduction of heart deaths is the recognition and treatment of two major cardiac risk factors, high blood pressure and elevated blood cholesterol levels. Every day, tens of millions of American men and women take

drugs that lower blood pressure or cholesterol, drugs that have been shown in controlled clinical trials to reduce the chances of premature cardiac death significantly.

Warnings about dietary risks have also yielded results, with millions of Americans drastically reducing their consumption of artery-damaging saturated fats and cholesterol and consuming more protective polyunsaturated and monounsaturated oils in their place.

Finally, advances in treatments like bypass surgery and angioplasty for people with known heart disease or clogged coronary arteries have reduced or delayed cardiac deaths in many.

## Preventing Cancer Deaths

There are very few comparable measures that can protect against cancer. For someone with chronic heartburn, taking a daily antacid and avoiding irritating foods and beverages can protect against damage to the esophagus that can eventually lead to deadly esophageal cancer.

But it takes about 10 years of not smoking for the body to counter the damage done to lungs by cigarette smoking. Whether the risk of other smoking-related cancers also declines with time is not well-established. And the damage caused by

exposure to some cancer-causing substances like asbestos can never be undone.

Cancer-protective dietary measures, like eating lots of fruits and vegetables and less meat, as well as getting regular exercise, may require a lifetime of effort to be very helpful, though adopting such measures at any time is hardly a bad idea.

One change in Americans — the steady rise in body weights — adds to the risk of both cancer and heart disease. No government or medical action required here: just personal responsibility.

Nonetheless, we know why deaths from certain cancers are on the decline, and expanding the use of protective measures can certainly save more lives. Early detection of cancer and precancerous growths can reduce the risk of cancer deaths, through routine mammograms to screen for breast cancer, Pap smears to pick up precancerous cells or early cancer of the cervix, colonoscopy to detect precancerous or cancerous polyps in the large intestine and probably P.S.A. blood tests to find early prostate cancer.

## Where We Are Now

Cancer is not going to go away anytime soon, though many leads, especially those involving molecular factors in cancer, are being hotly pursued both for early detection and more precise therapies.

This year in the United States, the cancer society estimates that 1,372,910 new cases of cancer will be diagnosed and 570,260 people will die from the disease. Thanks to early detection and improved treatments, however, five-year survival rates have been rising steadily, to 74 percent today from 50 percent in the 1970's.

Lung cancer, a largely preventable disease, remains the leading cancer killer in men and women, accounting for one in three cancer deaths in men and one in four in women. After several decades of rising lung cancer deaths among women, the rate has leveled off after millions of women got smart and quit smoking or chose not to start.

Deaths from the other leading cancers — breast cancer in women, prostate cancer in men and colon cancer in both men and women — can be reduced through early detection and other measures already known. Now it is up to every one of us to take advantage of them.



# Another Source of Air Pollution: The Home

By JANE E. BRODY

Can the air you breathe inside your home or office be more hazardous to your health than the outdoor pollution that has created so much public concern and regulation in recent decades?

According to a report in the journal *Preventive Medicine*, by Kenneth R. Spaeth, a University of Connecticut medical student, within their homes, "Americans are exposed to numerous pollutants, from heavy metals to volatile organic compounds." But while people spend the vast majority of their time indoors, Mr. Spaeth wrote, "the Environmental Protection Agency acts to limit the amount of toxins released into the outdoors."

Some pollutants commonly found in homes and offices are carcinogenic, others can aggravate existing problems like asthma and heart disease, while others may have untoward effects that have not yet been discovered. Now, in winter, people are spending more time indoors. Because of substances released in heating and cooking, cleaning agents, building and decorating materials and tobacco use, they are inhaling far more toxic substances than they are likely to encounter outdoors any other time.

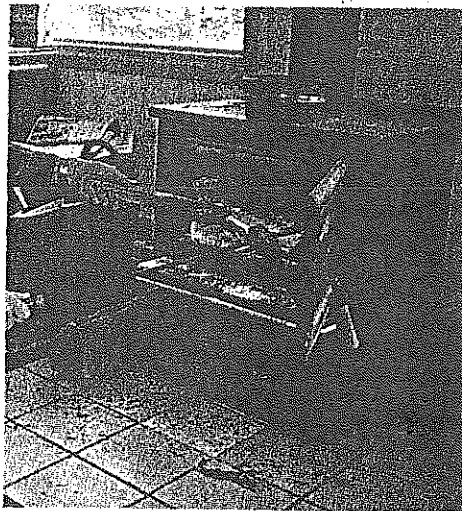
The problem of indoor pollution has been made worse in recent years by efforts to make homes and offices more energy-efficient. Building techniques aimed at airtight environments reduce heat loss but greatly increase exposure to toxic substances released within the home.

But you don't have to wait for research and regulation to clean up indoor air. The American Lung Association, among other groups concerned about public health, has many suggestions for clean up indoor air.

## Exposures of Concern

Data drawn from studies sponsored by the Environmental Protection Agency "indicate that the general population is exposed to unexpectedly high levels of carcinogenic substances in their homes," Mr. Spaeth wrote. "The results found that 'the highest personal exposures were 5 to 70 times the highest outdoor levels,'" he reported, with some toxin levels inside the majority of homes "greater than the levels that qualify as a chemical waste site for Superfund status."

For example, Mr. Spaeth noted, the average levels of exposure to benzene, a known carcinogen, was found to be three times as high indoors as outdoors. Its chief source was cigarette smoke, the greatest source of indoor pollutants. Others include incomplete combustion from cooking and heating systems, household deodorizers, dry-



Steve Kohls for The New York Times

Heating appliances like wood-burning stoves can pollute indoor air with carbon monoxide and other hazards.

cleaned clothes, air fresheners and cleaners, insect repellents and treated wood.

Heating appliances and systems, especially wood-burning stoves and fireplaces, can pollute indoor air with carbon monoxide, nitrogen dioxide, particulates, sulfur dioxide, unburned hydrocarbons and aldehydes. Carbon monoxide is insidious and potentially deadly; nitrogen dioxide, particulates and sulfur dioxide irritate the respiratory tract and are especially hazardous to people with asthma.

Little is known about the hazards of other combustion products and carcinogens of indoor air, but at least 6,000 cases of cancer a year are believed to be caused by exposure to second-hand tobacco smoke and other compounds and pesticides in indoor air. The pollutants are inhaled directly or become part of the dust and are then inhaled or, in the case of children who spend much time on the floor, transferred by hand to mouth. From indoor exposure alone, urban children may ingest as much benzo[a]pyrene, a potent carcinogen, as they would get from smoking three cigarettes a day, according to a 1998 report in *Scientific American*.

## Reducing Exposure

An important control measure is for those who smoke to quit, or, short of quitting, confine all smoking to the outdoors, where the pollutants can be diluted by the general atmosphere. The second most important measure is to allow more air to circulate within the home by opening windows or doors. Just a crack at night can help a lot. Consider purchasing one or more High Effi-

ciency Particulate Arresting (HEPA) air cleaners (especially for the bedrooms) and, if it is time to replace your vacuum, get one with a HEPA filter.

Install exhaust fans over the stove to reduce exposure to toxic combustion products and a ventilation system in the bathroom. Check the flame and pilot lights on gas furnaces and ranges. They should burn blue with at most a slight yellow tip. If the flame is too yellow or orange, it is spewing toxic substances into the air. Call the utility company to have the flame adjusted.

Remove the plastic bags from dry-cleaned clothes before you leave the store and let the clothes air out on the way home. Instead of air freshener sprays, light a match to deodorize the bathroom. To control mice, roaches and other vermin, keep all tempting food items (including pet food) in impenetrable containers (glass, rigid plastic or metal with tight lids) and don't leave pet dishes around with uneaten remnants. Boric acid can be used to control roach and ant infestations.

Have people remove their shoes on entering your home to reduce the amount of toxins that are tracked in. Also, consider eliminating carpets, which harbor lots of dust. At the least, vacuum carpets often, and clean under them every few months.

Properly install and maintain the systems you use to heat your home. Chimneys, stove pipes and furnaces should be inspected and cleaned annually, preferably before the start of the heating season. Filters can be installed within the heating unit and inside hot-air ducts.

Wood stoves and fireplaces can, if improperly used, expose people to enormous amounts of toxic and irritating combustion products. Instead of an open fireplace, use a glass-enclosed firebox.

Choose a stove or firebox no larger than needed to heat the space involved. Look for an E.P.A. certification label. A stove with a catalytic combustor is preferable (it reduces emissions the way a catalytic converter does on motor vehicles). Let a professional install it.

Burn only hardwood — maple, oak, beech, elm or ash — that has been air-dried for a year. Never use green, wet, painted or chemically treated wood, colored paper or lots of paper and twigs. Commercial firestarter bricks or sticks can help. After getting the fire started, use logs as large as the firebox will accommodate.

When adding wood, open the stove's damper fully to prevent smoke from being drawn back into the house. Let the fire burn for about 15 minutes before partially closing the damper. It is better to add logs fairly often than to overstuff the firebox. Soot on the furniture is a sign that the stove is releasing pollutants into the indoor air.

PERSONAL HEALTH | Jane E. Brody

# Updating the Rules for Skin Cancer Checks

Now, before you again don warm clothes, is a good time to note how much sun damage you incurred this summer. Are body parts that were not covered darker or more freckled than the skin you were born with? If so, you failed to cover your exposed skin and protect it adequately with sunscreen when out on both sunny and cloudy days.

Eventually, depending on your susceptibility and the extent of unprotected sun exposure, you could wind up with skin cancer, the nation's most common cancer by far. Even if you escape cancer, you will certainly speed the aging of your skin, and by midlife you might have a wrinkled, leathery surface that makes you look older than your years.

But unless you've already had one of the common skin cancers or a melanoma, the United States Preventive Services Task Force does not recommend a yearly head-to-toe checkup for skin cancer by you or a doctor.

In updated guidelines issued last February and printed in *The Annals of Internal Medicine*, the task force found insufficient evidence to justify periodic "screening for skin cancer by primary care clinicians or by patient self-examination."

You may wonder what the harm could be in such a checkup. Haven't you been repeatedly told that early detection is the secret to preventing a cancer that can threaten your life or well-being?

Research supports such testing for cancers of the cervix or breast. But in assessing whether routine screening for any disease is justifiable, experts must weigh the evidence for both benefits and risks. And the task force, an arm of the government's Agency for Healthcare Research and Quality, concluded that there was "a critical gap in the evidence" to assess the risks of routine skin cancer screening.

The task force found no direct evidence that whole-body skin exams by primary care physicians or patients "improves patient outcomes" and that studies were lacking to determine the extent of harm that could come from such screening. The possible risks it listed were "misdiagnosis, overdiagnosis and the resultant harms from biopsies and over-treatment."

In other words, there is not enough information to say whether the benefits of routine skin cancer screening outweigh the potential risks associated with examining and treating lesions that turn out not to be cancer.

## When to See the Doctor

This is not to say that if you notice something suspicious anywhere on your skin — like a mole that is changing, a rough spot on a sun-exposed part of your body, or a sore that bleeds or does not heal — you should ig-



nore it, hoping it will disappear on its own. Most dermatologists recommend periodic skin checkups, especially to catch early, curable melanomas, and any such lesion should be brought to a doctor's attention without delay.

Dr. Darius R. Mehregan, chairman of dermatology at Wayne State University School of Medicine in Michigan, agrees that for most adults an annual skin cancer checkup by a physician is not needed. Still, in an interview, Dr. Mehregan suggested that patients should do a monthly self-check for the "A, B, C, D and E" of skin cancer starting around age 50. This means looking for lesions with any of these characteristics: A for asymmetry, B for irregular border, C for multiple colors, D for a diameter greater than six millimeters (about a quarter-inch) and E for evolving (that is, growing or changing).

Dr. Gary N. Fox, who practices dermatology in Defiance, Ohio, a farming area where skin cancers are rampant, also sees little to be gained from routinely screening people who do not have risk factors for skin cancer. But in an interview, Dr. Fox emphasized the importance of insisting on a biopsy if someone had a lesion that "causes sufficient patient or doctor concern, even if it has been there for 20 years."

Furthermore, Dr. Fox said, unless the doctor doing the biopsy is very experienced in pathology, the biopsied tissue should be examined by a dermatopathologist, who is specially trained to diagnose skin disease. If there is any doubt about the finding, he said, "another pathologist should look at it since it doesn't hurt to ask for a second opinion."

Sometimes, he explained, a mole can be hard to distinguish from a melanoma.

Dr. Fox also cautioned doctors against freezing a lesion to see if it went away unless there was no doubt about its nature. For example, the common sun-induced lesion called actinic keratosis, in which cancer cells are confined to the top of the skin, can safely be frozen.

But he adds that anyone who has had a number of actinic keratoses should be regularly re-examined, since more are likely to occur and they can develop into an invasive cancer.

## Looking for Melanoma

Of course, if you have already had one skin cancer — a basal-cell or squamous-cell carcinoma or, more serious, a melanoma — you should be regularly examined as well. For example, Dr. Fox said, a person who has had one basal-cell cancer has a 50 percent chance of developing a new one within three to five years. He suggested repeat exams at three to four months, at six to eight months, and again at a year during the first year, and annually thereafter.

Since melanomas run in families, Dr. Fox added, anyone with a family history of the disease should start regular skin exams in their 20s. Likewise, Dr. Mehregan said, people who have many moles should get an early start on screening because it is difficult for patients to determine when a melanoma arises in a mole.

Dr. Fox explained that the main goal was to catch and treat melanoma "in situ" — that is, still confined to the site of origin and not life-threatening. He emphasized that a full skin exam for melanoma should be head to toe: the scalp (with hair parted by a hair dryer on cool setting) and all body surfaces, including the underarms, buttocks, genitals, palms, soles and nails.

However, he said, a check for the ordinary sun-related skin cancers — basal and squamous cell carcinomas — can be limited to sun-exposed body parts: the face, the trunk, the back, the arms, the legs and, in someone partly or completely bald, the scalp.

The best way to avoid skin cancer, these experts said, is to be diligent about sun protection. Wear a tightly woven hat with a wide brim and routinely use a full-spectrum sunscreen with an SPF rating of 30 (above that, there is little additional benefit), even when sitting behind glass or under an umbrella. And apply it generously: Dr. Mehregan notes that the SPF rating is based on using a tablespoon of the product for one arm.

Sun-protective clothing can help as well. Reapply sunscreen after sweating heavily or swimming, even if the product claims to be water-resistant.



ABCDE'S

# Skin Cancer



## A Symmetry



### SYMMETRICAL:

Benign (non-cancerous and non-malignant) moles are typically round.



### ASYMMETRICAL:

Melanoma (cancerous and malignant) lesions are typically irregular in shape.

## B Border



### EVEN:

Benign moles have smooth, even borders.



### RAGGED OR NOTCHED EDGES:

Melanoma lesions often have uneven borders.

## C Color



### SINGLE SHADE:

Benign moles are usually a single shade of brown.



### MANY SHADES:

Melanoma lesions often contain many shades of brown or black.

## D Diameter



### <6MM OR 1/4":

Benign moles are usually less than 6 millimeters in diameter.



### >6MM OR 1/4":

Melanoma lesions are often more than 6 millimeters in diameter.

## E Evolving



### FLAT:

Benign moles usually do not change size over time.



### ELEVATED:

Melanoma lesions often grow in size or change in height rapidly.



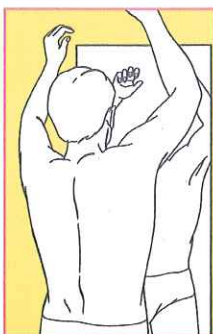
M E L A N O M A   A W A R E N E S S   A N D   E D U C A T I O N

SELF EXAMINATION

# *Skin Check*

HAVE YOU CHECKED YOUR **SKIN** LATELY?  
**5** EASY STEPS TO EXAMINE YOURSELF:

**STEP 1**



Examine body front and back in mirror, then right and left sides, arms raised.

**STEP 2**



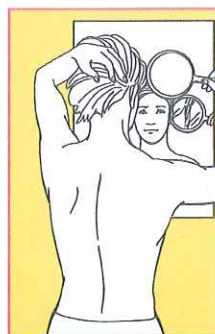
Bend your elbows. Look carefully at forearms, back of upper arms, and palms.

**STEP 3**



Next, look at the back of your legs and feet and spaces between your toes and soles.

**STEP 4**



Examine the back of your neck and scalp with a hand mirror.

**STEP 5**



Finally, check your back, buttocks and genital area with a hand mirror.

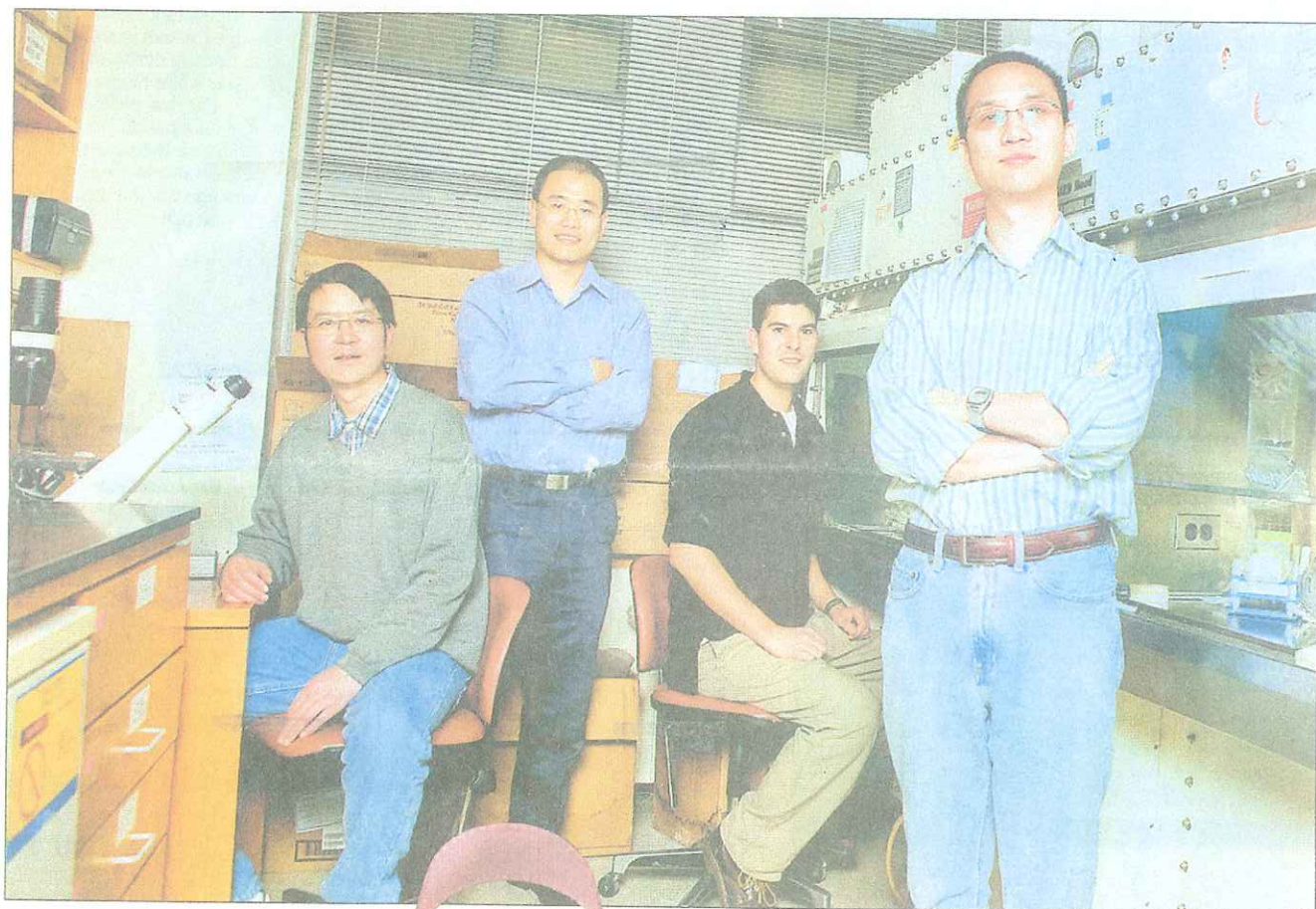


M E L A N O M A   A W A R E N E S S   A N D   E D U C A T I O N

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# Cancer code-breakers



Four of the researchers whose work showed why some breast cancer tumors resist chemotherapy drugs. From left, Yong Wei, Yibin Kang, Mario Andres Blanco and Guohong Hu.

## N.J. team pinpoints gene that helps tumors spread

By LINDY WASHBURN  
STAFF WRITER

A gene that makes breast cancer tumors more likely to resist chemotherapy and to spread to other organs has been identified by a team of New Jersey researchers.

The "metastasis gene" is turned on in 30 percent to 40 percent of breast cancer patients. When activated, it helps the tumor cells stick

tightly to blood vessels in distant organs and makes them resistant to chemotherapy drugs traditionally used to treat breast cancer, according to researchers from Princeton University and the Cancer Institute of New Jersey.

Their study is published in today's edition of the journal *Cancer Cell*.

With more than 180,000 women a year hearing the dreaded diagnosis of breast cancer, the potential benefit of See **CANCER** Page A-5

### In New Jersey

Breast cancer cases from 2001 to 2005:

Incidence	Mortality:
Bergen: 3,976	Bergen: 841
Passaic: 1,540	Passaic: 395
Morris: 2,036	Morris: 402
Statewide: 32,665	Statewide: 7,368

Source: New Jersey Department of Health

THE Record JAN 6<sup>TH</sup>, 2009

# Cancer: Triumph

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the research is great.

It could lead to the development of a test to screen for the gene in breast tumors and medication to block the gene's activity. A medication would not only help prevent metastases to distant organs, but enable chemotherapy to benefit more women, helping to prevent recurrences of breast cancer.

"There's the potential of coming up with one stone that hits two birds," said Dr. Yibin Kang, a molecular biologist at Princeton University who led the research. "If you come up with a therapy that inhibits the gene, it could make the tumor more susceptible to chemotherapy and at the same time reduce the chance for a tumor to spread."

The newly identified gene — called Metadherin, or MTDH — was found in 30 percent to 40 percent of the tumor samples examined.

"We are currently talking with companies like Johnson & Johnson for them to pursue development of antibodies to the gene," Kang said.

A test for the gene might be similar to the one that analyzes tumors for a variant of the HER2 gene, which makes cancer cells divide more rapidly. Women that test positive for HER2 can be treated with Herceptin, a targeted therapy that interferes with that gene's activity.

The gene also appears to play a role in prostate cancer metastases, said Kang, who is preparing an article on that research. The same genetic variant is found in about 20 percent of prostate cancer patients, he said.

The breast cancer study analyzed the genetic makeup of samples of breast cancer tumors from a tumor bank at the Cancer Institute of New Jersey.

The study found that tumors with the MTDH gene variant were more resistant to the common chemotherapy drugs paclitaxel, cisplatin and adriamycin.

Breast cancer is the leading cause of cancer death in women, claiming 40,000 lives a year in the United States. Metastasis, or the spreading of the cancer to another part of the body, and chemo-resistance are the two biggest challenges to curing breast cancer.

More than 90 percent of deaths due to breast cancer result not from tumors in the breast, but from those that have spread to other organs — most commonly the bones, lungs, liver and brain. If

confined to the breast, breast cancer is seldom fatal: chances of survival are 98 percent after five years. Once the cancer has spread beyond the lymph nodes to other organs, chances of survival are reduced to 27 percent, according to the National Cancer Institute.

Understanding cancer's spread to other organs has long been a goal of researchers. Cells break away from the primary tumor — usually found as a lump in the breast — and travel elsewhere in the body where they "seed" new cancers in a complex process.

The same issue of Cancer Cell published today includes a separate study about a newly identified enzyme that also plays a role in breast-cancer metastases. The enzyme "works by sending out signals to prepare a new area of the body for the cancer to set up a camp," according to the lead researcher, Dr. Janine Eler of The Institute of Cancer Research in London.

Scientists now believe that "this breaking away and seeding new areas happens continuously throughout the disease," said Dr. Michael Reiss, another author of the genetic paper and director of the Breast Cancer Research Program at the Cancer Institute of New Jersey in New Brunswick.

Every cancer metastasis "starts off as a single cancer stem cell spawning," he said. "They're relatively resistant to chemotherapy and much harder to kill."

A person's genetic information is contained in 23 pairs of chromosomes, which normally contain two copies of a given gene, conveyed by the mother and the father. The study found that a very small area of human chromosome 8 contained multiple repeats of the MTDH gene. This "over-expression" of the MTDH gene resulted in production of certain proteins that made the cells stick more readily to blood vessel cells and to resist chemotherapy.

The strategy used to pinpoint this gene will be valuable in further cancer research, Reiss said. It relied on bioinformatics, or computer analyses of massive databases of genetic information on breast cancer tumors, as well as experiments with mice engineered to test the effects of the gene variation. Finally, the results were checked against human tumor specimens. Ten scientists are listed as authors of the study.

The three-year study was funded by grants from the Department of Defense, the National Institutes of Health, the American

## Researchers

The team of 10 researchers from Princeton University and The Cancer Institute of New Jersey, part of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, who published the breast cancer study are:

**Yibin Kang**, an assistant professor of molecular biology at Princeton. He is a recipient of a \$3.8 million, five-year research grant from the Department of Defense Era of Hope Scholars program. He also is the recipient of an \$840,000 grant from the American Cancer Society, which cites him as an example of its fund-raising dollars at work in the fight against breast cancer.

**Guohong Hu**, the first author on the paper, a post-doctoral research associate in Princeton's molecular biology department.

**Michael Reiss**, director of the breast cancer research program at The Cancer Institute of New Jersey and a professor of medicine, molecular genetics and microbiology at UMDNJ-Robert Wood Johnson Medical School.

**Robert Chong**, a 2007 Princeton graduate and a research assistant in Princeton's molecular biology department.

**Qifeng Yang**, who was at UMDNJ-Robert Wood Johnson Medical School and is now in the department of breast surgery at Qilu Hospital of Shandong University in China.

**Yong Wei**, a post-doctoral research associate in Princeton's molecular biology department.

**Mario Andres Blanco**, a graduate student in Princeton's molecular biology department.

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## An Elusive Ounce of Prevention

Cancer prevention has proved more difficult than many researchers predicted. Only a few activities and drugs have been shown to help prevent cancers, and much of what Americans do in the name of prevention has not been shown to work.

### WHAT HAS BEEN SHOWN TO WORK



#### Not smoking

The surest way to prevent cancer is to avoid cigarette smoking. If no one ever smoked, the cancer death rate would fall by a third.



#### Not taking menopause hormones

National breast cancer rates fell sharply in 2003 after large numbers of women stopped taking estrogen and progestin as a hormone therapy for menopause symptoms.



#### Finasteride and Duasteride

A pair of studies have shown that the inexpensive, generic drug finasteride and its close cousin duasteride could reduce prostate cancer risk by about 25 percent.



#### Tamoxifen and Raloxifene

Two large clinical trials showed that two inexpensive drugs, tamoxifen and raloxifene, were equally effective in reducing breast cancer risk by 50 percent.

### WHAT HAS NOT BEEN SHOWN TO WORK



#### Beta carotene

Two large studies sponsored by the National Cancer Institute found that beta carotene supplements did not prevent lung cancer and might actually increase risk.



#### Exercise

Some studies show an association between strenuous exercise and lower cancer risk but the evidence remains inconclusive.



#### Fiber

Contrary to widely held beliefs, two rigorous studies found that high-fiber diets do not reduce the risk of colon and rectal cancer.



#### Fruits and vegetables

Public health experts have long recommended five servings of fruits and vegetables a day to prevent cancer, but the evidence is conflicting and far from definitive.



#### Losing weight

Links between obesity and cancer are inconsistent, though the strongest evidence is with breast cancer. There is little evidence that losing weight reduces cancer risk.



#### Low-fat diet

A large federal study randomizing women to a low-fat or normal diet found no effect on rates of breast cancer.



#### Selenium and vitamin E

A large clinical trial found that supplements of selenium and vitamin E offer no protection against prostate cancer.

## Oral Cancer In Men Associated With HPV

By NICHOLAS BAKALAR

The sexually transmitted virus called HPV, for human papillomavirus, is well known to lead to cervical cancer in women — which is why the federal government recommends that all girls be vaccinated for HPV at 11 or 12, before they become sexually active.

Now researchers are finding that many oral cancers in men are also associated with the virus.

A clinical trial testing therapies for advanced tongue and tonsil cancers has found that more than 40 percent of the tumors in men were infected with HPV. If there is good news in the finding, it is that these HPV-associated tumors were among the most responsive to treatment.

Of an estimated 28,900 cases of oral cancer a year, 18,550 are in men.

"The high risk of HPV-associated cancers in men suggests that vaccinating all adolescents is something that should strongly be considered," said the lead researcher, Dr. Francis P. Worden, a clinical assistant professor of medicine at the University of Michigan.

HPV can enter the mouth during oral sex. A study published in February by researchers at Johns Hopkins estimated that 38 percent of oral squamous-cell cancers are HPV related, and suggested that their increasing number might be a result of changing sexual behaviors.

The new study, published in two papers in *The Journal of Clinical Oncology*, included 51 men and 15 women with cancers of the tonsils or the base of tongue. The researchers were able to examine biopsies of 42 of the subjects before treatment. After tests for HPV, the researchers found that 27 tumors, nearly two-thirds, were positive for the virus. Of the 51 men, researchers found 22 with HPV.

Other experts found the results interesting, but said it was unclear what they would mean for treatment. Finding the answer to that question is the next step, said Dr. Maura L. Gillison, an associate professor of on-

### A vaccine for girls might be useful for boys too.

cology at Johns Hopkins who was not involved in the study.

"Clearly," Dr. Gillison added, "it should give people optimism that the vaccine that was approved largely for women and for cervical cancer could have broader implications, and also for other cancers that occur in both men and women. All of our clinical trials now will be designed for either HPV-positive or HPV-negative patients. Right now, these patients are treated the same way."

All the patients in the study were initially treated with induction chemotherapy, that is, an initial course to shrink the tumor. Those whose tumors did not shrink by at least 50 percent, 12 patients, were then treated with surgery. Most of those did not survive their illness.

Of the remaining group, 49 of 54 responded to the next step, combined chemotherapy and radiation. In that group, 78 percent needed no surgery, and 70 percent survived more than four years. Of the 49, almost half, 24, were positive for HPV, and all but 3 of those were men.

People with tumors with high HPV levels were significantly more likely to respond to treatment. They were also more likely to survive their cancer and to survive over all.

The researchers also tested these tumors for the presence of four genetic markers: EGFR, a cell receptor associated with various cancers; BCLXL, a repressor of cell death; and the tumor-suppressor proteins p53 and p16. The scientists found that these were also accurate predictors of the success or failure of the treatment. Women and smokers were less likely to be treated successfully.

"Patients who have HPV infections are at higher risk for these cancers," Dr. Worden said. "But the good news is that if that's the cause of their cancer, they're more likely to survive treatment. We still don't know what the ideal treatment regimens are. For example, these patients may benefit from less intense chemotherapy and radiation."

Although the researchers acknowledge that the number of patients in their study was small, they conclude that especially in patients with HPV-positive tumors, chemotherapy followed by combined chemotherapy and radiation appears to be an effective treatment.

An author of the papers has an interest in a company that is developing an HPV detection method.



## Vaccine Prevents Most Cervical Cancer

*The New Drug, if Approved, Could Be on the Market by 2006*

By DENISE GRADY

An experimental vaccine has proved highly effective at preventing cervical cancer in a two-year study involving more than 12,000 women, researchers reported yesterday.

The vaccine works by making people immune to two types of a sexually transmitted virus that cause most cases of the disease. It is the first successful vaccine ever developed specifically to prevent cancer.

The vaccine, Gardasil, is made by Merck & Company, which plans to apply for approval to the Food and Drug Administration before the end of this year and, if the vaccine is approved, to market it in 2006.

If widely used, the vaccine could save many lives. Worldwide, there are about 500,000 new cases of cervical cancer a year, and 290,000 deaths. Most of the cases and most of the deaths occur in poorer countries where women do not have regular Pap tests, which can detect cancers or precancerous cells early enough for them to be cured. In the United States, where Pap tests are common, 10,400 new cases are expected in 2005, and 3,700 deaths.

"The potential, particularly in the undeveloped world, particularly if they can overcome the logistics and get the vaccine to those women, could be enormous," said Dr. Deborah Saslow, director of breast and gynecological cancer at the American Cancer Society. The vaccine could prevent at least 70 percent of the deaths from cervical cancer, Dr. Saslow added.

But Dr. Allan Hildesheim, an epidemiologist at the National Cancer Institute, cautioned that even if women are vaccinated, they will still have to be screened regularly for cervical cancer because the vaccine does not prevent all cases of the disease.

"This is not a panacea," Dr. Hildesheim said.

The vaccination will require three shots over six months. Merck has not said what it will cost.

The ideal time to vaccinate girls is before they become sexually active

and risk being exposed to one of the cancer-causing viruses, said Dr. Eliav Barr, a research director at Merck. Once cancer develops, it is too late for the vaccine to help. The median age at which girls first have sex in the United States is 15.

It is not known yet how long the protection from the vaccine will last, or whether booster shots will be necessary, Dr. Barr said.

The vaccine works against viruses that belong to a group called human papillomaviruses, or HPV. Nearly every case of cervical cancer is caused by HPV. The viruses are sexually transmitted, extremely common and almost impossible to avoid. At least half the adults in the United States have been infected.

More than 30 types of HPV infect

*A drug could be a boon to poor nations, where most cervical cancer occurs.*

the human genital area. Only some types cause cancer; others cause genital warts. A type known as HPV-16 causes 50 percent of cervical cancers, and HPV-18 causes 20 percent. Other types cause the rest. But even the cancer-causing types are harmless in most people because their immune systems fight them off.

The virus persists in some women, however, causing abnormal growths on the cervix. Most of the growths go away, but some turn cancerous.

Gardasil protects against HPV 16 and 18, which together cause 70 percent of cervical cancers. It is also designed to prevent infection with two other virus types, 6 and 11, which cause 90 percent of cases of genital warts. The four virus types can cause non-cancerous cervical growths that lead to nerve-racking false alarms on Pap tests, and the vaccine is expected to spare many

women the abnormal test results.

Merck scientists were scheduled to present the results of the two-year study today at an infectious disease conference in San Francisco.

Their test group included more than 12,000 women, ages 16 to 26, from 13 countries. Half got Gardasil and half placebos.

Among the women who received all three doses of vaccine and did not have HPV infection when they started the study, the researchers found no precancerous cells or early cervical cancers associated with HPV 16 or 18. But among those who got placebos, there were 21 cases.

The findings mean the vaccine was 100 percent effective at preventing the cancers caused by types 16 and 18. But some women in the vaccinated group did develop precancerous cells caused by other HPV types; the company did not disclose how many.

The vaccine is made up of proteins that are normally found on the outer shell of HPV. The proteins, called viruslike particles, are produced by yeasts that have been spliced with viral genes. They provoke a strong immune response that can then prevent infection.

Although Merck will first seek permission to vaccinate girls and women, the company plans eventually to seek approval to use Gardasil in boys and men as well. The company hopes the vaccine will appeal to men because it may prevent genital warts, which can turn into large, ugly growths on the penis.

Vaccinating men might protect their sexual partners as well, including not just women but men who have sex with men, a group at risk for anal cancer caused by HPV. However, Merck has not disclosed any data on whether the vaccine works in men.

Another drug maker, GlaxoSmith-Kline, is also working on a cervical cancer vaccine, one that does not include wart protection. The company did not respond to several telephone requests for information on the status of its vaccine.

# New Vaccine for Cervical Cancer Could Prove Useful in Men, Too

By DAVID TULLER

The new vaccine against human papillomavirus, which became available last summer, could potentially prevent thousands of cases of cervical cancer. But doctors hope the vaccine will be able to prevent a less well-known, but potentially fatal, disease in gay men, anal cancer. The same strains of HPV cause both cancers.

Although anal cancer can affect anyone, it is most common among men with histories of receptive anal intercourse — an annual rate of about 35 cases per 100,000, and perhaps twice that for those infected with H.I.V., which weakens the immune system.

The Food and Drug Administration approved the HPV vaccine last year for girls and women from 9 to 26 after studies indicated that it was extremely effective against infection by four of the dozens of strains of HPV, including the ones responsible for most cases of cervical and anal cancer, as well as genital and anal warts.

"The cervix is similar biologically to the anus, so there's plenty of hope that it will work there also," said Dr. Joel Palefsky, a professor of medicine at the University of California, San Francisco.

But he cautioned that its effectiveness against anal cancer remained to be proved.

The anal cancer rate for gay men is simi-

years ago. "I had no idea about it because no one ever talked about it, although these days more gay men seem to be aware of it," said Mr. Maxim, who was successfully treated with radiation and chemotherapy.

Regulators in Australia and the European Union have approved the vaccine, called Gardasil and made by Merck, for boys ages 9 to 15. They cited data showing that it produced an immune response in boys, though its effectiveness in preventing infection in sexually active men has not been proved.

As with prescription drugs, doctors in the United States can provide the vaccine "off label" to anyone. "The approval is for marketing and distribution, but medical providers can use it in ways they feel is appropriate," said Dr. Jeffrey Klausner, director of S.T.D. prevention at the San Francisco Department of Public Health.

Dr. Eliav Barr, a director of clinical research at Merck, said he had heard that some men were receiving the vaccine, but added that the company was barred from promoting it for men unless the F.D.A. approved it for that use.

That is unlikely to occur for at least a couple of years. Merck is sponsoring a clinical trial of Gardasil in 4,000 men, including 500 self-identified gay men. The first results are expected toward the end of next year.



Peter DaSilva for The New York Times

**PREVENTION** Dr. Jeffrey Klausner at City Clinic, an S.T.D. clinic in San Francisco.

lar to cervical cancer rates before the advent of Pap smears, the test that can detect precancerous cell abnormalities. In recent years, some doctors who treat gay men have advised their patients to undergo anal Pap smears as part of routine preventive care.

HPV is the most common sexually transmitted infection in the United States, with 6.2 million people infected each year, according to the Centers for Disease Control and Prevention, though many people clear the virus without having symptoms or knowing that they were infected.

Many gay men do not realize they have an elevated risk of anal cancer.

David Maxim, an artist in San Francisco, said he had vaguely heard of HPV when he learned that he had anal cancer several

Recruiting gay men has been challenging, researchers said. The vaccine is intended to prevent an initial infection with the virus, but many people become infected soon after becoming sexually active. For the gay arm of the study, Merck has recruited men from 16 to 26 who have had no more than five sexual partners. The difficulty is that many gay men come to accept their sexual orientation only after an experimentation period.

"These have to be men who have sex with men but who have not had too much sex with men," said James Maynard, a program officer at the Fenway Institute, a research organization in Boston that focuses on gay and lesbian health and is a site of the HPV trial. "The more sex you've had, the greater the probability you've been infected with HPV."



PERSONAL HEALTH | Jane E. Brody

# No Single Path for Cancer Care in Elderly

Elliot was 83 when a routine checkup that included a digital rectal exam suggested prostate cancer. A biopsy then revealed that he had an aggressive form of the disease. His doctor recommended treatment despite Elliot's age and several existing problems, including mild cases of high blood pressure, Type 2 diabetes, depression and angina, all of which were being treated with medication.

Elliot also has leg pain that limits his walking. But none of his health problems interferes with his weekly bridge game or nights out for the theater, concerts and dining. When cancer popped into the equation, Elliot, a man with a self-deprecating sense of humor always at the ready, said he was just not inclined to let it end his life.

So when the doctor suggested hormone and radiation therapy, five days a week for nine weeks, Elliot did not hesitate. Except for some radiation-induced fatigue that he noticed only after therapy was over, he sailed through the treatment. Three months after finishing his therapy, his P.S.A., a blood test for possible cancer, registered zero, suggesting that the malignancy was destroyed.

The outcome for Elliot is a direct assault on the oft-given advice that most cancers affecting people his age be left to take their course. The theory is that either the treatment will kill them or destroy their quality of life, or some other health problem will kill them before the cancer does.

But there is a great paucity of factual information to support either a wait-and-watch approach or an aggressive approach to treating cancer in the elderly.

Although about 60 percent of newly diagnosed cancers occur in people 65 and older, there is little research to help doctors and patients decide how, when and even whether to treat the many forms of cancer that afflict older people, especially those with other ailments that can complicate therapy.

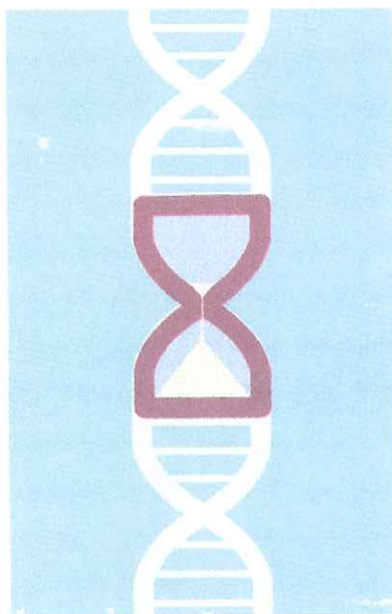
## Limited Research

For a variety of reasons, older cancer patients are rarely included in clinical trials that test new therapies, so relatively little is known about potential responses to treatment under various circumstances.

Research protocols commonly eliminate people with chronic health problems, in case the therapy makes those problems worse or the medications patients are taking interact poorly with the treatment being studied. Another deterrent is limited longevity in the elderly, making it difficult to determine the long-term effectiveness of a treatment.

Patients themselves can be a problem, if they fear "being experimented upon," if they are not physically able to get to treatment facilities, or if the research protocols are too difficult for them to understand and follow.

Despite the limited research, one fact is clear: there is no "one size fits all" treatment for cancer in the elderly. Whether the patient is 60, 80 or 100, a host of factors — medical,



YAREK WASZUL

practical and emotional — must be taken into account when devising a therapeutic plan. To the distress of some families, decisions are too often based more on a patient's chronological than physiological age.

"The doctor may be dealing with two 65-year-old patients with the same disease," Dr. Jerome W. Yates, national vice president for research at the American Cancer Society, said in an interview. "Yet one is like a 55-year-old, healthy, strong and resilient, and the other is more like an 85-year-old, frail and chronically ill. Each should be treated differently."

Treatment decisions should be influenced by patients' physical and mental health, of course, but also by their financial status, living situations, family support systems and ability to get to and from the treatment facility, Dr. Yates said.

## Don't Forget the Patient

Still another consideration, Dr. Yates said, and not a small one, is what the patient wants. He described a former patient, a 78-year-old woman with diabetes who had lost a leg to osteogenic sarcoma. The cancer had spread to her lungs, and she faced possible treatment with chemotherapy that would cause nausea and hair loss and carried the risk of a fatal lung infection. Her four college-educated children agreed with the doctor's suggestion to skip chemotherapy and administer comfort care, since treating her cancer was likely to kill her.

"But she said she wanted to be treated — she was adamant," recalled Dr. Yates, who will be leaving the cancer society for the Na-

tional Institute on Aging. "To my surprise, she had a dramatic response to the treatment. Her lung tumors all but disappeared, and she lived another two years."

Barbara and Charles Given, family care cancer specialists at Michigan State University, told a national conference on cancer and aging in 2007 that older patients, "when they are selected carefully, appear to tolerate and respond well to cancer treatments."

They added that older patients who have had surgery for lung cancer or have been treated for cancers of the colon, rectum, breast or prostate, or non-Hodgkin's lymphoma, "all have tolerated and shown positive responses to their treatments." And those with a life expectancy of more than five years have also benefited from additional therapies, like postoperative radiation or chemotherapy, they reported.

Still, out of fear that the side effects of cancer treatment will hasten an older patient's death or destroy the quality of the remaining years of life, doctors often undertreat the elderly, indirectly hastening their death with less-than-optimal therapy.

In other cases, elderly cancer patients are overtreated despite the likelihood of life-threatening complications, because doctors fear being accused of giving up or are pressured by family members to provide therapy that is medically inappropriate.

## Full Disclosure

One of the greatest challenges clinicians face with elderly cancer patients is incomplete information about their health.

"There is often a lack of documentation about pre-existing problems," Dr. Yates said. "A patient may suffer from chronic alcoholism or a psychiatric condition that would interfere with cancer treatment, yet such problems are often not disclosed. Or, if an older person has five or six medical conditions, it's not unusual for them to mention only the most prominent condition, the one that bothers them most at the moment."

Patients should be prepared to give their full medical history, and caregivers and family members should help fill in the blanks if necessary. In addition, Dr. Yates suggested that treatment decisions for the elderly be family decisions, since older patients must often depend on their children to make therapy happen.

But he also warned that family members should not insist on aggressive treatment that the doctor considers futile. If the family has good reason to doubt the doctor's judgment, an independent second opinion should be sought, he said.

There are nonthreatening ways to expand the conversation about treatment options, Dr. Yates said, starting with a couple of perfectly reasonable questions for the doctor: "Is this the best option? If this were your mother or father, what would be your recommendation?"