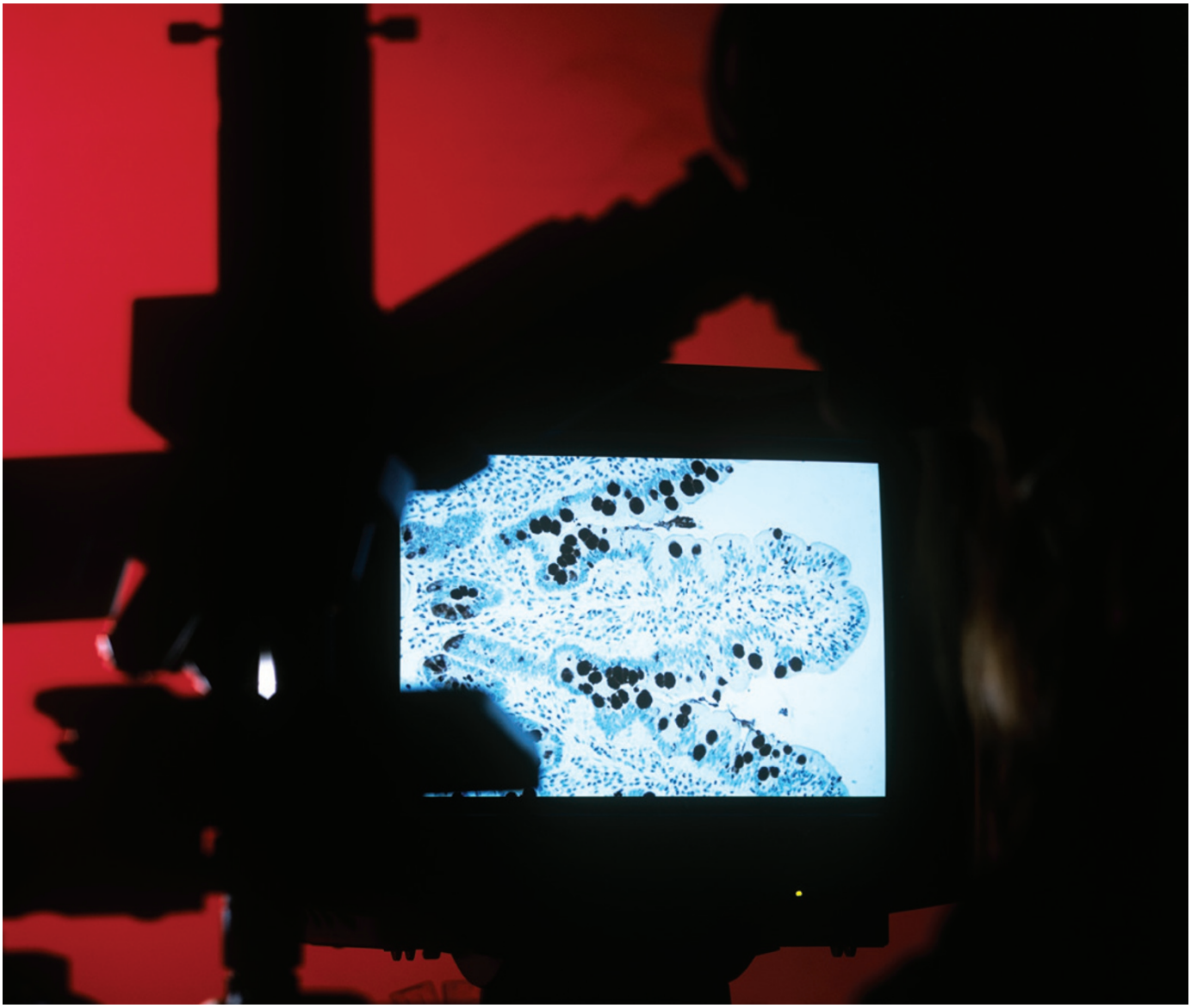

COLIN CUTHBERT/SCIENCE PHOTO LIBRARY

The search for suitable targets for anticancer drugs in the human intestine as seen through a microscope (antibodies are joined to a tags viewed as black dots).

CANCER

Solving an age-old problem

Is cancer ancient, or is it largely a product of modern times? And can the latest research on prevention and treatment strategies make cancer a disease of the past?

BY BARBARA DUNN

Cancer has been around since before the first humans walked the Earth. Fossilized dinosaur bones show evidence of tumours, and archaeologists have discovered a 2,700-year-old human skeleton with evidence of prostate cancer that had spread through its bones. The Greek physician Hippocrates named the disease after the Greek word for 'crab', perhaps because the tumour and its branching network of blood vessels reminded him of the multilegged creature. But was cancer common in ancient times, or is it largely a product of our modern industrial age? Can the latest biology and high-tech genomics research help us devise treatments that target each cancer's vulnerabilities or, better yet, can they prevent the disease?

Some scientists consider cancer to be a recent phenomenon, arguing that it was relatively rare in ancient times. Over the past century, population-based cancer incidence has increased dramatically. These higher rates are probably due to two factors: first, we are living longer; and second, our modern age has increased our exposure to cancer-causing chemicals in our environment and to radiation through X-rays, plane travel and other sources[1].

A century ago, life expectancy in the United States was 49 years. People were more likely to die of infections, heart attack or complications from other conditions such as diabetes than

they are today. Our improved sewage systems and community hygiene mean we are exposed to fewer infections than previously, and modern antibiotics help us survive many of the infections we do get. Effective medications have also reduced deaths from heart disease and diabetes. Today, we live about 30 years longer than we did in 1900. In addition, cancer is more common in older tissues, so many more of us now grow old enough to get cancer.

Decades of laboratory and clinical research dedicated to human health have shown that this ancient disease called cancer is not one disease but more than a hundred. Each type of cancer is named after the cell that becomes cancerous. For example, lymphoma is a disease of white blood cells called lymphocytes, and glioma is a disease of glial cells, which support neurons in the brain. Carcinomas that occur in the skin, breast, prostate, colon and lungs are often referred to as solid tumours, and are named according to the tissue they come from. They account for more than 80% of cancers. Leukaemias are cancers of the blood, sometimes referred to as 'liquid tumours', and results from aberrations in the division of blood cells.

This article will focus on tumours that are malignant, which means they can invade and damage nearby tissue and spread to other parts of the body. It will not cover benign tumours, which are growths that are spatially confined and do not spread. Once removed, benign tumours do not usually grow back.

All types of malignant cancer arise from changes or mutations in a cell's DNA that allow it to divide indefinitely[2]. Normally, cell division is tightly controlled by signals within and between cells. A cancer cell breaks free from this system of checks and balances. The deadliest changes occur when cancer cells break away from their tissue of origin, travel through the body, lodge in a distant tissue and begin growing again. This process, called metastasis, is responsible for nine out of ten deaths from cancer.

GARBLING THE GENETIC CODE

All multicellular organisms rely on cooperation and communication among their cells. What causes the body's cells to stop cooperating as they do in cancer?

In 2010, a group of scientists from the United States, Australia, Canada, Germany and France decoded the genome of *Amphimedon queenslandica*, a demosponge from the Great Barrier Reef. The scientists found that the sponge's genome contains 90% of the genes known to be involved in human cancer. Many of those genes are important in cell communication, growth signalling, apoptosis (cell suicide) and DNA repair. Each of these functions is crucial to the survival and function of a multicellular animal. When these functions are disrupted in a cell, cancer can result.

This sponge tells us that the potential to develop cancer is not new: sponges are some of the oldest multicellular animals and existed 635 million years ago. But it also tells us that cancer is an unfortunate consequence of multicellular life. Some of the same genes that allow us to function and thrive can be our downfall if they are damaged. That applies to humans as well as sponges.

Cancer results from mutations in genes that normally control growth, division and DNA repair and cell death. How do these mutations occur? Sometimes it's accidental: when a cell replicates, part of the genetic code is 'misspelled'. At other times, environmental factors, such as chemicals and radiation, or viruses can damage DNA. Chemical and biological mutagens may insert themselves into the DNA or damage the DNA so that when the cell replicates, its genetic code is forever changed.

Some mutations have no effect. They are like minor typing errors: there's a letter wrong, but the message still gets through. Other mutations can upregulate or downregulate a gene, increasing or decreasing the number of protein copies it makes. Some errors disable genes altogether, and others snap off parts of chromosomes and reattach them to other chromosomes in a cellular version of mix and match. This last process is the type of genetic change that occurs in a cancer called chronic myelogenous leukaemia.

"Researchers are now monitoring people exposed to the 2011 nuclear-reactor meltdown in northern Japan for cancer."

Some genes, called oncogenes and tumour-suppressor genes, serve to encourage or repress cancer, respectively. They are a bit like the accelerator and the brake of a car. In their normal states, oncogenes help cell division occur, and tumour-suppressor genes tell it when to stop. In half of all cancers, one important tumour-suppressor gene, called p53, is mutated and no longer does its job. When it or similar genes are mutated, cell division gets out of control.

It takes years, and usually decades, for a normal cell to acquire a combination of mutations that transforms it into a cancer cell. This is why cancer is more common in older people. It takes a long time for the right combination of mutations to accumulate without being repaired.

SOOT, BOMBS AND CIGARETTES

How do we know there are things around us that cause cancer? In the eighteenth century, Percivall Pott, an English physician, noticed that several of his patients were chimney sweeps with cancer of the scrotum (later identified as squamous cell carcinoma, a type of skin cancer). They often worked naked to avoid dirtying their only set of clothing. In 1775, Pott wrote an essay about 'chimney sweeper's cancer' that led to an Act of Parliament preventing men under the age of 16 from becoming chimney sweeps and forbidding men under 21 from entering a chimney. By the 1950s, chimney sweeper's cancer had all but disappeared, probably due to a combination of improvements in personal hygiene and chimney cleaning methods.

Pott's observations and methods are still being used today. He is considered one of the fathers of cancer epidemiology, a type of research that focuses on disease patterns in populations and looks for associations between certain exposures and cancer.

Epidemiological studies also helped clarify the dangers of radiation exposure. First, studies of fruitflies in the 1920s indicated that ionizing radiation, X-rays, gamma rays and ultraviolet light could cause genetic mutations. Then, in the largest epidemiological study of the effects of radiation on humans, researchers began following Japanese survivors of the atomic bombs dropped on Hiroshima and Nagasaki in the Second World War. Since the war, researchers have been comparing the number and type of cancers in the Hiroshima survivors with similar people not exposed to the bombs. They found that the Hiroshima survivors are at greater risk for cancer than the general population. In one study of more than 10,000 survivors, the most commonly diagnosed cancers occurred in the lung, colon, breast, thyroid and bladder, as well as the blood (leukaemia). Building on this knowledge, researchers are now monitoring people exposed to the 2011 nuclear-reactor meltdown in northern Japan for cancer and other radiation-related illnesses.

Today, it is common knowledge that smoking can cause cancer. Until the early twentieth century, however, some physicians believed that tobacco could be an effective medicine for everything from colds to headaches. By the 1930s, research was starting to indicate a link between smoking and lung cancer. Even so, tobacco companies gave out millions of free cigarettes to soldiers in the Second World War. Advertisements for cigarettes included endorsements by doctors and sports stars, and smoking rates continued to rise. After the 1964 US surgeon general's report described studies that definitively linked smoking with lung cancer, television and radio advertisements for cigarettes were banned. Since then, smoking among US adults has declined from 42% in 1965 to about 20% in 2009.

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Tobacco contains more than 250 harmful chemicals, of which at least 69 are mutagens[3]. Researchers who analysed the entire genome of a lung cancer cell found nearly 23,000 mutations

and calculated that smokers sustain one genetic mutation for every 15 cigarettes they smoke.

TREATING CANCER

Today, someone diagnosed with cancer is often treated by a combination of surgery, radiation and chemotherapy. However, few treatments for cancer are uniformly effective. Why does a particular treatment help one person with colon cancer, for example, while someone else with the same cancer getting the same treatment succumbs to the disease? Researchers are digging deep into the genomics of cancer to answer that question and devise better therapies.

Stinging nettle, edderwort, cucumber, heather, frankincense, honey, hedge mustard — what sounds like a grocery list for a wizard at Hogwarts is actually an inventory of ancient Egyptian treatments for cancer. These cures combined medicines with spells because Egyptians thought that such diseases were caused by evil gods or demons. Ancient texts also describe early forms of surgery to remove some breast cancers using cauterization with a tool called a fire drill[4].

A modern list of medicines is more likely to include methotrexate, paclitaxel, cisplatin, doxorubicin, gemcitabine, etoposide and fluorouracil. Like the ancient Egyptian treatments, some of these cancer therapies come from nature, but others are made in chemistry labs. Drugs to treat cancer are often extremely powerful and can have serious side effects.

Why are cancer cells so difficult to kill? Many anticancer drugs work by killing all the dividing cells — not just the cancerous ones but healthy cells as well. The resulting side effects range from bothersome to deadly. Radiation and chemotherapy damage and destroy rapidly dividing cells, including cancer cells as well as normal cells such as those in the hair follicles, the lining of the mouth and digestive tract, and the bone marrow. As a result, patients can lose their hair, experience severe nausea, vomiting and diarrhoea, and become susceptible to serious infections.

Scientists are trying to design 'targeted' therapies that can kill cancer cells without harming healthy cells. Such therapies depend on understanding what makes cancer cells unique, however. Cancer cells do not look like normal cells or behave like normal cells. So what distinguishing characteristics can researchers exploit to make targeted therapies?

Targeted therapy has had some striking successes, including treatments for certain leukaemias and breast cancers. The first targeted cancer therapy focused on the receptor for oestrogen, a female sex hormone that fuels the growth of some breast cancers. Targeted drugs that block the receptor stop cancer growth by preventing oestrogen from binding to the receptor. Today, several drugs work this way; they are called selective oestrogen-receptor modulators, and tamoxifen is the most widely used.

Other drugs block an enzyme called aromatase that the body uses to produce oestrogen. These drugs are called aromatase inhibitors. They lower oestrogen levels, slowing or stopping the growth of oestrogen-related tumours. Both selective oestrogen-receptor modulators and aromatase inhibitors result in increased survival rates and decreased risk of cancer recurrence in women with oestrogen-related breast cancers. In 1975, 75% of women diagnosed with breast cancer were still alive five years later; for women diagnosed between 2001 and 2007, this figure had risen to 90%. These data indicate the benefits of oestrogen-targeting drugs. Both treatments are useful in preventing breast cancer in women who are at high risk for the disease.

Another targeted therapy has turned a cancer that was almost always fatal into one that is nearly always treatable. Brian Druker, a researcher at Oregon Health and Science University in Portland, wanted to help his patients with a type of blood cancer called chronic myelogenous leukaemia (CML). He was studying the genetics of CML, which is caused by a chromosome translocation dubbed the 'Philadelphia chromosome'. Discovered in 1973 by Janet Rowley, the Philadelphia chromosome results from a reciprocal translocation: part of the long arm of chromosome 9 is fused to part of chromosome 22. The result is a fusion gene called *BCR–ABL*, which encodes an abnormal type of tyrosine kinase.

"Researchers found that smokers sustain one genetic mutation for every 15 cigarettes they smoke."

Tyrosine kinases trigger cells to divide, but the BCR–ABL form stays active longer than it should, causing cells to proliferate out of control. Why not create a drug to stop this rogue kinase? At first, no drug company thought it was possible, assuming that drugs would also block normal kinases and prevent all the cells from dividing.

As research progressed, however, Druker became convinced that a drug could be made to block the BCR–ABL kinase without blocking the others. He teamed up with Swiss pharmaceutical company Ciba-Geigy which was using computer modelling to develop new drugs. The company had found a chemical compound that appeared to block the BCR–ABL kinase almost completely, without seriously affecting other kinases.

By the late 1990s, this compound — eventually named Gleevec (imatinib) — was tested in a clinical trial of 31 people with CML. In a cancer clinical trial, researchers are usually happy if the experimental treatment shrinks tumours in 20% of patients. In the 1999 trial of Gleevec, 100% of CML patients went into complete remission after taking Gleevec. Their cancers disappeared and their blood appeared normal. In a second study, 53 out of 54 people with CML had complete remissions after taking Gleevec. The US Food and Drug Administration approved Gleevec in 2001 as a treatment for both CML and a rare form of stomach cancer.

Gleevec increased the five-year survival rate for patients with CML from 30% to nearly 90%. It was called a 'magic bullet' and was hailed as a miracle treatment. Even so, some patients found that their cancers came back. Why did that happen, and what could researchers do about it?

Cancer cells continuously have mutations in their genes. Some of these mutations changed the shape of the BCR–ABL kinase, allowing it to avoid being targeted by Gleevec. Charles Sawyers of the Memorial Sloan-Kettering Cancer Center in New York was one of the researchers who discovered that these mutations were happening. He was part of a team that developed another drug, dasatanib (marketed as Sprycel), to block the new kinase. A third drug, nilotinib, is also available for people with CML who aren't helped by Gleevec.

CANCER STEM CELLS

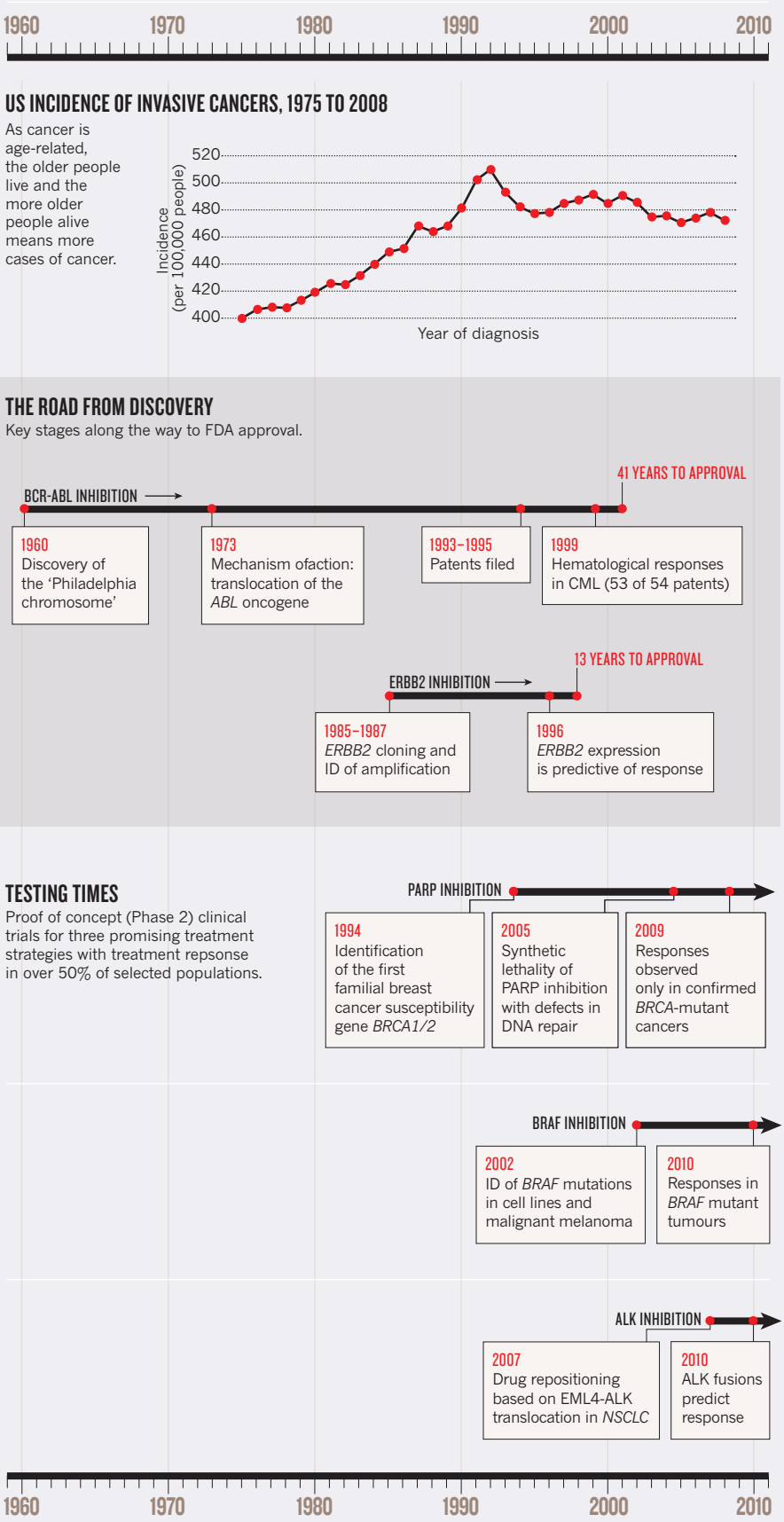
These drugs all had high success rates. Researchers hoped that these advances would quickly lead to similar progress in other cancers. Indeed, some drugs with exciting trial results are moving more quickly through the research pipeline now because of the greater understanding of cancer biology and genetics[5]. For most cancers, though, researchers have not yet found the critical protein or signalling pathway that drives the cancer. What else do we need to know?

Our knowledge of the human genome is helping us understand what goes wrong with genes in cancer tissue. We know that cancer comprises more than a hundred diseases, but it is even more complicated than that. Even within one tumour, there are different types of cancer cell. Some cancerous tumours can become resistant to drugs because they contain cancer stem cells. These cells divide asymmetrically, giving rise to two types of daughter cell: one type differentiates into regular cancer cells, and the second type remains as cancer stem cells that can self-renew and give rise to more cancer cells. The second type seems to be resistant to cancer-fighting drugs.

How were these cells discovered? Years of research suggested that most human acute myeloid leukaemia (AML) cells do not divide much and that there might be some 'parent' cancer cells that produce leukaemia cells. One group of scientists found that when they transplanted AML cells into mice, one type of cell moved to the bone marrow and began churning out leukaemia cells. The scientists identified this type as a cancer stem cell.

How can we stop cancer stem cells? Scientists have found three molecular pathways that cancer stem cells use when they divide: the Notch pathway, the Hedgehog pathway, and the Wnt/beta-catenin pathway. Researchers are currently

CANCER THROUGH THE DECADES



developing drugs to target molecules in these pathways that will shut down their cancer-causing activities.

PREVENTING CANCER

Can we stop cancer before it starts? Dozens of studies suggest that preventing some cancers has become a real possibility. One way to prevent cancer is to limit exposure to a carcinogen. This approach worked for those young chimney sweeps in nineteenth century England. It is also clear that not smoking cigarettes reduces lung cancer risk. Ten years after quitting, a former smoker has only about half the risk of lung cancer compared with someone who still smokes.

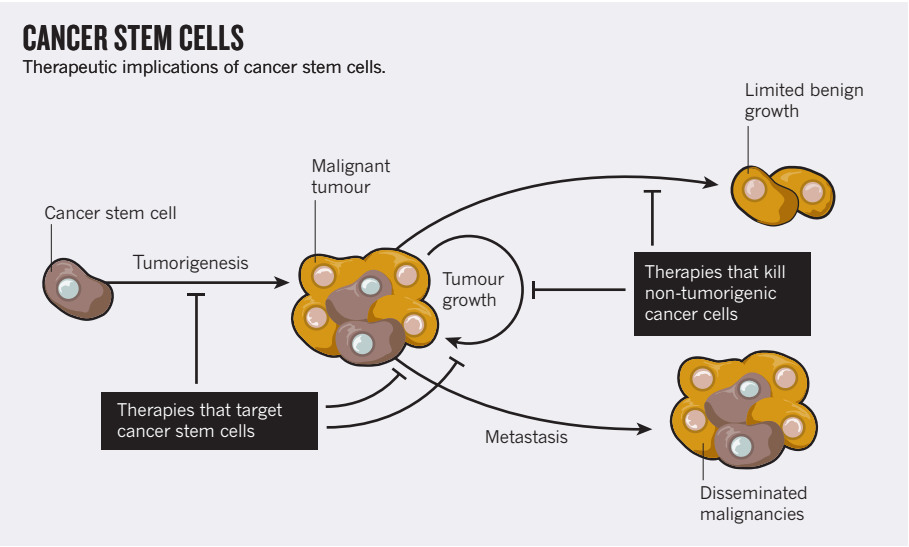
Changing addictive behaviours such as smoking is hard, but there may be other ways to prevent cancer. Researchers have recently developed a cancer-preventive vaccine, and others are testing nutrients that may protect against certain cancers.

The human papillomavirus (HPV) vaccine is an important new tool for preventing cervical cancer. HPV is a common virus spread by skin-to-skin contact during sexual activity, and it is the main cause of cervical cancer. Cancer of the cervix is the second most common cancer in women worldwide, with about 500,000 new cases and 250,000 deaths each year[6].

Like most research, development of these vaccines did not progress in an orderly fashion. Cervical cancer was blamed on a wide range of causes: the herpes virus, having an uncircumcised sex partner, having sex during menstruation, and even eating too much salt. But by the 1980s, scientists had linked HPV with cervical cancer. By 1999, they knew that HPV infection was necessary for cervical cancer to occur and that two specific strains of the virus, HPV-16 and HPV-18, are responsible for 60–80% of cervical cancers worldwide. Preventing cervical cancer means preventing infection with this cancer-causing virus.

Some vaccines work by using a weakened form of the live virus: measles, chickenpox and mumps are live vaccines. But the HPV vaccine could not be created with a live virus because there was a chance that it could lead to infection. Instead, researchers created the vaccine using a harmless viral particle that induces the immune system to produce antibodies to the active virus. After years of basic research and clinical trials involving thousands of women, two vaccines, Merk's Gardasil and GlaxoSmithKline's Cervarix, proved effective and were approved for use in the United States and several other countries in 2006 and 2009, respectively. Because the vaccine is effective only when given before infection, the US Centers for Disease Control and Prevention recommends inoculation for girls aged 11 or 12, before the start of sexual activity, but says that young women up to 26 should receive the vaccine if they haven't already.

For people who are at high risk for cancer because of their age, family history or other risk factors, chemoprevention drugs are being



developed. Because the hormone oestrogen encourages the growth of many breast cancers, scientists have developed several drugs to block oestrogen. In a recent study of more than 4,500 postmenopausal women with at least one risk factor for breast cancer, an aromatase inhibitor called exemestane, which works by lowering oestrogen levels in the body, was beneficial. The drug reduced the occurrence of invasive breast cancer by 65% over three years.

A HEALTHY DIET

Scientists are also re-examining ancient ideas about the benefit of a healthy diet by isolating beneficial nutrients and providing them in pill form. Many chemicals in foods have been shown to kill cancer cells in laboratory studies and to prevent cancer in animals. Some of the dietary components being studied are selenium, vitamin E, polyphenols (from green tea), lycopene (tomatoes), resveratrol (grapes and red wine) and omega-3 fatty acids (oily fish). These compounds work by many different mechanisms. For example, many nutrients — such as epigallocatechin gallate (EGCG) in green tea, resveratrol in red wine, and sulforaphane in broccoli — prevent cells from going through the cell cycle, which stops them dividing and giving rise to new cancer cells.

Sometimes a large prevention study shows that a compound that prevents cancer in laboratory and animal studies shows no benefit when tested in humans. For example, animal studies and epidemiological studies in people indicated that diets rich in two nutrients, beta-carotene and alpha-tocopherol (vitamin E), reduced the risk of lung cancer. Both molecules are antioxidants, compounds that may prevent carcinogens from damaging DNA and other cellular systems. However, large clinical trial of cigarette smokers in Finland that tested the two nutrients for their ability to prevent lung cancer found that those taking beta-carotene or alpha-tocopherol did no better, and in some cases did worse, than the men who took no supplements. Surprisingly, men who took alpha-tocopherol had fewer cases of prostate cancer. This finding led to another study that tested whether selenium and vitamin E prevented prostate cancer. Unfortunately, in this study, both vitamin E and selenium failed to prevent prostate cancer. These results demonstrate that researchers can't be sure about a compound's effectiveness until it is tested in the people who could potentially benefit.

Epidemiological studies also suggest that vitamin D is associated with a lower risk of a variety of cancers. Researchers are now testing it in clinical trials to see if it reduces the risk of breast and prostate cancers. Curcumin, the active ingredient in the Indian cooking spice turmeric, also seems to have cancer-prevention properties and is now in trials to see if it can prevent colon cancer. Resveratrol, which has antioxidative properties and slows down cell proliferation, is now being tested in trials for several diseases, including whether it can prevent or treat colon cancer.

Understanding the biology of cancer and the steps a cell goes through as it becomes cancerous helps make cancer screening possible. Cancer does not appear suddenly — most common cancers take many years to develop. Screening, or testing for early cancer or precancerous cells takes advantage of that long time frame. Screening does not prevent cancer, but it often detects the disease before it becomes dangerous.

Doctors use blood tests, computed tomography (CT) scans, colonoscopies, mammograms and other tests to screen for cancer. If someone is screened regularly, suspicious cells should be found early, sometimes even before they become cancerous. For example, during a colonoscopy, a screening procedure recommended for people aged 50 or over, a tube with a lens is inserted into the colon so the doctor can look for any abnormal growths called polyps. These polyps can be removed during the procedure so they never get the chance to grow further and become cancerous.

Modern cancer research has focused on improving our understanding of the way cancer cells differ from normal cells genetically and functionally. There is growing interest in learning how cancer cells interact with the normal cells and non-cellular substances that surround them (the microenvironment). These interactions will determine whether a cancer grows or not, and whether it metastasizes to distant parts of the body.

What about the body's natural immune response to cancer cells? Can we stimulate the surrounding areas and the immune system to reject tumours? Considerable research is focused on finding the cancer cells that give rise to cancer and cause resistance: the cancer stem cells. These are the progenitor cells that give rise to all the cells within a tumour and support cancer recurrence. Is there a way to aim treatments directly at these cells?

Prevention approaches in the past century centred on identifying and eliminating cancer-causing substances, such as tobacco. Today, researchers are focusing on ways to intervene with beneficial agents such as drugs, nutrients and vaccines to actively prevent cancer. Could vaccines one day be as effective against some cancers as they were against smallpox?

We need better screening methods to find common cancers early or even in precancerous stages. Can we develop imaging technologies to visualize the earliest cancer cells? Are there biomarkers in the blood or urine that offer an early signal that a cancer is growing?

Finally, we must consider the issues of cost and accessibility. In 2006, the United States spent US$104 billion on medical care for people with cancer. The United Kingdom spends 5.6% of its public healthcare budget on cancer, compared with 7.7% in France, 9.2% in the United States and 9.6% in Germany. One of the biggest challenges is to develop effective cancer treatments and preventive measures quickly and cheaply — the high cost of new targeted drugs is a major economic and political issue. As cancer care becomes more personalized, it also becomes more expensive. The future promises to be exciting as we come to understand the molecular differences among the myriad cancers, but we face a great challenge in ensuring that the therapies we develop are not beyond the reach of the patients who need them. ■

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