FT Health Combating Cancer

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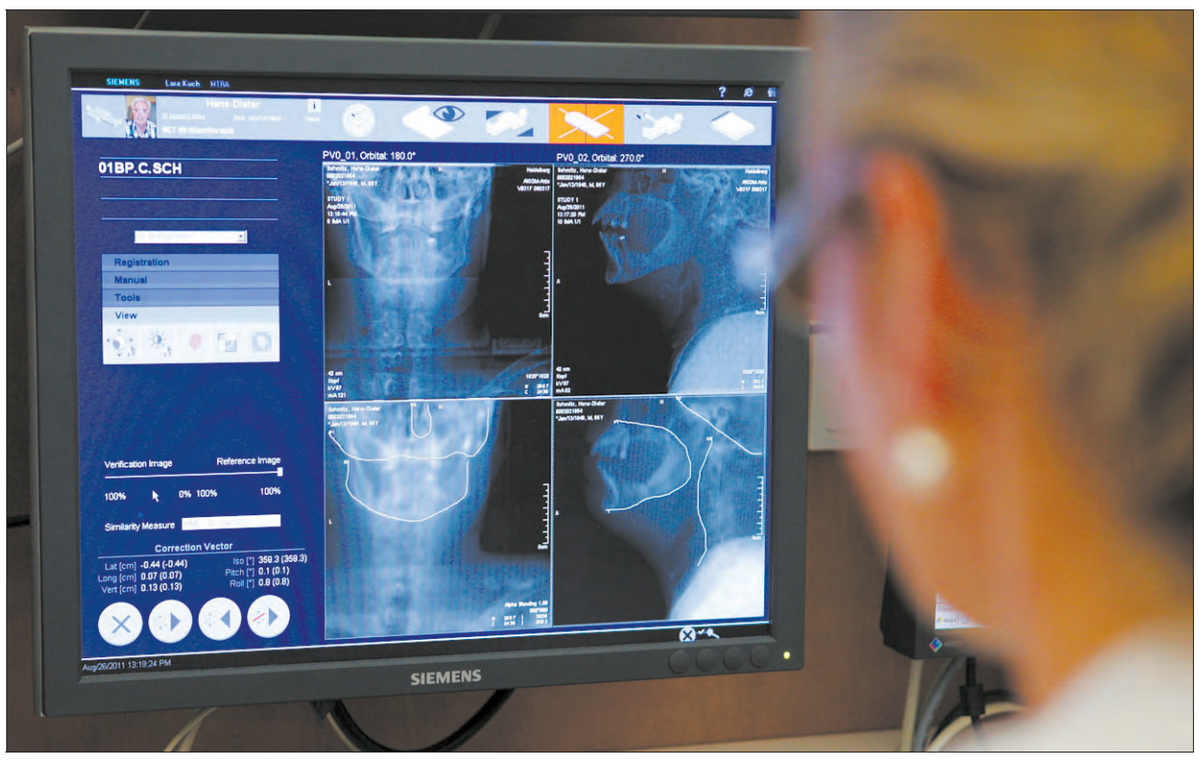
Chances of survival are on the rise



Significant advances have been made by scientists in the battle against the disease but victory remains elusive, says *Andrew Jack*

Forty years ago, inspired by the moon landings and frustrated by the festering conflict in Vietnam, US President Richard Nixon signed up to a bold new goal: a "war on cancer" supported by an unprecedented surge in government funding for research.

Since then, significant advances have been made by scientists in their "battle" against the disease, but long after south-east Asia became peaceful and the cold war tensions driving Nasa disappeared, victory against cancer remains elusive.

Harpal Kumar, chief executive of Cancer Research UK, says: "Progress has been very significant, but to declare ever that we are going to have defeated cancer is a stretch. We've come a very long way but the challenges are huge."

Poor quality data – in identifying cases, registering outcomes from treatment and confirming deaths from cancer – means precise figures are difficult. Yet estimates from 2008 suggest that, at least 12m people around the world contract the disease annually, 8m die from it and nearly 30m are living five years after diagnosis.

While the survival chances have risen for individual patients diagnosed early with a number of cancers, the global burden continues to increase. Prevention and treatment are having some impact in richer countries, but the effect is being offset by an ageing population surviving other diseases and becoming more susceptible to cancer.

In developing countries, the number of new cases identified continues to grow through both improved diagnosis and lifestyle changes, intensifying a "double burden" alongside regions still trying to cope with the impact of communicable diseases.

And while much emphasis has been placed on treatment, other areas offer potential to deliver greater impact.

Chris Wild, director of the International Agency for Research on Cancer, says: "We've really neglected the understanding of the causes and prevention of cancer. We can't treat our way out of this problem."

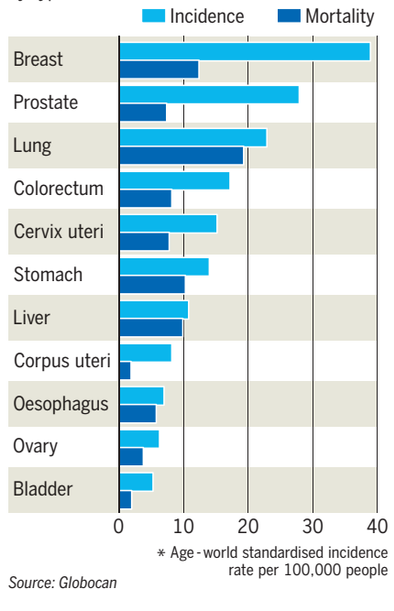
Undeniable progress has been made in drug development.

Glivec has provided a cure for many patients with chronic myeloid leukaemia; Rituxin and Herceptin have substantially boosted survival rates for other cancers. The therapeutic area continues to attract a substantial share of pharmaceutical industry investment.

Newer approaches include innovative combinations of drugs, molecules that cut off the blood supply to tumours rather than simply poisoning them and much else in the body besides, and "bispecific antibodies" that bind simultaneously to different sites or targets.

Harold Varmus, head of the US National Cancer Institute, is among those exploring with regulators, scientists and companies ways to test combinations of novel drugs and make clinical trials more flexible so that participants can be switched to the relevant therapies more rapidly. "This is a big, important topic," he says.

Estimated incidence and mortality
By type of cancer*, 2008



Source: Globocan

Screening: advances in imaging offer the potential not only to diagnose cancers more precisely and early, but also to study progress in treatment

Advances in imaging offer the potential not only to diagnose cancers more precisely and early, but also to study progress in treatment in detail to see more rapidly whether drugs are proving effective or should be switched.

Efforts to sharply reduce radiation levels in screening and therapy alike are helping cut risks and boost efficacy.

"The centre of gravity has often been based around the therapy," says Ger Brophy from GE Healthcare Medical Diagnostics, who sees a shift towards partnerships with drug companies around screening, imaging and companion diagnostics.

An explosion in genetic understanding has helped revolutionise understanding, revealing complex

Continued on Page 2

Inside »

Cruel hand of fate still has a role to play

Prevention Some factors may be beyond our control but others are not, says *Ling Ge*

Although many people believe that cancer is "in the genes", scientific research estimates that only 5 to 10 per cent of cancers are caused by inherited faulty genes alone. The risk also depends on environment and lifestyle factors that damage our DNA – many of which we have the power to change.

Recent reports by the Union for International Cancer Control (previously the International Union Against Cancer), World Cancer Research Fund and Cancer Research UK demonstrate the extent to which people can cut the risk of developing cancer by changing their lifestyle.

"The evidence is clear – about half of some cancers can be prevented by healthy lifestyles," says Sir Michael Marmot of University College London, who chaired the World Cancer Research Fund study. "A diet rich in fruit and vegetables and white meat, consuming little or no alcohol, being physically active for 60 minutes a day, and not smoking are key."

Smoking is the single largest preventable cause of cancer, causing 22 per cent of all cancer deaths and 71 per cent of lung cancer mortality worldwide, according to the World Health Organisation.

Tobacco smoke contains 70 cancer-causing chemicals. These carcinogens can damage important genes, making cells grow and multiply out of control. Both the number of smokers and deaths from lung cancer have halved in the UK in the past 50 years.

Every year, alcohol is associated with 3.6 per cent of all cancers worldwide, based on the WHO Global Burden of Disease project. The ethanol does the damage, regardless of the type of drink (beer, wine, or spirits), according to the World Cancer Research Fund. As few as three units (the amount in a pint of premium lager) a day can increase the risks.

A study by the US National Cancer Institute found that people who both smoke and drink are much more likely to get cancer than non-smokers and non-drinkers, because tobacco and alcohol act together to multiply the damage to the cells. Alcohol may act as a solvent and make it easier for the mouth and throat to absorb the harmful chemicals in tobacco smoke, or may slow the body's ability to break down malicious substances.

Diet accounts for nearly 10 per cent of all cancers if a lack of fruit and vegetables, too little fibre, too much red or processed meat and excessive salt are included. "Five a day" can help maintain a healthy body weight and reduce the risk of bowel, breast, kidney, womb and oesophageal cancers. Fibre activates the production of helpful chemicals that can stop the growth of tumours in the bowel.

By contrast, red and processed meat contain an iron pigment, called haem, that can stimulate the bacteria in guts to produce cancer-causing chemicals and damage human cells. Diets high in smoked and pickled foods are known to increase the risk of stomach cancer. Salt can harm the lining of the stomach, cause inflammation and interact with a bug that causes stomach ulcers and cancers.

Obesity and overweight are a cause of more than 5 per cent of cancers overall. The fat tissue in overweight people produces more hormones than those in people of a healthy weight. High levels of some of these hormones, including the female sex hormone oestrogen, can stimulate breast cancers.

Max Parkin, the epidemiologist who led the Cancer Research UK study, says "We didn't expect to find that eating fruit and vegetables would prove so important in protecting men against cancer. And among women we didn't expect being overweight to have a greater effect than alcohol."

Bounceback: exercise helps protect against certain cancers and 30 minutes a day, five days a week, can have a positive impact on health Dreamstime

Physical exercise helps protect against breast, bowel and womb cancer. Thirty minutes a day, five days a week, of moderate activity (such as walking, cycling, dancing, gardening or housework) can have a positive impact on health.

In relation to breast cancer, the World Cancer Research Fund analysed 7,000 studies and found that breastfeeding cuts the risk by 5 per cent by lowering the levels of cancer-related hormones in the mother's body.

For skin cancers, excessive sun exposure and sunbeds are linked to more than 10,000 cases in the UK each year. Sunburn can double skin cancer risks, so it is important to avoid the sun when it is at its most intense during the middle of the day. Sunbeds also emit harmful UV rays that damage the DNA in skin cells. They are estimated to cause about 100 deaths from melanoma every year in the UK.

In low-income countries, up to 20 per cent of cancer deaths are the result of infections by the hepatitis B virus, which causes liver disease and cancer, and by human papilloma virus which causes cervical cancer. They can be prevented too through vaccines (such as Merck's Gardasil and GlaxoSmithKline's Cervarix).

> 'Individuals can only choose healthy lifestyles if they have control over their own lives'

Other risk factors include occupations such as working with asbestos, radiation and using hormone replacement therapy (HRT).

While small changes to lifestyles can have a big effect on cancer risk, in reality it takes commitment to change the habits of a lifetime.

For example, although 50 per cent of bowel cancers in the UK in 2010 were ascribed to lifestyle, only half of this number is preventable on a 20-year timescale, the Cancer Research UK study estimated.

"Individuals can only choose healthy lifestyles if they have control over their lives. And that requires addressing the conditions in which we are born, grow, live, work and age: the social determinants of health," says Sir Michael.

"Quality early years, primary and secondary education; access to fair and decent employment; adequate income to afford healthy choices; living in safe environments and quality housing; and addressing the causes of healthy behaviours are critical," he says.

Big Tobacco's market place battle

Smoking

Manufacturers face increasingly stringent regulation, says *Christopher Thompson*

Despite the steady march of smoking bans in offices, restaurants and public spaces, tobacco use continues to kill nearly 6m people each year.

Accounting for one in every 10 adult deaths, smoking is arguably the most widespread public health threat in the world and the single biggest preventable cause of cancer.

While the vast majority of those killed are either smokers or ex-smokers, an estimated 600,000 die from the effects of inhaled second-hand smoke.

Little wonder that the Geneva-based World Health Organisation describes the habit as an "epidemic".

The government of Australia, which already has one of the lowest smoking rates in the world, plans to implement the world's toughest antismoking laws, dubbed "plain packaging".

All cigarettes would be sold in olive green packets, with the brands in standardised font and graphic health warnings – pictures of mouth cancer and other smoking-related illnesses – taking up most of the pack.

Unsurprisingly, Big Tobacco has fought back. The world's four biggest cigarette companies outside China – Japan Tobacco International, British American Tobacco, Philip Morris International and Imperial Tobacco – are suing the government.

They argue they are being stripped of their intellectual property. But, in August, the companies lost their first case in Australia's high court.

Nicola Roxon, the attorney-general, whose father, a smoker, died of cancer when she was a child, hailed the ruling as a watershed moment. "The message to the rest of the world is Big Tobacco can be taken on and beaten."

Plain packaging is due to be implemented in December. Alarmed that such regulation could spread to more profitable markets, some tobacco companies have provided support to Ukraine and Honduras – which have significant tobacco interests – in making a formal complaint against Australia at the World Trade Organisation.

In addition to being anti free-trade, Big Tobacco argues that plain packaging will make cigarettes easier to counterfeit and smuggle and therefore would not reduce cancer rates.

Nicandro Durante, chief executive of BAT, says: "It's a bad piece of regulation that's not going to meet public health goals."

Nevertheless, Britain, Norway, New Zealand, Canada, India and France are considering similar measures. The EU is expected to address the issue this year.

Gregory Connolly, director for the Centre for Global Tobacco Control at Harvard University, says tobacco companies are right to worry. "A nation such as Australia can adopt a very high ceiling," he says. "There's no level playing field [on regulation], so companies have to adapt and it drives the tobacco multinationals crazy."

But the bigger question is whether such regulation will expand into emerging markets, where 80 per cent of the world's 1bn smokers live and where cancer deaths could rise markedly.

> Smoking is arguably the most widespread public health threat in the world

Puffed: smoking kills nearly 6m people each year PA

Prof Connelly says: "In the 20th century, there were about 100m deaths from smoking in the west. We will have 1bn deaths in the 21st, the vast majority of them in the developing world."

Some developing countries are leading a fightback.

In March, Brazil announced a ban on all flavoured tobaccos – such as menthol cigarettes. It argued that such products lured youngsters into smoking.

In Uruguay, health warnings must cover 80 per cent of a cigarette packet, while smoking outdoors is banned near hospitals and schools.

But two of the world's biggest markets maintain a light touch when it comes to regulation.

A US federal court recently barred the government from requiring tobacco companies to put health warnings on cigarette packs on the grounds that they violated free speech laws.

As for China, where a third of the world's smokers live, the enforcement of smoking bans outside the main cities is lax.

For health campaigners, a more unlikely source of support may be found in tobacco companies themselves. Big Tobacco and a host of independent companies are betting that e-cigarettes, vaporisers and nicotine inhalers may be future alternatives.

Paul Triniman, chief executive of UK-based Kind Consumer, which is developing a cigarette substitute, says: "If you can allow smokers to get the nicotine hit without tar, there would be a significant improvement on a harm-reduction basis, whereby they can satisfy their craving without carcinogens and toxins."

Last year, BAT established Nicoventures, a division devoted to cigarette alternatives. It plans to launch a nicotine inhaler by the end of 2014. Philip Morris plans to launch what it describes as a healthier version of its cigarettes under the Marlboro brand in 2016.

But with Big Tobacco continuing to drive cigarette volumes in emerging markets, it is within national governments where the battle ground between public health and tobacco commerce lies.

"There are two trains coming – one is the tobacco companies and the other is states' exercising national sovereignty based on public health principles."

Nowhere left to hide

Vaccines

Clive Cookson reports on the scientific excitement surrounding therapeutic advances

Last week, CureVac of Germany completed what is likely to be the European biotechnology sector's largest private equity financing round this year, raising €80m to develop therapeutic vaccines for prostate and lung cancer.

CureVac is one of many biotech companies working on different types of vaccine – and related immunotherapy – to treat cancer. Its successful funding illustrates the appeal of this approach, which is still in its infancy.

When people think of vaccines, the first thing that comes to mind is inoculation to prevent bacterial or viral disease.

This type of "preventive vaccine" does have a role in cancer, blocking infection with viruses that can lead to cancer.

Hepatitis B vaccine, commercially available for 30 years, has reduced the incidence of liver cancer, for which the virus is a risk factor.

Two recently introduced vaccines against human papilloma virus (HPV) – Gardasil from Merck and Cervarix from GlaxoSmithKline – were developed more specifically to prevent cancer.

They protect against infection by two types of HPV that cause about 70 per cent of all cervical cancer worldwide.

But Cervarix and Gardasil are an extension of traditional preventive vaccination.

The scientific excitement is more about therapeutic vaccines designed to treat cancer already present in the patient.

These vaccines are designed to get the immune system to recognise and attack cancer cells, which are normally very good at hiding from it.

There are several ways of doing this. The first commercially available therapeutic vaccine – Provenge, made by Dendreon of the US – was approved by the Food and Drug Administration in 2010 for use against metastatic prostate cancer. Unlike many other cancer vaccines, Provenge, is customised for each patient. A brief description of its production will illustrate the complexities of cancer vaccines

Immune system cells, called antigen-presenting cells, isolated from the patient's blood, are cultured by Dendreon with a large protein called PAP-GM-CSF. This consists of an antigen found on prostate cancer cells (PAP) linked to a component that stimulates the immune system (GM-CSF).

The whole construct – antigen-presenting cells with PAP-GM-CSF – is then infused into the patient in three rounds of treatment.

Antigens – proteins on cancer cells that the immune system can attack – are the key to successful vaccination. Scientists have identified many cancer-associated antigens and some candidate vaccines are loaded with a number of them.

For example IMA910, a colorectal cancer vaccine developed by Immatics, another German company, contains no fewer than 13 tumour-associated antigens.

There are many ways of presenting antigens. Some cancer vaccines include whole cells and others have proteins or protein fragments (peptides). Another class contains DNA or RNA with the genetic instructions for making antigens, which are then carried out within the patient's body; the genes may be injected on their own or inserted into a harmless vaccine which carries them into the patient.

CureVac's technology uses single strands of messenger RNA (mRNA) that produces tumour antigens when injected into the patient's skin. "This is very safe but it gives a powerful immune response," says Ingmar Hoerr, CureVac chief executive.

Oncolytic cancer vaccines represent another promising approach. They are based on live viruses that preferentially kill cancer cells rather than normal cells. In the process they raise an immune response to the cancer.

The leading oncolytic vaccine company, BioVex – with a product called OncoVex in Phase 3 trials for malignant melanoma – was bought last year by Amgen, the US biotech giant, for $425m cash and up to $575m in additional payments, depending on performance of the BioVex portfolio.

PsiOxus, a small UK company that has just raised £22m in equity financing, offers an interesting twist on the idea of oncolytic vaccines.

> Proteins on cancer cells that the immune system can attack are key to vaccination

Its ColoAd1 product – on the brink of clinical trials for colon cancer – uses the power of natural selection to generate a new strain of adenovirus with extra power to kill cancer cells.

John Beadle, PsiOxus chief executive, says: "Our approach has been to develop a particularly potent cancer-killing virus through directed evolution. We set up a pool of viruses and use cancer cells as a way of screening for the best viruses.

"At each round, we select the viruses that most effectively kill cancer cells, so our lead virus has lost the ability to replicate in normal cells while being very potent in cancer cells."

Some companies are trying to boost the activity of the immune system to fight cancer, without involving specific antigens on tumour cells.

For example ZioPharm of the US is working with Interleukin-2 (IL-2), a signalling molecule that regulates the activities of the white blood cells responsible for immunity.

IL-2 is too toxic to be used on its own as a cancer drug, so ZioPharm is developing gene-based techniques for regulating its activity.

Jonathan Lewis, ZioPharm chief executive, says: "We have two alternative approaches [both in early clinical trials] to make IL-2 supercharge the immune system against cancer, while making sure the patient's cells do not produce too much of it."

Victory is still elusive

Continued from Page 1

varieties of conditions previously lumped together such as "breast" or "pancreatic" cancer. The evolution of "companion diagnostics" in response means the blunt instruments of the past are becoming more refined treatments that work more effectively in patients with particular mutations.

Susan Galbraith, head of the oncology iMed unit at AstraZeneca, says her company is cooperating with others developing rival drugs to jointly run trials, screen patients and determine the best treatment based on genetic tests.

Others call for earlier use of experimental drugs and their more swift "conditional" approval, even with limited data, notably in diseases such as pancreatic and lung cancer.

Yet the high prices already charged are triggering a growing backlash in many countries, including the UK, where the National Institute of Health and Clinical Excellence, the medicines' advisory body, has recommended against use of a number of cancer therapies as not cost effective.

In the developing world, the same pressures are coming to a head. This year, India issued its first "compulsory licence", overriding Bayer's patent on its cancer drug Nexavar, for which the company was charging patients $5,500 a month.

Spurred by the competitive threat from low-cost generic producers, other innovative manufacturers such as Roche are beginning not only to bolster drug donation programmes in poorer countries but also to introduce discounted "differential pricing" to build sales.

But for healthcare systems seeking better value for money, the intense focus on treatment risks are proving misplaced. "Drugs only have a quite modest impact on overall survival rates," says Prof Sir Michael Richards, the UK government's "cancer tsar". "Surgery remains most important, and radiotherapy comes second."

The greatest weakness today is early diagnosis, he says. "We have not done enough to get patients to come forward sooner."

> A quarter of British patients are diagnosed after turning up at emergency rooms

With about a quarter of British cancer patients still diagnosed only after presenting in the hospital emergency room, there is greater scope for public awareness campaigns to back screening breast, cervical and colorectal cancers. More open to debate is the use in some countries of the PSA test for prostate cancer, a source of "false positives" and often unnecessary surgery.

Still earlier options for prevention include two vaccines for infection-caused cancers: Hepatitis B which ultimately attacks the liver and HPV which causes cervical cancer.

More generally, an estimated 40 to 50 per cent of cancers around the world have environmental causes.

Healthier lifestyles, less red meat and alcohol, and reduced exposure to some pollutants and the sun could also have an enormous impact. Most important of all, lung cancer, one of the greatest killers, could be tackled with tougher controls on smoking.

Yet even as the burden drops in western countries as a result of declining use, tobacco companies are shifting attention to emerging countries and fighting public health initiatives.

New drugs have an important role to play, but many other parts of the "cancer continuum" require greater attention. That includes the impact of two generic drugs at the extremes of the spectrum for which there should be more funding and focus: aspirin for prevention and morphine for millions of patients who die without adequate pain relief.

The war on cancer may be far from won, but some of the cheapest and most effective existing weapons could still be far better deployed.

Science Research is advancing more quickly than any other important medical field and a vast number of new medicines is being tested by industry and academics, writes *Clive Cookson*

Fight is taken to a higher plane

Last week, the University of Texas MD Anderson Cancer Centre in Houston launched a $3bn research initiative – unprecedented in ambition for an individual medical institution – to "accelerate the pace of converting scientific discoveries into clinical advances that reduce cancer deaths".

The 10-year Moon Shots Programme, as the university calls it, takes its inspiration from the famous speech that President John Kennedy made in Houston exactly 50 years ago, announcing that the US would put men on the moon during the 1960s.

Although the MD Anderson initiative may sound uncomfortably like the ultimately unsuccessful "war on cancer" that President Richard Nixon launched in 1971 in the wake of the lunar landings, the scientific foundation for progress is far stronger now than it was 40 years ago.

Indeed, cancer research is advancing more quickly than any other important medical field, because cancer is ultimately a disorder of DNA – the result of genetic faults that may be inherited but more often are triggered by the vicissitudes of life – and new DNA reading technology is for the first time enabling scientists to unravel the complex chain of genetic events responsible for the disease.

A new projection by Cancer Research UK shows a 17 per cent fall in the rate of people dying from cancer by 2030

Cell work: DNA reading technology is enabling scientists to unravel complex chain of events responsible for the disease

The discoveries being made in cancer genomics illustrate why the disease has been so hard to beat. Cancer starts when a mutation in a single cell takes off the biological brakes that normally prevent uncontrolled proliferation. Then, natural selection, working on myriad random mutations that occur in rapidly dividing tumour cells, drives changes that enable tumours to grow – and develop resistance to drugs.

Genomic studies are revealing an unexpected genetic "heterogeneity" within individual patients, particularly those with more advanced disease, as tumours develop multiple evolutionary branches. In one sense, this diversity is bad news for diagnosis and treatment but, since knowledge is power, it provides a way forward.

The scientific message is that genomic profiling of cancer must become routine as soon as possible – which should not be a problem in the industrialised world if the costs of DNA sequencing continue to fall as fast as they have over the past few years – and treatments must be aimed at the genetic weak points in the individual's tumour.

It is clear too that multiple drug combinations are the future for chemotherapy, as they are for fast mutating viral diseases such as HIV/Aids. Cancer cells, like viruses, find it much harder to develop resistance to several drugs simultaneously.

Against this background the global pharmaceutical and biotechnology industry, in collaboration with academic researchers, is testing a vast number of new medicines. The Pharmaceutical Research and Manufacturers of America (PhRMA), the industry's trade body, says that almost 1,000 cancer drugs and vaccines are in clinical development – far more than for any other disease.

Unfortunately, only a small proportion of cancer drugs make it through the development process.

According to Ronald DePinho, MD Anderson president, 95 per cent fail at some stage during clinical trials, with 56 per cent of failure occurring in expensive late-stage testing.

So one aim of the Moon Shots Programme is to improve "translational research", the process by which drug candidates move from lab studies through animal testing into clinical trials. MD Anderson plans to use new organisational models with decisive milestones that weed out failures earlier in the process, to accelerate the speed and raise the success rate of the handover from academia to industry.

"The programme will not simply discover the genetic mutations that cause cancers, and not simply develop the drugs," Dr DePinho says.

"It will put into place the right kinds of clinical trials that test these drugs at a faster pace than the current system."

There are similar translational initiatives elsewhere. In Britain, Cancer Research Technology, the commercial arm of the charity Cancer Research UK, recently set up a £50m investment programme in partnership with the European Investment Fund to bridge the funding gap between cancer drug discovery and development.

The so-called CRT Pioneer Fund aims to speed the passage of "the most exciting scientific discoveries made by Cancer Research UK scientists" and by other academic groups from their labs through to the start of Phase 2 clinical trials.

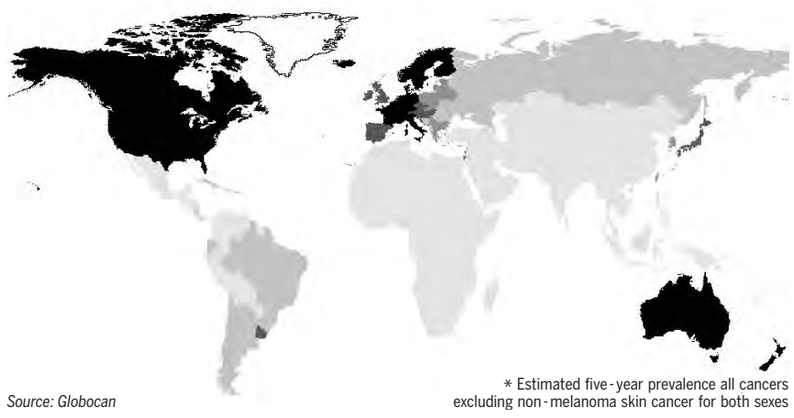
Cancer is such a complex challenge that it would be naive to expect a total transformation of the prospects for patients over the next 10 or indeed 20 years. The Apollo programme could claim success when astronauts walked on the moon and returned home to tell the tale; there is no such clear endpoint for cancer research.

But we can certainly expect a significant reduction in the number of people dying prematurely of cancer, even as the number living with the disease rises. A new projection released this week by Cancer Research UK shows a 17 per cent fall in the rate of people dying from cancer by 2030.

"For many cancers, adjusting for age, death rates are set to fall sharply in the coming decades," says Peter Sasieni, Cancer Research UK epidemiologist. "What's really encouraging is that the biggest cancer killers – lung, breast, bowel and prostate – are part of this falling trend."

Cancer prevalence

Estimated pervalence per 100,000 adult population*, 2008



Source: Globocan

* Estimated five-year prevalence all cancers excluding non-melanoma skin cancer for both sexes

Bid to put an end to carpet bombing

Chemotherapy

Alan Rappeport reports on efforts to sharpen one of medicine's bluntest instruments

Chemotherapy is widely considered to be among the bluntest of medical instruments, destroying healthy cells and attacking taste buds and hair follicles as it attempts to kill off cancerous tumours.

But researchers are working to make chemotherapy a more targeted treatment while reducing some of its more painful side effects.

Chemotherapy advances will be a big part of "Moon Shots" programme recently announced by the MD Anderson Cancer Centre in Houston, which will invest $3bn in cancer research over the next decade.

"Chemo is and will remain a mainstay of treatment for advanced and early stage cancer," says John Heymach, of MD Anderson. "We need to learn how to use chemo more effectively and we're developing markers to determine which chemo works best."

Chemotherapy is known for leading to hair-loss, fatigue and neuropathy. A new study in the journal, Cancer, found that the treatment can also have long-term cognitive effects, reducing the ability to speak clearly and to process information quickly.

"We found that chemotherapy-treated patients performed worse than non-cancer controls in processing speed, executive functioning and verbal ability, says Paul B Jacobsen, associate centre director for Population Sciences. "These domains may be the domains most affected by chemotherapy."

Dr Heymach says the Moon Shots programme will use genomics to help learn about genetic mutations in cancer cells so that doctors can choose the most effective chemotherapy treatments for their patients.

Genomics can also help provide a deeper understanding of why cancerous tumours mutate and become resistant to treatment. "Besides matching people with the right drug, we want to figure out why it doesn't work for some people," says Dr Heymach.

New studies are seeking answers to that very question. Earlier this month, researchers from University of California-Irvine located a genetic pathway in melanoma cells that can block them from detecting the damage that chemotherapy imposes.

This has the potential to prevent cancer from building up a resistance to the chemotherapy, making the tumours more treatable. "If we can find a way to turn off the pathway responsible for this resistance, melanoma tumours would suddenly become sensitive to therapies we've been using for the last 20 years," says Anand Ganesan, assistant professor of dermatology and biological chemistry at UCI.

Another recent study in the journal Nature Medicine, found that resistance to chemotherapy is the result of an increase in a protective protein that develops around a tumour during chemotherapy treatment, allowing the cells to grow and invade surrounding healthy tissue.

'You might hit your target but you'll hit lots of other targets as well'

The scientists, led by the Fred Hutchinson Cancer Research Centre, are looking for ways to block the development of the protein to improve the effectiveness of the chemotherapy.

"Cancer therapies are increasingly evolving to be very specific, targeting key molecular engines that drive the cancer rather than more generic vulnerabilities, such as damaging DNA," they wrote. "Our findings indicate that the tumour microenvironment also can influence the success or failure of these more precise therapies."

Because of the toxic nature of chemotherapy, cancer research is being increasingly dedicated to finding innovative ways of avoiding it or limiting its use.

According to Dr Heymach, immunotherapy could be the next frontier in cancer treatment. New medicines hope to enhance the immune system to better fight cancer, while blocking mechanisms that allow tumours to suppress the immune system. "Chemo is sort of like carpet-bombing," Dr Heymach says. "You might hit your target but you'll hit lots of other targets as well."

Robotics are a 'game changer'

Surgery

Sophisticated tools are now available for what used to be inoperable cancers, says *Sarah Murray*

A robot that looks like a mechanical snake could soon be added to the growing number of sophisticated tools helping surgeons operate on previously untreatable cancers.

Some believe these kinds of technologies have the potential greatly to increase access to sophisticated treatments.

"Robotics is changing the game in surgery," says Raphael Pollock, head of the division of surgery at the University of Texas MD Anderson Cancer Center in Houston. "This is because the technology is continuing to evolve rapidly."

With cameras attached to them and a series of complex hinges, microscopic robotic hands can replicate the action of the wrist. Opto-electronic display systems allow the surgeon to manipulate the robot while watching a high-density, high-resolution screen.

"A human hand can only do so much in deep, tiny critical structures," says Steven Kalkanis, a neurosurgeon and director of the Center for Cancer Surgery at the Henry Ford Hospital in the US.

"But," he adds, "a robot remotely controlled by a human surgeon using something like a joystick, can perform manoeuvres such as tying a knot or putting two vessels together that otherwise would be physically impossible."

Other technologies and navigation procedures are also enhancing the precision with which surgeons can remove tumours. This means they can eliminate more cancer cells, lowering the chance of recurrence, while also protecting normal tissue surrounding the tumour.

Among those recently to emerge is interoperative MRI, which allows surgeons to visualise tumours as they are operating on a patient. This has important implications for brain surgery, where it is essential to avoid damaging healthy surrounding tissue.

"But it's not just the interoperative MRI that's important," says Dr Kalkanis. "It's also all the new tools, software and tagging devices that go with it."

By conducting functional tests on patients before surgery, surgeons can see where, as the patient is speaking, different parts of the brain light up and can use those tests to map individual brain function. "We beam those images to our interoperative scanner so that, in addition to the anatomic view, it can give us a functional view of the fibres and pathways that are important for this person."

The patient can be woken during the procedure to give surgeons real-time feedback on the functioning of their brain.

"Even 15 years ago," says Dr Kalkanis, "you would have had to use your anatomical teaching to estimate the location of a lesion and avoid structures that would affect a person's ability to speak, see or move. This gives us an entirely different world."

As well as being able to offer patients greater precision in surgery, the medical community is also anxious to find new ways of bringing cancer treatments to a larger number of people to combat the rising incidence of cancer in a global population that is ageing rapidly.

Experts believe robotics offers great potential. The promise lies partly in the fact that the technology allows procedures to be performed remotely, opening the way for surgery to be offered to those currently unable to gain access to certain forms of treatment.

$37bn

Amount needed to correct the shortfall of surgeons

Robotics will allow greater use of tele-surgery. For there is little difference between having a surgeon sit in an operating room using a console that is seven metres from the patient and having one sitting hundreds of miles away.

This will allow surgery to be taken to increasingly remote areas – even to the battlefield, for example – while also extending the provision of surgery to patients who are unable to gain access to sophisticated services run from cancer centres, which tend to be located in large cities.

Further ahead, robotic technology could also be used to shorten the time needed to train surgeons.

This will be critical, not only because of the rising incidence of cancer in ageing populations but because insufficient numbers of surgeons are being trained to cope even with current demand.

Dr Pollock believes using robotics in surgical simulation training could shorten the five-to-seven years it takes to train a surgeon.

"We're going to experience a shortfall of surgeons in the next decade," he says.

"Conservative estimates are that correcting the shortage in the US using current training methodologies would require an infusion of $37bn – and that's just not going to happen."

Better, pricier and still too rare

Radiotherapy

Treatments are improving, but are still not readily available. *Sarah Murray* reports

Since 1903, when doctors first reported the successful use of radium to treat cancer, increasing the accuracy of radiotherapy and reducing damage to healthy tissue has been a big concern.

Today, new technologies are facilitating high-precision treatments. Yet with global incidence of cancer rising rapidly, the cost of some new technologies is at odds with the pressure to find affordable ways to treat increasing numbers of patients.

Certainly, the advances being made in precision delivery of radiation are a cause for optimism. Driving this is imaging technology, that enables doctors to obtain a much clearer view of tumours.

Simon Powell, chairman of the department of radiation oncology at New York's Memorial Sloan-Kettering Cancer Centre, says: "If you have a tumour that sits on your auditory nerve, behind the ear and next to the brain and you only want to hit a 5mm spot, that can now be localised with pinpoint accuracy by a range of image-guided radiotherapy machines."

The technology also means that physicians can use higher doses of radiation while limiting damage to healthy tissue.

Imaging is particularly helpful when treating lung, liver or pancreatic cancers and other tumours that lie close to the diaphragm and so move around as the patient breathes.

"In the past, we could only get a snapshot of the tumour, usually not representing the whole picture," says K.S. Clifford Chao, chief of radiation oncology at New York-Presbyterian Hospital. "But advances in four-dimensional imaging allow us to see the tumour while it is moving, to what degree it moves and in what direction it moves, so that radiation can pinpoint it."

Tumour tracking will be enhanced by technology currently in development, whereby radio frequency beacons are implanted into a tumour. "They transmit where they are, just like a GPS system," says Dr Powell.

Meanwhile, many see potential in proton therapy – an ionised hydrogen atom that is positively charged.

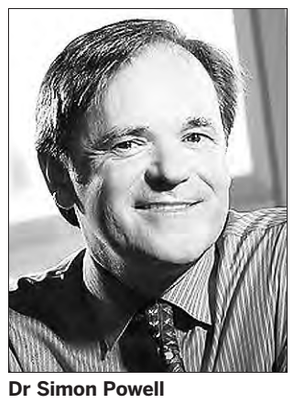
The disadvantage of X-ray beams delivered using a linear accelerator is that they need to have high energy to penetrate human tissue and reach their target, and they travel in one direction, exiting the body on the other side, affecting healthy tissue along the way.

By contrast, high-energy protons can penetrate a human body but because a proton is a charged particle, it has different properties, travelling a certain distance into the body and stopping to deposit all its energy.

"It's like stealth bomber," says Dr Powell. "It doesn't do much on the way in, doesn't exit at all and you can fine-tune where the radiation goes."

Advances in the precision of radiation treatment play into another area of development – the use of radiation in combination with drugs that make cancer cells more sensitive to radiation therapy.

Because these drugs increase the receptivity of cancer cells to radiotherapy, they also make it possible to use radiation in lower doses. When this is combined with technologies allowing precision application of radiation, radiotherapy's therapeutic benefits can be further increased.



Dr Simon Powell

However, while the sophistication of cancer treatments is increasing, many come at a high price.

Dr Powell says: "The cost of building a proton therapy machine is about $40m to $50m a unit, whereas to buy and install a linear accelerator is about $6m."

The cost increases further when it comes to building the infrastructure needed to house and operate these machines.

For many countries, this kind of investment is not possible. Meanwhile, budget cuts and restricted access to capital in mature economies mean that less money is available to support widespread use of certain healthcare technologies.

Set against this is the rising demand for cancer treatment equipment. Dr Chao cites World Health Organization estimates that, to treat cancer adequately, a radiation therapy machine would be needed for every 250,000 citizens.

"Using that estimate, the world would need 20,000 more treatment facilities to conquer cancer today – yet existing vendors can only produce about 1,000 a year," he says.

"So we must look at the overall global need, understand the whole scope of the technology and look at the bigger picture."

Millions lack access to painkillers

Palliative care *Andrew Jack* reports on failures in the terminal stages of disease

India may be one of the world's largest legal cultivators of poppies, but its population has scant access to the cheap opium-based painkillers such as morphine that are made from them.

Like their counterparts across much of the developing world, cancer patients in India suffer not only from poor quality diagnosis and treatment but also great problems in the terminal stages of the disease of being able to die with dignity and in comfort.

In recent decades, much effort has gone into improved prevention and new drugs to tackle cancer globally, but there is still much less attention paid to those for whom such interventions are no longer relevant.

In even the best resourced countries, that is reflected in concerns over where and how people are cared for. Elsewhere, there is a gap in even basic access to the most rudimentary forms of support.

M R Rajagopal, director of the Trivandrum Institute of Palliative Sciences in Kerala, India, says: "The developing world has 80 per cent of the global population, but most either have no access to treatment or, in huge countries like India and China, they can obtain the most expensive modern forms of treatment but not simple cheap things like painkillers. It is a paradox that is very difficult to understand and accept."

He says that the low price of generic painkillers means there is little financial incentive for drug companies to lobby for or improve distribution.

He emphasises that Kerala has more enlightened policies on access than most of India, but says: "Even major high-tech hospitals here very often do not have morphine. Patients have to go through severe agony, and have access only when they are brought to palliative care units."

One of the principal reasons for limited supplies of painkillers in much of the world has been what Raymundo Escutia Gutiérrez, a pharmacist at the University of Guadalajara in Mexico, calls "opiophobia". Suspicion of abuse, diversion and narco-trafficking has dominated much international and local thinking, with the needs of legitimate patients largely dismissed.

"We estimate that 90 per cent of patients cannot get access to morphine in Mexico," he says. "Abuse of morphine is not a big problem. Mexico is famous for narco-trafficking, but it is mainly marijuana and cocaine. There is not much abuse of opiates."

Poppy paradox: India is one of the world's largest legal cultivators of poppies, but its population has little access to morphine and instead resorts to herbal cures being prepared above Alamy

He says that tight controls on the use of painkillers by the authorities mean that few pharmacists are authorised to stock them, and patients who travel long distances to gain access often experience delays because of difficulties in obtaining prescriptions with suitable wording.

Pharmacists themselves are sometimes afraid to stock painkillers because of fear of theft.

Globally, the International Narcotics Control Board and the UN Office on Drugs and Crime have long focused more on stamping down on criminal abuse of drugs than understanding patients' needs.

Diederik Lohman, acting head of the health and human rights division at Human Rights Watch, says that has changed significantly in recent years, with current initiatives to encourage a more enlightened approach.

But he says that the traditional enforcement-oriented control mentality still permeates many individual countries.

"Patients tend to be invisible to policy makers," he says. "They are so sick they can't really advocate for themselves, and their relatives tend to be overwhelmed by taking care of someone dying of cancer with a lot of pain and anxiety."

Even where a growing number of countries has pledged renewed commitment to palliative care on paper, implementation is rare. He cites the example of Ukraine, which has a strong written policy on end-of-life care with plans for nine specialist centres. "But while there are allocations for prevention, detection and curative treatment, there is no budget line for patients who are no longer curable," he says.

> Suspicion of abuse, diversion and narco-trafficking has dominated thinking, with the needs of patients neglected

That leaves a final cultural issue that affects patients around the world in need of palliative care: the attitude of the medical profession, which is often poorly trained or prepared to deal with death and may be tempted to keep people in hospital and on painful treatments even when there is little point.

"We've got a long way to go in dealing with medical personnel and the public's perception of death," says Jayne Chidgey-Clark, regional nursing manager for Marie Curie Cancer Care in the south-west of England. "We all have to die at some point, but for some clinicians it's still seen as a failure. It's only a failure if it's not a good experience."

She highlights the need for greater emphasis on the "four pillars' of physical, emotional, social and spiritual support. That requires more open discussion with patients and their families, both dealing with anxieties such as drawing up wills and in understanding where best they want to die.

For some, that might be at home in their garden surrounded with family; for others, in a hospice, with quiet and room for relatives to be with them and grieve.

Nonetheless for too many, it is in hospitals, where limited space and privacy impair the experience.

Much more could be done to prevent and treat cancer, but palliative care can sometimes seem more neglected than everything else.

Continent left behind in battle

Africa

Some diseases receive more attention than others, says *Andrew Jack*

Long after new medicines have turned HIV into a treatable disease, the cancer that 30 years ago was often one of the first signs of the infection remains a powerful scourge across Africa.

Kaposi's sarcoma, which causes lesions on the skin and within the body, has historically been identified as an important ailment in Africa.

Its expansion, linked to HIV and its continued burden, even as antiretroviral treatment has spread across the continent, highlights continued imbalances in attention to different types of disease.

It is just one example of the many cancers in Africa receiving inadequate support. In 2008, there were nearly 700,000 new cases and an estimated 500,000 deaths, and in 2030 projections suggest there will be 1.3m new cases and 1m deaths.

"Unfortunately, there has been very little investment in prevention, diagnosis and care of people with cancer," says Alex Coutinho, head of the infectious diseases institute at Makerere University in Uganda.

Much support has been provided to HIV and other infectious diseases in the region – and much of the rest of the developing world – since the turn of the millennium.

Yet cancer remains neglected, even as experts warn that its burden is set to increase sharply.

Isaac Adewole, vice-chancellor of the University of Ibadan in Nigeria, says: "There is poor infrastructure, human resource needs and the money is not there. Although communicable disease is important, it's appropriate in the 21st century to talk about a double burden with cancer."

Traditionally, donors have been drawn to other diseases, led by HIV, whose treatment is funded via bilateral aid agencies and multilateral organisations led by the UN-backed Global Fund to fight Aids, TB and Malaria.

David Kerr, a professor of cancer medicine at Oxford university, who organised a conference in London this month to boost research collaboration on cancer in Africa, calls for a shift away from specific diseases towards strengthening health systems in general.

Yet, he says he has struggled to win support from the UK government to allocate more of its development budget to chronic diseases. But Ted Trimble, head of the US National Cancer Institute's Center for Global Health, says that, while many US institutions began by supporting their African counterparts with work on HIV, they are now extending their activities to cancer.

Pressure rising for cheaper cancer treatments Alamy

There is plenty of scope for additional research, although it is sparking debate about how to boost research and clinical trials.

There are some distinctive aspects to cancer in Africa, with a far higher proportion than elsewhere linked to infection. The sexually transmitted HPV virus, for example, causes cervical cancer, and Hepatitis B, leads to liver cancer.

> 'There is very little investment in prevention and care of people with cancer'

That highlights the potential for greater prevention programmes, since both could be sharply reduced with wider use of existing vaccines.

Some researchers are investigating genetic variations that may explain differences in the prevalence of certain cancers. Luiz Antonio Santini, head of Brazil's National Cancer Institute, says: "It's a myth that cancer is the same around the world."

Regardless of genetic variation, malnutrition and the differential impact of other diseases, including HIV, the choice and dosage of cancer drugs in Africa may in any case need to be different from those used in other parts of the world. Lower reported rates are partly linked to under-diagnosis.

That highlights the importance of improved registries to identify and record the cause of death and better understand disease trends.

Much diagnosis remains crude. Christine Berling, head of the international affairs department at the French National Cancer Institute, says that one "telepathology" programme designed to provide analysis remotely found that more than half of women operated on for breast cancer in one African country did not in fact have the disease.

Researchers see clear evidence of an expansion in cancers linked to increasingly "western" lifestyles, with more passive working patterns and dietary changes.

Some have suggested that a decrease in breastfeeding may be driving an expansion in breast cancer, for instance. Most argue that more efforts should focus on halting the growth in smoking, just as the tobacco companies expand in Africa as their more established markets decline.

There is at least one other parallel between cancer and HIV. Just as the need for affordable antiretroviral medicines became a point of conflict at the start of the decade, so pressure is rising today for cheaper cancer treatments.

"Cancer is my next humanitarian target," says Yusuf Hamied, head of Cipla, one of India's leading generic companies which led the charge. He may primarily be manufacturing in India, but his focus is again turning to Africa.

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