50 YEARS OF GLOBAL HEALTH PROGRESS

STORIES OF PROGRESS: Cancer

Persisting in research and innovation to deliver better patient outcomes

CANCER

Present Day...

JANE'S BREAST CANCER JOURNEY

Jane discovers a lump in her breast and is diagnosed with breast cancer. The tumor is removed, followed by a course of chemotherapy, after which she undergoes hormone therapy to reduce the risk of it returning.

Fifty years ago...

In 1968, Jane would have undergone a radical mastectomy, surgically removing the entire breast and much of the underlying musculature, and her cancer would still have a high likelihood of returning.

In the future...

Jane hopes that targeted therapies will be developed that can defeat all hard-to-treat and metastatic cancers. Immuno-oncology therapies offer hope that people’s own immune systems can destroy all types of cancer cells, preserving healthy cells.

Cancer is not a single disease but a group of over 100 diseases, each one incredibly complicated. Treatment is a complex process with many stages, varying in each patient and from one type of cancer to another. This complexity calls for many more specializations within diagnostics, surgery, radiotherapy and beyond than other disease areas. Early detection is often the difference between life and death.

In the past 50 years understanding of cancer has advanced considerably, and treatments are far more effective, and less punishing. From 1991 to 2015, nearly 2.4 million cancer deaths were averted in the US alone, primarily as a result of new and innovative therapies. Some cancers that were once terminal in every case are now generally treatable. In 1968, a child with acute lymphoblastic leukemia (ALL) had a diagnosis that was almost uniformly fatal. Today’s best treatments provide cure rates approaching 90% for ALL.
These gains have been hard won. Fifty years ago, doctors had few tools to treat cancer, success was limited and interventions often difficult for patients to endure. The development of successful treatments for cancer has followed our understanding of the biology of the disease, attained through incremental advances and occasional moments of great insight.

The fight, however, is far from over: cancer remains the second leading cause of death globally. There has been tremendous progress in some areas, but there is also huge disparity in results depending on the type of cancer, and by geography. Approximately 70% of deaths from cancer occur in LMICs,261 where many of the improved outcomes seen in well-resourced settings have not carried over. With around one-third of deaths from cancer due to the five leading behavioral and dietary risks,262 cancer prevention remains one of the key priorities for public health.

KEY MILESTONES

1968: Studies of cancer in nonhuman primates provided compelling new evidence that the Epstein-Barr virus, discovered four years earlier, can lead to cancer in humans.263

1971: Discovery of tamoxifen for breast cancer.264

1971: The hypothesis that tumor growth is angiogenesis dependent (the physiological process through which new blood vessels form from pre-existing vessels) and that inhibition of angiogenesis could be therapeutic, is first proposed.

1975: Technique for producing monoclonal antibodies265 is developed. MABs help the immune system to attack cancer. Many different MABs are available today to treat cancer, with more in clinical trials.

1981: Trials organized by Bernard Fisher, a Pennsylvania surgeon, show that removing just the tumor and not the whole breast works equally well for early breast cancer.266

1983: The first study demonstrates the function of a cancer-causing gene, the sis oncogene.267

1984: Harald zur Hausen268 discovered HPV16 and HPV18 responsible for approximately 70% of cervical cancers.

1998: Trastuzumab, a monoclonal antibody drug aimed at hormone-sensitive breast cancer, is licensed.269

2003: Completion of the human genome project, turning point in cancer research.270

2006: HPV Vaccine licensed in the US.271

2011: The FDA approves the first medicine, ipilimumab, using a new treatment approach which harnesses the body’s own immune system to fight cancer, called immunotherapy or immuno-oncology.272

2013: Research reveals 80 new genetic variations that increase the risk of breast, ovarian and prostate cancers.272

EARLY TREATMENTS WERE INCREDIBLY HARSH, AND RARELY EFFECTIVE

The discovery that specific toxic chemicals administered in combination can treat certain cancers ranks as one of the greatest innovations in modern medicine. Childhood leukemia, testicular cancer, and Hodgkin’s disease – previously fatal – are now generally curable through chemotherapy. Advances in surgical procedures and radiotherapy were also remarkable and often life-saving.

The approach of using chemotherapy to kill cancer cells – which unavoidably also kills non-cancerous cells – had severe side effects. Many patients did not survive this aggressive treatment, and some found that chemotherapy itself could cause cancer. This approach dominated the 1960s and 1970s.

By the 1970s, breast cancer was among the leading causes of death among American women.277 The radical mastectomy – an extreme surgery removing the breast, lymph nodes and musculature – was pioneered at the turn of the 20th century.278 This was based on the flawed understanding that cancer spread outwardly in a concentric fashion from a central point, making surgery a primary means of saving life.

In 1971, the US embarked on a ‘war on cancer’ beginning an era of huge investment in cancer research. Limited understanding of the disease meant that research was based on trial and error, and progress was slow. Scientists were deeply divided over competing theories. Treatments lacked an understanding of the underlying mechanism of cancer, and inflicted damage while saving some lives. Ultimately, patients demanded less punishing and more effective treatments.

2014: Development of CAR-T cell therapies - programmed T cells aim to hunt, bind to, and eliminate cancer cells that have a specific antigen on their surface - such as CD19.274

2015: Approval of oncolytic viral therapy for the treatment of advanced melanoma, talimogen laherparepvec. The treatment is directly injected into melanoma tumors.275

2017: The FDA approves pembrolizumab, a checkpoint immunotherapy against all advanced solid tumor types regardless of the site of the tumor. Pembrolizumab blocks a protective mechanism of cancer cells and allows the immune system to destroy those cancer cells.276
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ADVANCING OUR UNDERSTANDING OF THE DISEASE

The focus of research in the 1970s was on finding treatments without much more than a basic understanding of the disease.279 There were three competing theories about what causes normal cells to turn cancerous: viruses, chemicals in the environment, and our genes.280 Each had evidence behind it, but without an understanding of carcinogenesis, researchers were divided.

As the field of microbiology advanced significantly, oncogenes and tumor suppressive genes were discovered in a major breakthrough: genes in our bodies that cause normal cellular growth, but if disrupted, can lead to cancer.281 With a better grasp of the metastatic process, cancers such as breast cancer began to be understood as systemic, rather than local. Enough was known about cancer to move beyond trial and error, and a new era of targeted therapies could be envisioned.

And the need for more effective treatments was more urgent than ever. By 1986, there had been great strides in the understanding of the disease, but few new treatments.282 The fact that people were simply living longer, combined with diet and lifestyle factors such as smoking, meant that mortality from cancer was growing. Governments and health institutions began to focus on prevention.

By 1985, a clinical trial examining the effectiveness of the radical mastectomy found favor for the much less extreme lumpectomy.283 With an understanding of the metastatic process, chemotherapy, and systemic drugs such as tamoxifen were found to be effective in combination with surgery. These advances, along with improved diagnosis and detection methods, greatly benefited patients, bringing the five-year survival rate in the US up from 75% in 1975 to over 90% today.284

Oncologists started to use their newly acquired understanding of oncogenes and of monoclonal antibodies to develop targeted treatments. Monoclonal antibodies are custom-designed antibodies that can target a given substance or cell type. They are a class of ‘large molecule’ drugs, much more complex than traditional small molecule drugs and can interact with more challenging targets. In the 1980s, scientists identified a potential antitumor target, CD20, for non-Hodgkin lymphoma. Monoclonal antibody rituximab was developed to specifically bind to CD20 and eliminate the cancerous cells. This led to the development of more than a dozen new monoclonal antibody cancer treatments, not least among them, trastuzumab, which blocks a particular oncogene and can affect the growth of breast cancer.285 Trastuzumab, in combination with chemotherapy, increased breast cancer survival rates by 37% with virtually no additional side effects, a significant achievement in the history of cancer medicine.286

In 1973, geneticist Janet Rowley identified the specific genetic mutation in Chronic Myelogenous Leukemia (CML): effectively, the cells at the ends of two different chromosomes switched places.287 In the 1990s, Ciba-Geigy invented a drug that seemed to wipe out CML cells.288 In 1998 the results were out: imatinib was a huge breakthrough and would later help increase the five-year survival rate for people with CML from 31% in 1993 to 66% between 2006 and 2012.289

Another huge breakthrough was the discovery in 1984 by Harald zur Hausen that two strains of HPV were responsible for approximately 70% of cervical cancers, winning him the Nobel Prize.290 This led to the development of the HPV vaccine, which has the potential to virtually wipe out cervical cancer through vaccination.

The discovery of oncogene-based treatments like trastuzumab and imatinib, along with the completion of the Human Genome Project in 2003, contributed to a growing optimism for a new era of targeted cancer treatments. But with the launch of the Cancer Genome Atlas in 2005, it became clear that the cancer genome is much more complex than originally thought.

UNDERSTANDING OF THE HUMAN GENOME HAS GREAT POTENTIAL TO TAILOR-MAKE MEDICATIONS AND IS ENABLING MAJOR STEPS FORWARD IN DRUG AND VACCINE DEVELOPMENT.

David Heymann, London School of Hygiene and Tropical Medicine

FROM A DEEPER UNDERSTANDING TO IMPROVED PATIENT OUTCOMES

Understanding of the human genome has great potential to tailor-make medications and is enabling major steps forward in drug and vaccine development.

David Heymann, London School of Hygiene and Tropical Medicine
As scientists and companies began to pursue drugs targeted at specific genes, the struggle was to find molecules that could target a single gene perfectly without causing toxicity to the patient. And there was a new problem: many of the new drugs that had been developed stopped working in patients after a matter of months. Researchers soon understood why: when cells become cancerous, they also become 100 times more likely to genetically mutate than regular cells.291

Through DNA and genome mapping, researchers are advancing our understanding of the specific mutations that are important to target. It is now understood that there are around 200 genes in breast and colorectal cancers alone that exist and operate under specific pathways, and that those pathways themselves can be disrupted.291 With the cost of genetic sequencing plummeting, it may be possible to treat each cancer patient with a personalized combination of drugs.

Despite these advances, the vast majority of cancers today are still primarily treated with chemotherapy. Survival rates, and rates of cure, are much improved, particularly for early stage breast, colon, and prostate cancer. Several approaches have been developed which improve the activity and reduce the side effects experienced by patients undergoing chemotherapy.293

In many cases, where you were born and who you were born to still decides whether you will have access to cancer treatment or not.

Mariângela Simão, WHO

Cancer treatment is costly, which relates to the complexity of the disease: clinical research for new cancer medicines takes an average of 1.5 years longer than treatments for other disease areas.295 But improving access to cancer treatment does not have to require significant increases in costs. Countries with similar levels of cancer spend currently have very different survival rates for the same types of cancer.296

The inequalities of access are felt most keenly in developing countries, where population ageing, unplanned urbanization, and the uptake of unhealthy lifestyles means that cancer and other NCDs are on the rise. A lack of capacity for prevention, public education, screening, and early detection, diagnosis, and treatment, means that the response to this public health issue is limited.300

In tackling health care challenges of the developing world, collaboration with others holds enormous promise. For example, Access Accelerated brings together 23 global R&D-based biopharmaceutical companies, teaming up with the World Bank, the UIICC, and Boston University in an effort to demonstrate that significant progress can be made addressing NCDs through cooperative action.301 In 2006, Sanofi set up the My Child Matters program to fight childhood cancer which, through 55 projects in 42 countries, has contributed to train 20,000 healthcare professionals and treat over 75,000 children.302

In a landmark for cancer on the global health agenda, the 2017 WHO Cancer Resolution reaffirms cancer control as a critical health and development priority.303 This is an opportunity for national governments to use the momentum of the Resolution’s adoption to drive action on cancer and seek new and effective partnerships.
The latest and most exciting development in our search for a cure for cancer is in the growing field of immunotherapy or immuno-oncology. These therapies enlist and strengthen the power of a patient’s immune system to attack tumors. The class of immunotherapies called PD-1 inhibitors have already achieved FDA approval in a range of other cancers, including certain types of melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, head and neck cancer, liver cancer and classic Hodgkin’s lymphoma.

Another immunotherapy approach called adoptive cell transfer (ACT) collects and uses a patient’s own immune cells to treat their cancer. One of the more advanced forms of ACT is CAR T-cell therapy. CAR-T cell therapy employs the use of T-cells, which play a critical role in orchestrating the immune response and killing cells infected by pathogens. With the potential for this treatment to be effective against a wide variety of aggressive cancers, expectations and hopes are running high.