Research and the Changing Landscape of Oncology: The Journey of Cancer Control

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**Introduction**

Cancer, though defined simply as the uncontrolled growth and spread of cells,\(^1\) is one of today's most complex and significant global health burdens, accounting for approximately 1 in 7 deaths worldwide. This accessibility has fuelled a powerful and effective drive for research into cancer control over a long period of time, and hence an ever-transforming landscape of oncology. Research has been the single greatest catalyst for positive change within oncology, manipulating the field as it empowers us with greater understanding and more effective methods of cancer control.

This essay will explore how research has served to change the landscape of oncology over time; from where we have come, to where we presently stand. It will discuss important contributions from research along the way that have effected change and served to significantly shape the field; in domains of prevention, screening and detection as well as treatment; and also examine the future direction of cancer control. Finally, the significance of this to students of medicine as they prepare to work with and for patients in this dynamic field will be considered.

**Laying the Foundations of Oncology**

*"You cannot move forward in changing the landscape of cancer without knowing what that landscape was and is and how it can be influenced in the future."*

— Siddhartha Mukherjee, MD, PhD

Recognition of the process of cancer dates as far back as 2500BC in Egypt, when a report on removal of "tumours of the breast" was written.\(^2\) It stated the tumour was cauterised, with the note “there this no treatment.”\(^3\)

Research, in the form of autopsies, began to broaden the landscape of oncology from the 16\(^{th}\) century. It was precisely this task that saw the birth of research into cancer; a dismissal of spiritual or religious aetiology and a drive to prove or disprove theories through science. Autopsies had a dramatic effect on our understanding of the human body, with the discovery of the lymphatic system and the hypothesis that abnormalities within it were the primary neoplastic cause.
The advent of anaesthesia in 1846 expanded the scope of surgery, and research into cancer flourished alongside it. Treatment of cancer advanced; with development of procedures such as the radical mastectomy. This, combined with the use of the modern microscope, allowed the correlation of disease with micropathology. Research through this format was able to identify cancerous cells as well as the concept of metastasis. Treatment thus changed, with surgeons Bilroth, Handley and Halsted pioneering operations that included removal of the primary tumour in conjunction with regional lymph nodes. The landscape of oncology evolved indelibly.

Through surgery and the pathologic study of cancer, research up until this point in time provided firm foundations for modern day oncology.

**Modern Day Landscape**

**The Genetic Basis of Cancer**

In 1953 the chemical structure of deoxyribonucleic acid (DNA) was deduced, by Watson and Crick. Knowledge of the human genome (which was to be extended some years later by the Human Genome Project) enabled researchers to soon develop an understanding that cancer was caused by mutations in genes, either inherited or spontaneous. This was a turning point in cancer research, sparking a novel era of genetic research, with a focus on nucleic acids, receptors and signal pathways.

Two important discoveries that followed on from here were that of oncogenes – genes that drive uncontrolled proliferation of abnormal cells – by Bishop and Varmus, and tumour suppressor genes – genes that work to oppose proliferation of aberrant cells, by Knudson. From here, scientists were able to identify specific genetic changes that could lead to cancer, which had groundbreaking implications for clinical oncology, in areas of prevention, detection and treatment, moulding its landscape in a revolutionary manner.

**Prevention & Screening**

An “early detection and treatment” philosophy dominated until the 1960s, with renewed research into carcinogens. By 2014, the World Health Organisation (WHO) had
identified over 100 chemical, physical and biological carcinogens. Phenomenal reductions in cancer incidence and mortality have occurred through our knowledge of these, and today one third of cancers are preventable.\textsuperscript{10}

The impact of preventative research is best evidenced by the transformation of our approach to cervical cancer. Micropathological research led to the development of the Pap test in 1928.\textsuperscript{11} This simple screening test allowed abnormal cervical cells to be identified and removed, prior to cancerous transformation. Australian cervical cancer incidence and mortality has halved since introducing its screening program in 1991.\textsuperscript{12} Compounding this research was the later discovery that persistent infection with high-risk strains of human papillomavirus (HPV) was responsible for the vast majority of cervical cancers worldwide, having huge implications for cervical cancer control.\textsuperscript{13}

It was Australian research that led to the development of a cervical cancer vaccine, Gardasil, which protects against high-risk HPV types 16 and 18.\textsuperscript{14} It has largely been tested as successful, with an almost 100% rate of preventing cervical cancer.\textsuperscript{15} Thus, Australia implemented a school-based National HPV program in 2007, which is forecast to cause significant reductions in cervical cancer incidence and mortality, with studies already highlighting reductions in cervical abnormalities.\textsuperscript{16}

It is now understood that virus-related cancers represent approximately 15\% of total cancer incidence globally,\textsuperscript{17} and continued research into this area of prevention hence holds great potential.

**Detection**

Breast cancer in particular has benefited from research into innovative and improved detection methods. Detecting breast cancer early and while it is relatively smaller is strongly associated with increased treatment options\textsuperscript{18} and improved survival.\textsuperscript{19} Prior to imaging, clinical breast examination was the sole non-invasive diagnostic tool, which showed little to no evidence of benefit.\textsuperscript{20} Modern mammography – x-ray examination of the breast – thrived from the 1970s, allowing visualisation of any associated masses, enabling earlier detection, and was shown to reduce the number of breast cancer deaths considerably.\textsuperscript{21}
Australia’s mammographic screening program, BreastScreen Australia, was established in 1991. Evidence shows the size of breast cancer detected is markedly smaller than in the period prior to screening,\textsuperscript{22} benefitting patient prognosis. Although results are variable, it is now estimated to have reduced mortality in participants by up to 50\%\textsuperscript{23}.

Improvements in detection of cancer were powerfully bolstered by research into ultrasound, utilising sound waves in real time to form an image of internal organs, assisting to differentiate benign and malignant lesions\textsuperscript{24} as well as guide fine needle aspiration of suspicious tissue. Ultrasound is now used to assist diagnosis in many different types of cancers, including breast, testicular and liver.

As imaging technology continues to develop and improve, cancers will be detected earlier, providing greater treatment potential and improved outcomes.

\textbf{Treatment}

The 20\textsuperscript{th} century saw considerable advances in the treatment of various cancers, in the “primary triad of cancer patient care”: surgery, chemotherapy and radiation,\textsuperscript{13} in conjunction with further development of supportive and palliative care regimes.

\textbf{Progress in surgery}

Surgery has been a mainstay of treatment since ancient Egypt, however it is research that has propelled it from crude techniques to exploratory surgery involving laparotomy to less invasive procedures using fiberoptic and laparoscopic technology. Knowledge of cell biology and biomechanics, development of imaging modalities and refinement of surgical technique have led to procedures which are less invasive, less disfiguring, and more effective at maximising removal of cancerous cells.\textsuperscript{13} A prime demonstration of progress is the fact that clinical trials have found surgical lumpectomy with radiation equal to radical mastectomy in the management of breast cancer.\textsuperscript{25}

\textbf{Progress in chemotherapy}

Medical oncology was not considered a clinical specialty even by the 1960s.\textsuperscript{26} However, research into chemotherapy drastically changed the previously surgery-dominated field of oncology. Discovered fortuitously from research into agents of warfare,
chemotherapy began with the revelation that nitrogen mustard worked against lymphoma, and that by damaging DNA, rapidly dividing cancer cells could be killed.

A significant breakthrough was made in 1965 when researchers Frei, Holland and Freireich proved that a combination of chemotherapeutic drugs, each with a different mechanism of damaging DNA, could cure acute lymphoblastic leukaemia, a pioneering effort that laid the foundations of modern day chemotherapeutic regimes.

This paved the way for what is now known as adjuvant chemotherapy. Comprehension of metastasis signalled a need for change in the surgically-oriented approach to tumour management. Two landmark studies published in the mid-1970s, reporting on the effective use of adjuvant chemotherapy – one with L-phenylalanine mustard and the other a combination of cyclophosphamide, methotrexate and 5-fluorouracil – with mastectomy in breast cancer patients, showed a significant decrease in relapse of patients. It was this research that launched an intense and sustained interest in adjuvant chemotherapy, with results of decreased mortality and relapse rate we are benefitting from today. Chemotherapy is now used in a variety of solid tumour cancers, including breast, colorectal and testicular, having been credited with curing the latter, and significant research continues to optimise its use.

**Progress in radiation**

Modern day radiotherapy involves the use of x-rays, gamma rays and charged particles to kill cancer cells and shrink tumours. Radiation was first utilised to cure basal cell carcinomas of the face in 1903. However, its passage into a treatment regime for cancer was interrupted by the discovery that it too caused cancer.

Research in physics and technology allowed its use in a more defined manner. Conformal radiation therapy (CRT) utilises CT images to view a cancer in three dimensions, enabling more precise control of delivering the dose to the cancer, with minimal exposure to normal tissue. Intensity-modulated radiotherapy (IMRT) further builds on this, combining the precision of CRT with the ability to adjust the intensity of radiation, minimising toxicity. This has been imperative to head and neck cancer treatment, due to the proximity of important tissue to the tumour. Compared to CRT, IMRT can reduce the risk of side effects such as xerostomia from damage to the salivary
glands, when the head and neck are treated.\textsuperscript{36} Evidence\textsuperscript{37} suggests it is effective in a variety of sites, including the prostate, and reduces toxicity to the patient.

Such progress through research has meant that cancers which were previously inoperable became curable. Today, radiotherapy is used in a wide variety of tumour types, and is part of the management of 40\% of cured patients.\textsuperscript{38}

**Future Direction: Personalised Medicine**

Knowledge of the genetic basis of cancer, the Human Genome Project and further research in molecular biology and genomics has led us to an era in which we can now identify characteristics of an individual's tumour – biomarkers – in order to directly target these in treatment regimes. This is slowly transitioning oncology into a field of "personalised medicine," beyond the "one size fits all" approach that previously presided.

Rational drug development, the development of drugs based on knowledge of biomarkers, is a core component of personalised medicine. It is well demonstrated by the treatment of metastatic melanoma, a disease of extremely poor prognosis\textsuperscript{39} and limited therapies with no survival benefit. In 2002, researchers found about 50\% of melanomas carry the BRAF-V600 mutation,\textsuperscript{40} resulting in an oncogenic signalling pathway. Subsequent research delivered vemurafenib, a drug that specifically inhibits BRAF-V600, shown to significantly improve survival in patients with this mutation.\textsuperscript{41, 42} This is particularly pertinent locally, with Australia maintaining the world's highest incidence of melanomas.\textsuperscript{43} Importantly, this remarkable research may impact on a variety of other cancer types, as the same mutation is found in thyroid, ovarian and colorectal tumours.

Hormonal therapies have long since become an integral part of personalised medicine. For example, the use of selective oestrogen receptor modulators such as tamoxifen in oestrogen and/or progesterone receptor positive breast cancers, which have shown great efficacy in both suppressing recurrence and improving mortality.\textsuperscript{44} Approximately 75\% of breast cancers in Australia carry these receptors and will benefit from this therapy.
Biomarkers are increasingly used to determine individuals at risk of developing disease, and thus develop measures to prevent or reduce carcinogenesis. Individuals possessing a mutation in the adenomatous polyposis (APC) gene, at increased risk of developing colorectal cancer, can be offered endoscopic surveillance, non-steroidal anti-inflammatory drugs or, more radically, a colectomy, to help prevent occurrence. Australian researchers are now pioneering efforts to catalogue such genomic abnormalities in both pancreatic and ovarian cancers.

These successes prove that increased understanding of genetic and molecular biology through research has significantly improved patient care in the field of oncology. Further research into biomarkers will guide rational drug development, expand treatment options and potential for prevention, and continue to shape the field of oncology in a more personalised direction.

**Personalised Medicine in Australia**

The future of personalised medicine in Australia is largely dependent on current discourse regarding economy. The National Health and Medical Research Council emphasises the increasing need to develop a balance between lowering health care costs through prevention, and the increased expense of tailored drugs produced for a small population, which major pharmaceutical companies will be more reluctant to produce. Australia is moving forward in terms of educating doctors, with genetics becoming a subspecialty within the Royal Australian College of Physicians. This is increasingly important as the role of not only management but follow up, will be placed on oncologists and general practitioners alike, as we benefit from targeted therapy.

**Application to Medical Education**

Cancer is responsible for 10% of hospitalisations in Australia, requiring regular and effective contact with junior doctors. The impact of research on clinical oncology is hence highly relevant to medical students as they prepare to enter the workforce.

The problem-based learning model of most universities in Australia allows for a diverse appreciation of clinical oncology. The Cancer Council has also developed the *Ideal Oncology Curriculum*, including fundamental cover of cancer biology and genomics. This is becoming increasingly important knowledge as we usher in the era of
personalised medicine, with the Australia Law Reform Council recommending comprehensive knowledge of genomics for future doctors.49

In the ever-changing nature of oncology, it is also crucial for students to develop competency in critically appraising the literature, in order to best apply this research for patients' benefit. These invaluable skills will serve students the breadth of their career, ensure they have knowledge that is relevant and current, and can best care for their patients.

Finally, the importance of appreciating the patient's perspective in their journey through cancer cannot be understated. Research in cancer, though significant, has further to go, and an ability to interact with, empathise, and understand patient needs is as important to effective management as knowledge of clinical oncology itself, and teaching a sound combination will ensure the best patient care is delivered.

**Conclusion**

Today cancer is still one of the leading causes of morbidity and mortality worldwide. However, borne out of the discoveries and developments delivered to us from research, we have improved mortality and are better equipped to support patients through their journey; progressing from “no treatment” in ancient Egypt, to developing personalised management today.

Though it is important to recognise how far we have yet to go, it is clear the impact of developments through research has been invaluable to oncology. This research has placed us in excellent stead for continued and significant progress overcoming challenges in the future; ever-changing, but ever-striving towards effective and comprehensive cancer control.
References


