Research and the Changing Landscape of Oncology:

*Past, Present, and Future Trends*

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Introduction

The field of oncology has rapidly evolved since the advent of modern medicine. Although once heralded as a death sentence, drastic improvements to all areas of cancer care have resulted in promising outcomes worldwide.\(^1\) This is demonstrated by data highlighting a marked decrease in mortality and improved survival rates – telling signs that cancer no longer bears the bleak outlook it once possessed.\(^2\) At the crux of the changing face of oncology lies the efforts of contemporary scientific inquiry and its impact in spawning a flurry of paradigm shifts that have enabled a more intimate understanding of oncology. Cancer research has since expanded into vast territories with the evolution of its methodology, and now encompasses a myriad of approaches ranging from molecular to population-based studies. This has served as an impetus for reshaping the scene of clinical practice - namely, the detection, prevention, and treatment of many common cancer types. As a result, surgery, radiotherapy, and chemotherapy now witness an influx of innovations at a staggering pace. Indeed, as the complexity enveloping cancer now begins to unravel at an exponential rate, research underpins an important frontier for ushering society into a golden age of cancer control.

This essay explores the advancements of knowledge at the molecular, biological, and epidemiological levels and how the approaches to cancer research in these areas have changed. Screening, prevention, and treatment are explored, and landmark achievements in cancer research that have shaped these respective areas of oncology are examined. Furthermore, the implications that these changes have had on clinical practice in the Australian health system are also highlighted. Next, the trajectory of oncology is discussed. Finally, health professionals and medical students are called upon to embrace this ever-shifting environment as the growing tide of cancer continues to encroach on all aspects of healthcare in Australia.

The Past

Understanding the genetics of cancer

Knowledge of the molecular basis of tumour biology has been fundamental to the successes seen in the current setting of oncology. Historical evidence suggests that past perceptions surrounding cancer lacked a unifying theory capable of explaining its behaviour and, thus,
research at the time did not have a clear direction.\textsuperscript{3} A myriad of hypotheses were postulated in an effort to explain the phenomena – imbalances in bodily fluids, trauma, parasites, and lymphatic fluid by-products.\textsuperscript{3,4} However, the conception of cancer research truly began after the discovery of deoxyribonucleic acid (DNA), which served as a vital platform in underscoring the link between genetic abnormalities of cancerous cells and the biological characteristics conducive to further growth.\textsuperscript{4,5}

As the focus of research shifted towards the identification of important genetic associations, it opened new opportunities for understanding the complexities of carcinogenesis, the development of cancer cells. The ensuing discovery of vital genes critical to this process followed suit, first beginning with the recognition of oncogenes and tumour suppressor genes, key coding regions responsible for cellular proliferation and inhibition of growth respectively, through experimentation on animal and human cell models.\textsuperscript{6} Subsequent discoveries of cancer-critical genes that regulate cellular growth and differentiation, preserve genetic integrity, and protect against damage have since been made.\textsuperscript{6,7} Additionally, many of these genes are now recognised as common denominators among different cancer types and subtypes.\textsuperscript{6,7,8} The significance of discovering this homogeneity among cancers was two-fold – it provided a guide for the classification of cancer subtypes and identified potential shared treatment targets.\textsuperscript{3}

Further genomic sequencing revolutionised cancer ideology by disproving previous notions that cancer was a single, discrete anomaly, and instead began acknowledging its highly diverse and dynamic behaviour.\textsuperscript{3} This represented a turning point in oncology; although cancers may originate from a single cell, it is the reiterative process of clonal proliferation, genetic diversification through mutations, and subsequent selection of favourable cells that is ultimately responsible for the tremendous heterogeneity of malignant tissue.\textsuperscript{3,9,10}

With the ‘multistep theory of carcinogenesis’ model now established as the archetypal paradigm in cancer genetics, the very definition of cancer changed from a well-defined entity to a complex spectrum of diseases.\textsuperscript{3,7,9} Moreover, this contemporary view of carcinogenesis was key to explaining many facets of oncology including disease behaviour and progression, optimising cancer medicine, and therapeutic resistance.\textsuperscript{3,10}
The influence of cancer biology

Advancements in understanding cancer genetics have had equally significant downstream effects in developing principles quintessential to the future of oncology. One such progress is seen in cancer biology, where it is now hypothesised that carcinogenesis is dictated by a framework, unlike the chaotic phenomenon that was once purported. In a seminal paper describing the hallmarks of cancer, eight common traits are believed to be responsible for altering normal cell physiology towards malignancy: self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of programmed cell death, limitless replicative potential, sustained growth of new blood vessels, tissue invasion and metastasis, reprogramming of energy metabolism, and evading immune destruction.

Without a doubt, the reconceptualization of cancer biology into these categories primes all aspects of current oncological research towards greater advances. This is exemplified by the current transition now seen in the detection of cancer at genetic and biochemical levels, assessing the cancer susceptibility of individuals, and the development of unique therapies. At the same time, carcinogenesis in specific cancer types are now becoming increasingly delineated, as seen through the colorectal adenoma-carcinoma sequence which theorises the stepwise mutations from benign cells to bowel cancer.

Expansions in epidemiological studies

Many of the notable achievements in research and prevention have occurred in the context of population-based studies in cancer epidemiology. With the cause of mortality shifting primarily from infectious diseases to chronic disease during the latter part of the 20th century, study methods began to adopt the notion that cancer had multiple causes. This ultimately resulted in the recognition of extensive risk factors implicated in carcinogenesis including diet, cigarette smoking, alcohol, occupational exposures, radiation and sunlight exposure, infections, and hormonal factors.

The identification of these exogenous influences has been crucial to the scene of cancer prevention in Australia, where changes to the exposure to risk factors have reduced incidence rates in several cancers. For example, establishing an association between UV radiation and skin cancers has allowed for cost-effective solutions, such as the SunSmart awareness and
prevention program, to be implemented widely across the nation.\textsuperscript{19,20} Recent trends illustrate the efficacy of these initiatives, with plateauing skin cancer incidence rates attributed to a combination of attitude, behavioural, and structural changes.\textsuperscript{21}

Similarly, the distinguishing of tobacco smoking as a major risk factor for developing many cancers, including lung, bowel, kidney, stomach, and cervical, has been central to curbing both incidence and mortality rates through various means.\textsuperscript{22, 23} The human papillomavirus (HPV) vaccine against cervical cancer is one such innovative example of intervention.\textsuperscript{22, 24}

One systematic review reiterates the need for large changes in infrastructure as the trends in cancer outcomes begin to shift.\textsuperscript{14} This is demonstrated with the establishment of a number of centralised bodies such as the Australasian Association of Cancer Registries and Cancer Council Australia, as well as dedicated research units that encourage interdisciplinary collaboration – for example, the Victorian Comprehensive Cancer Centre, Lowy Cancer Research Centre, and the Ludwig Institute for Cancer Research.\textsuperscript{14, 16, 20, 25}

**The Present**

As cancer research becomes steadfast in the Australian culture, its effects are becoming increasingly tangible in many areas of clinical oncology. Current population data is alarming as the number of new cases of cancer detected in 2014 was 2.6 times greater than in 1982.\textsuperscript{17} Although the ageing population and changes in risk factor exposure are thought to be responsible, advancements in early detection through screening programs is central to this rising trend.\textsuperscript{22} Early detection of disease is known to lead to a higher probability of survival in many cancer types.\textsuperscript{22, 26} For this reason, Australia’s current national screening programs, though currently limited to breast, cervical, and bowel cancers, have reflected this tenet with greater rates detected shortly after their implementation.\textsuperscript{2, 22, 27}

Techniques involved in these screening procedures are also undergoing major transitions with the aid of clinical research, thereby adding further layers of complexity and accuracy to the diagnosis of cancer. Emerging evidence suggests that previous screening, which relied solely on the microscopic confirmation of disease, could be more specific with the aid of molecular and immunochemical tests aimed at improving the yield of early precancerous changes.\textsuperscript{27, 28}
Such instances include HPV DNA testing for cervical cancer, and immunochemical faecal occult blood tests for bowel cancer.\textsuperscript{28, 29}

Furthermore, the detection of cancer biomarkers in blood tests are also in the midst of a similar transition as longitudinal trials assess their accuracy in a multitude of cancers including breast, ovarian, bowel, prostate, and leukaemia.\textsuperscript{27, 30, 31, 32, 33} Many of them are now considered mainstay in determining treatment regimens - for instance, describing breast cancers based on the composition of hormone receptors and the well-recognised biomarker, HER2.\textsuperscript{34, 35, 36}

While this wide array of markers can aid in screening, classifying, and guiding treatment plans, they can often be detrimental and cause more harm than good.\textsuperscript{37} A prime example of this is the reliance on prostate specific antigen (PSA) for prostate cancer screening in asymptomatic men which has led to the over-diagnosis and overtreatment of suspected cancers.\textsuperscript{37}

Wide improvements in cancer treatment and the greater use of combination therapy have led to positive outcomes among oncology patients – most notably, decreasing mortality.\textsuperscript{2, 17, 22} Over the last two decades, the survival rate of common cancers in Australia have risen by 30%; reflecting overall changes to both the type of treatment and its increasingly multidisciplinary input.\textsuperscript{2, 22} Surgical techniques have grown to become less invasive and, in turn, less destructive to the patient.\textsuperscript{38} In breast cancer surgery, the evolution from mastectomy to breast conservation surgery now allows for deformities to be avoided almost entirely while still enabling the complete excision of tumours.\textsuperscript{38, 39} Likewise, utilising axillary dissection for determining the spread of breast cancer, which often rendered women with intractable arm pain and swelling, has been superseded by the minimally invasive technique of sentinel lymph node biopsy in certain cases.\textsuperscript{40, 41}

In oncology’s second arm of treatment modalities, radiotherapy, developments have been most prevalent through technological improvements.\textsuperscript{42} This has permitted more precise imaging of tumours, thus allowing exact doses to be delivered to tumours at all times during radiotherapy.\textsuperscript{42} With newer devices introduced yearly, they are now encouraging meaningful changes to the delivery of radiation.\textsuperscript{42}

Even as the improvements in surgical and radiation oncology so far have been promising, arguably the most evident manifestation of evolving oncological treatments has been in cancer medicine. With evidence supporting the effectiveness of combination therapy, regimens
consisting of multiple chemotherapeutic agents have since been devised, each specific for a cancer type. Moreover, previous principles now act as roadmap for creating highly targeted novel anti-tumour agents and also a revision of previous agents to inflict fewer adverse effects.11, 12

One such medication is Herceptin, a drug used to target HER2-positive breast cancer, which has shown to improve disease-free survival rates by 46%.44 In Australia, the 30% decrease in mortality rate of breast cancer is credited to the introduction of Herceptin in clinical practice.45

More recent innovations are epitomised in melanoma treatments which have traditionally proven to be a futile expense in displaying survival benefit over supportive care.46 The recent introduction of world leading clinical trials in melanoma research now sets Australia in the map of oncological research.46 Drawing inspiration from the hallmarks of cancer, the development of current generation chemotherapeutic agents do not target tumour cells, but rather potentiates the normal immune response to cancer.47, 48 With recent data underlining an increase in 1-year survival from 30% to 80%, these treatments are indeed extraordinary in the face of a disease once considered untreatable.47, 48

The Future

With the trajectory of oncology heading towards a positive direction, many additions to the existing base of knowledge are expected. It is believed the trend will continue towards a highly tailored style of medicine, with personalised molecular tests driving therapeutic planning.49 Further discovery of useful cancer biomarkers is expected, and they will guide the classification, diagnosis, and treatment of cancers with a higher specificity.49 In addition, as the effects of signalling and metabolic pathways affecting cancer at the microscopic level become clearer, oncology will likely be pushed into an endless pool of new cellular interactions that represent novel therapeutic targets.15, 16, 49

Cancer medicine is likely to once again change with the amalgamation of gene therapy and vectors.54 These particles, which mimic viruses, have shown promising evidence of efficacy against cancerous cells while preserving normal tissue – especially against cancers still considered untreatable.50, 51 Certainly, they symbolise the next generation of truly non-invasive cancer therapy.51

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Demographics are now expected to be reshaped through the combined effect of increasing incidence, improved survival rates, and decreased mortality.\textsuperscript{22} As a result, cancer is expected to be more prevalent in the Australian society as this survivorship population grows.\textsuperscript{22}

The refocusing of cancer control towards the consequential effects after treatment is therefore an imperative.\textsuperscript{22} Cancer survivors are prone to persistent psychological distress which can have wide reaching and persistent effects on family, friends, and caregivers.\textsuperscript{22, 52} As such, further research into psycho-oncology and how it can be best prevented will surely gain traction with the maturity of cancer survivorship programs.\textsuperscript{53}

Lastly, the importance of educating the future generations of health professional must be underscored. As they will inevitably face cancer as a common comorbidity in the setting of other health conditions, it is paramount that they possess a rigid foundation of knowledge to be competent in managing these complex medical issues. The proposed medical education curriculum by Cancer Council serves as a basis to introduce fundamental principles in all areas of oncology to medical students and junior doctors.\textsuperscript{54} The complexities and nuances in oncological practice can then be added through other Cancer Council Australia resources directed at health professionals. To match the overwhelming and ever-evolving scope of research, medical students can be presented with opportunities to learn the fundamentals in scientific methodology and conduct their own studies, thereby enabling them to foster a personal interest in cancer research.

**Conclusion**

The evidence presented here is a mere snapshot into this expansive field of medicine. The close interactions between all areas of cancer research – from biology to epidemiology – proves that they are equally important forces in improving cancer control. Although much has been learned, the prevalence of cancer in the 21\textsuperscript{st} century is a testament to how little is known. Yet, as new accomplishments in research are appearing on a daily basis, oncology will only continue to change and adapt until a cure is finally discovered. With juniors doctors now handed the responsibility of a changing demographic, they must embrace this knowledge requirement and become the bastions for improving the future landscape of oncology.


