Ageing and Cancer: A complex relationship

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Introduction

Ageing and cancer are entwined in an intricate and abstruse relationship. Epidemiological data demonstrate that both cancer incidence and mortality increase exponentially with age and thus age is regarded as a prime risk factor for cancer.\textsuperscript{1, 2} However, the biological mechanisms that underpin this correlation are still being uncovered. Additionally, the unique aspects of cancer management in an elderly cohort, relating to decision making, co-morbidities, prevention, diagnosis, treatment and clinical trial representation, continue to be recognised at the interface of geriatrics and oncology.

This essay explores the demographic changes, biological theories and clinical considerations that link cancer and ageing. It highlights the implications of these associations in the context of Australia’s population and health system, with a focus on preventative strategies, research imperatives and delivery of cancer services. Furthermore, the essay discusses how to best prepare the most junior of the medical profession to manage a growing number of senior cancer patients. Overall, it underscores how all elements in the relationship of cancer and ageing need to be considered and incorporated into a framework that facilitates a holistic approach to cancer control.

The relationships between ageing and cancer

Epidemiological: cancer in an ageing population

Demographic trends worldwide herald the ‘age of cancer’. Ageing populations are experiencing an unprecedented upsurge in both cancer cases and cancer deaths, with the average age of cancer diagnosis in developed countries tracking towards 70 years of age.\textsuperscript{2, 3}

Population changes and predictions for the future cancer burden in Australia mimic those of other developed countries. In 2012 cancer was reported to be the largest contributor to disease burden and a leading cause of premature death in Australia.\textsuperscript{4} In spite of this, by 2025 it is predicted that the number of cancer diagnoses in Australia will further increase by 60%.\textsuperscript{5} Moreover, it is expected that 65% of these diagnoses will be made in people aged over 65 years, a cohort that by then will have expanded to comprise 20% of the overall population.\textsuperscript{5} As such, both the number of older patients and older cancer patients in Australia are projected to increase significantly during the next decade, a shift that has implications for all areas of healthcare.
Biological: the science of ageing and cancer

Unravelling the mechanistic interplay between ageing and cancer is central to addressing the growing cancer epidemic. The increased risk of cancer with age is rationalised by the well-known multistep model of cancer. The concept entails that cells accumulate the DNA mutations necessary for malignant transformation over a prolonged period of time and thus cancer coincides with, but is not necessarily due to, ageing. However, emerging evidence suggests that the two processes are more intimately related. In fact ageing, a process marked by physiologic and psychosocial decline, may itself create a tissue microenvironment conducive for cancer initiation and progression.

It is proposed that ageing can influence carcinogenesis through several molecular mechanisms. Telomeres, the non-coding DNA caps that protect the end of chromosomes, are thought to play a crucial role. With each cell division there is continued shortening of telomere length until a critical limit is reached and the cell enters senescence, a state of growth arrest. This process is considered to be a driver of ageing as well as an important tumour suppressive mechanism. Several studies indicate that shorter telomeres are a risk for cancer and telomere dysfunction is believed to promote malignancy. Additionally, it is speculated that the accumulation of senescent cells with age creates a tissue environment permissive to cancer. The age-related deterioration of mitochondria is thought to promote the production of reactive oxygen species that interfere with DNA and protein function, facilitating cancer development. Changes in the activity of enzymes involved in the activation of carcinogens are postulated to make older tissues more receptive to the effects of carcinogens. Other age-associated genetic modifications including DNA hypermethylation, point mutations and chromosomal translocation are thought to groom ageing tissues for neoplastic development.

A decline in immune and endocrine function has also been implicated in the convergence of ageing and carcinogenesis. It is recognised that inflammatory markers increase with age, while immunological surveillance, a process where neoplastic cells are detected and destroyed, is less efficacious. This may promote the growth of immunogenic tumours. Changes in body composition with age result in a greater percentage of body fat and higher levels of obesity. This has been associated with higher levels of inflammatory cytokines and increased incidence of certain cancers, including breast, prostate and bowel.

Despite these observations and theories, the biological links between cancer and ageing are not clear cut. For instance, paradoxically, there is data to indicate that in the oldest of the old, centenarians, cancer is less prevalent and characteristically different. A systematic review reported that very advanced age was associated with decreased cancer prevalence, decreased metastatic rate and decreased cancer mortality, but an increased incidence of incidental tumours. These findings suggest that tumour biology changes with age. The altered behaviour
may be due to reduced angiogenesis, capillary sclerosis, increased apoptosis, changes in hormonal receptor expression and altered immune responses in elderly patients.\textsuperscript{7,10,11}

**Clinical: managing elderly cancer patients**

In a clinical setting, older cancer patients can present with a complex array of issues relating to functional, cognitive and sensory impairment, psychosocial problems, polypharmacy and co-morbidities.\textsuperscript{1,12} However, given the variability in the ageing process, there is considerable heterogeneity for any given chronological age. Consequently, geriatric assessments designed to indentify vulnerable patients are being integrated into cancer care.\textsuperscript{13,14}

Decisions pertaining to cancer management are influenced by different considerations in elderly patients. Factors such as premorbid function, life expectancy, treatment tolerance and socio-economic status along with endpoints such as independent living and expected quality of life all swing the balance between the benefits and harms of proposed treatments.\textsuperscript{7,15} However, discussing such information with elderly patients can be difficult in the context of cognitive and sensory deficits.\textsuperscript{13} It is documented that older patients tend to ask fewer questions and are less proactive about treatment when compared to younger patients. Health literacy has been identified as an issue in this population group.\textsuperscript{14} Additionally, it is reported that doctors do not spend as much time communicating with elderly cancer patients.\textsuperscript{12} These factors potentially contribute to issues of delayed diagnosis and incomplete workup which have been reported in an older patient cohort.\textsuperscript{1}

From a physiological perspective, the decline in functional reserve with ageing fuels uncertainty about the efficacy and tolerance of cancer therapeutics. Age-related physiologic changes can impact upon pharmacokinetics, pharmacodynamics and toxicities of chemotherapy and radiotherapy regimes and success of operative approaches. Decreased cardiac function increases the risk of heart failure and arrhythmias with some chemotherapeutic agents.\textsuperscript{1} Reduced gastrointestinal motility, absorption and blood flow can exacerbate gastrointestinal side effects of mucositis and diarrhoea. The sequelae of which can be more hazardous in older patients as they are more susceptible to the effects of fluid shifts and poor nutrition.\textsuperscript{1,16,17} Both reduced hepatic and renal clearance may affect loading doses, maintenance doses and dosing intervals of many drugs.\textsuperscript{17} However, it is reported that both elective cancer surgery and radiotherapy are well tolerated by most older patients.\textsuperscript{3}
Overcoming the challenges of ageing and cancer

Prevention and screening strategies: it’s never too late

Although the incidence of cancer is predicted to increase in Australia over the next decade, it is estimated about 25% of cases could be prevented through risk reduction strategies, including smoking cessation, alcohol reduction, sun protection, weight loss, increased physical activity and healthy diets. While these behaviours should be encouraged from a young age, there is evidence to suggest that the adoption of a healthy lifestyle later in life is still beneficial for disease prevention. Accordingly, brief intervention techniques that promote healthy lifestyles should be encouraged in all areas of medical practice. At a population level, the ‘National Cancer Prevention Policy’ outlines key public health initiatives and policies aimed at reducing the incidence of preventable cancers in Australia. Research initiatives such as the CLEAR (Cancer, Lifestyle and Evaluation of Risk) study, conducted by the NSW Cancer Council, will direct future prevention strategies.

Screening for the early detection of cancer is another aspect of cancer management in Australia. Population screening for breast, cervical and most recently bowel cancer is available and there are plans to expand the age groups targeted in both BreastScreen and National Bowel Cancer Programs to individuals between 50 and 74 years. However, in an ageing population there are suggestions that screening protocols should be considered in the context of life expectancy rather than rigid upper age cut-offs. Randomised controlled trials assessing mammography and faecal occult blood tests have suggested benefit of screening for individuals with a life expectancy of at least 5 years.

Delivery of cancer services: integration with aged care

With an ageing population and corresponding expansion of the aged care sector, there is a recognised need to strengthen the integration between health and aged care services. The dialogue surrounding ageing in Australia has identified needs for improved access to health services including palliative care and advance care planning. Australian government reforms such as ‘Living Longer Living Better’ are looking to address these issues and develop new models of healthcare delivery whereby older patients with complex health needs have better access to multidisciplinary teams. Within the field of oncology, there have been recommendations to advance the subspecialty of geriatric oncology, develop clinical care pathways for older cancer patients, offer speciality clinics and link in with age care and community services. The fruition of these ideas will depend on the collaborative efforts of key government and non-government groups such as Cancer Australia, Cancer Councils and The Clinical Oncology Society of Australia.
The geographical distribution of the older population within Australia impacts upon the provision of cancer services. High mobility rates are recognised amongst older age brackets, particularly in the 85-94 age group, as people relocate to be close to family and support services.\textsuperscript{25} Additionally, the ‘sea change phenomenon’ sees the migration of older people from larger metropolitan areas to smaller coastal towns.\textsuperscript{25} By 2025 it anticipated that 22\% of the Australian population will reside in non-metropolitan areas and given that geographic remoteness has been associated with limited access to secondary treatment and higher cancer mortality, the development of oncology infrastructure to address these shortcomings will be critical.\textsuperscript{17} Initiatives such as the Cancer Service Networks National Program and telehealth programs are seeking to resolve such disparities.\textsuperscript{26} Projects like the ‘Care Coordination for Older Australians with Cancer’, which assessed the feasibility of a focused geriatric oncology service in a regional setting, will help develop models of integrated cancer, aged and community care in rural Australia.\textsuperscript{14}

**Research: recruiting the elderly**

Notwithstanding the uncertainties surrounding the clinical management of elderly cancer patients, they have historically been under-represented in clinical trials. This stems from an overall low recruitment of older participants as well as stringent inclusion criteria that only permit relatively healthy older adults to be included.\textsuperscript{16} Such research has revealed that fit older patients derive similar benefits from treatment as their younger counterparts, but are more susceptible to treatment toxicities.\textsuperscript{11, 15} However, it is tenuous to extrapolate these findings to guide the management of frail, elderly patients with multiple co-morbidities.\textsuperscript{11}

Given the rapidly ageing population, there is a priority to conduct high-quality research in geriatric oncology.\textsuperscript{16} It is recommended that some form of comprehensive geriatric assessment is undertaken in such trials to capture parameters of functional ability, co-morbid conditions, mental state, nutrition and social support of study participants. It has been reported that these domains act as independent predictors of morbidity and mortality and therefore affect cancer-specific outcomes.\textsuperscript{1} Other factors such as transportation, financial barriers, carer responsibilities, hospital discharge and institutionalisation also need to be addressed in clinical trial logistics to facilitate appropriate enrolment and follow-up.\textsuperscript{16}

It is hoped that focussed research will help generate targeted treatment algorithms that stratify patients based on geriatric assessments. Categorising older patients into subsets of fit, vulnerable and frail, rather than a reliance on chronological age, may prove more valuable in determining optimal treatment regimes.\textsuperscript{1} As with healthcare reform, sustained research in geriatric oncology will rely on collaborations between local and international organisations. The recent ‘McKeon review’ outlined strategies for optimising medical research in Australia.\textsuperscript{27}
**Medical education: teaching the young to care for the old**

Regardless of the discipline that medical students eventually practice in, they can expect to be managing oncology patients in some capacity. Accordingly, medical students should attain a solid foundation in oncology principles relating to screening, prevention, diagnosis, treatment and appropriate referral pathways for common cancers. An ideal oncology curriculum that outlines essential cancer clinical experiences for medical students has been developed by Cancer Council Australia.\(^{28}\)

In an ageing population, medical students should understand the nuanced aspects of geriatric medicine. They should develop skills that facilitate effective communication with their elderly patients.\(^{12}\) Furthermore, students should become cognisant of age bias, the inappropriate use of age as a factor for determining treatment options offered. For instance, studies have shown that both medical students and doctors demonstrate age bias when recommending breast conservation in older breast cancer patients.\(^{11, 29}\) However, denying treatment on the assumptions of age alone is discriminatory as appropriate case selection of older patients has been shown to confer similar cancer-specific survival as younger patients for treatment of a range of malignancies.\(^{3, 11}\) Finally, medical students should acquire skills in evidence-based medicine to allow them to critically appraise and contribute to research that will help close the knowledge gaps in geriatric oncology.

**Conclusion**

In conclusion, ageing and cancer are engaged in a fascinating relationship that has epidemiological, biological and clinical significance. Continued research into these affiliations will be necessary for directing future cancer prevention strategies, devising new treatment modalities and ultimately reducing the anticipated burden of cancer. However, when managing older cancer patients it may be appropriate to divorce cancer from chronological age and consider interventions and management in the context of an individual’s frailty, treatment tolerance and life expectancy.

The government, in collaboration with the medical fraternity, needs a coherent framework that combines aged care and cancer services. This framework must facilitate the ongoing findings of research and provide the next generation of doctors with sufficient knowledge to confidently communicate with and provide optimal care to the elderly.
References

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