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CANCER FORUM

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Authors are advised to read the "Information for contributors" printed on the inside back cover.

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Editorial

FORUM: Cancer Screening

Guest editor: Karen Canfell

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As the March 2014 Forum provided an in-depth review on colorectal cancer, screening for colorectal cancer is not included in this issue.

EDITORIAL

FORTY YEARS ON: REFLECTIONS ON CANCER FORUM AND THE WORLD CANCER CONGRESS, 1974

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This edition of *Cancer Forum* is published for distribution at the Union for International Cancer Control (UICC) World Cancer Congress in Melbourne during 3-6 December 2014. The edition is also singular in another respect: this year marks 40 years of publication of *Cancer Forum*. As current Chair, and longest serving member of the Editorial Board, I'm immediately conscious that, as a cancer researcher working in Sydney, 1974 was the year I attended the World Cancer Congress, then known as the International Cancer Congress, for the first time. The Congress was held in Florence. Florence, Italy, to use today's terminology.

From the outset, *Cancer Forum* was, and is, arguably the clearest expression of collaboration between Cancer Council Australia and the Clinical Oncology Society of Australia (COSA), the 2014 Annual Scientific Meeting of which coincides with World Cancer Congress here in Melbourne. Concerning both *Cancer Forum* and the World Cancer Congress, reflection on circumstances prevailing in 1974 throws up many memories, and I describe a few.

The following anecdotes are accurate so far as I am aware, but this is a personal reflection rather than properly-documented history. To that extent, I must immediately apologise to all those who played key roles in events I describe and whom I fail to mention; such failure on my part is due to lapsed memory rather than there being too many people to mention. I also acknowledge my failure to specify national and other honours, appropriately accorded to many mentioned below.

Though *Cancer Forum* is immediately identifiable as a publication of Cancer Council Australia, this was hardly the case concerning the then Australian Cancer Society. The organisation was not well known. In 1974, the Australian Cancer Society had a staff of two, including Executive Officer Giles Pickford and Medical Director Ken Cox (then professor of surgery) operating from offices at St George Hospital, Sydney. Back then, the forerunner of Cancer Council Australia was completely overshadowed by the various state and territory-based cancer bodies (they were not all 'Councils') whose separate paths, and lack of involvement in each other's affairs, were epitomised by an amazing diversity as among their then respective names, statutory bases and organisation.

In 1974, despite being located at the then School of Pathology, University of NSW in Sydney, I perceived that the then Anti-cancer Council of Victoria (ACCV) was the premier state cancer organisation. I was conscious that ACCV funded cancer research conducted internally by the Council itself, and externally through provision of grants. Primarily such research involved two giants. Internally, Nigel Gray was the Director, and apart from other responsibilities undertook research on tobacco, specifically involving tar yields from locally-marketed cigarettes; much later Nigel was President of UICC. Externally, Don Metcalf at the Walter and Eliza Hall Institute was in receipt of the largest cancer research fellowship in Australia and, no doubt among many other things, chair of Cancer Council Australia's Medical and Scientific Committee when I was asked to join.

Also, atop everything else so far as I was concerned, the Council funded part of my research during 1974-7. I collaborated with Gordon Hard, who headed a carcinogenesis research lab at the Baker Institute (Alfred Hospital), Melbourne, a collaboration that arose since, at independent sites in London, we'd both worked on nitrosamine-induced renal cancer in rodents. The Council provided me with air travel to Melbourne at my discretion, and I timed one such excursion to attend a COSA Annual Scientific Meeting for the first time. COSA had been established in 1973, primarily through the efforts of Brian Fleming, a head and neck surgeon in Melbourne, the late Robert Melville, breast cancer surgeon in Sydney, and the late Leicester Atkinson, also from Sydney. I readily identified with the then Experimental Oncology (now Cancer Biology) Group of COSA. This, in turn, lead to my involvement in the only COSA Annual Scientific Meeting ever held at Prince of Wales Hospital in Sydney; Leicester Atkinson, Director of the Hospital's Institute of Radiotherapy chaired the Organising Committee.

Then, as for decades later, COSA Annual Scientific Meetings were rigorously structured to address the needs of members as they affiliated with particular groups. There were four initial founding groups: the Breast, Paediatric, Head and Neck and the Experimental Oncology Groups. Leicester challenged us to propose topics for plenary sessions. Being conscious that the alkylating nitrosamines on which I worked were similar to certain therapeutics, I

said: “How about a session on the mechanism of action of cytotoxic drugs?” The suggestion was not well received: “I imagine that may appeal to the paediatricians”, said Leicester, “But I don’t think the subject will be of interest to anyone else.”

With suitable plenary sessions duly scheduled, the COSA conference went ahead, and a reception followed the first day’s proceedings. There, drink in hand, I was approached by Lawrie Wright, recently appointed Executive Officer of the Australian Cancer Society and (the late) Gordon Sarfaty, Chairman of the COSA Experimental Oncology Group. Would I accept a responsibility for the content of *Cancer Forum*? To my knowledge, the journal had, to that point, been managed on an ad hoc basis through the Australian Cancer Society’s office. I accepted the responsibility that was offered; the opportunity it afforded me has yet to be withdrawn.

Having responsibility for *Cancer Forum*, I quickly learned that I was not alone. Indeed, I was junior to a towering authority in pathology and oncology, (the late) Fred Gunz. Fred, then Editor-in-Chief of the College’s journal, *Pathology*, was also accorded responsibility for Cancer Forum. Fred and I would meet at the Australian Cancer Society offices, located a couple of floors up in the then Bank of New South Wales building, corner of King and Castlereagh Streets in the Sydney CBD. Lawrie Wright, being Chief Executive of the Australian Cancer Society and Executive Officer of COSA, hosted such meetings. Lawrie’s dual function, often marked by letters he wrote to himself in one capacity and received in another, meant that over a period of decades *Cancer Forum* was, and certainly continues to be, a joint enterprise of Cancer Council Australia and COSA.

Concerning 1974, I can’t readily associate my links to COSA, Cancer Council Australia or *Cancer Forum* with my participation in the World Cancer Congress in Florence, 1974. The imperative to be in Florence followed immediately from my research. I was fortunate to be working in the field at the forefront of cancer biology: chemical carcinogenesis. Such research went way beyond any consideration of precisely which substances were carcinogenic. Tumour induction by chemicals was then the vehicle for elucidating the nature of malignancy and its relationship to normal tissue growth.

From Cologne, I was driven to Florence by another colleague from my research time in London: a neuropathologist, Paul Kleihues (later Director of the International Agency for Research on Cancer, Lyon), who’d come to our lab in the early 1970s because the only reliable rodent model for glioma involved administration to rats of the N-nitrosoureas. In discussion as we drove, we agreed that the recently reported covalent binding of benzo[a] pyrene to DNA confirmed the views of our immediately-past supervisors, (the late) Peter Magee and (the late) Emmanuel Farber, that modification of DNA is key to tumorigenesis rather than structural change in proteins as championed for some time by, among others, (the late) Charles Heidelberger.

At the World Cancer Conference in Florence, as best I recall, posters were not then the principal vehicle for proffered papers; all papers were presented orally. Occasionally, a slide projected back-to-front, a phenomenon I later contrived to brighten up a dull PowerPoint presentation, though the bewildered students were not amused. But the nature of material presented, rather than the technology, dominates my memory of that conference when I consider UICC Melbourne.

As a cancer researcher, my goal in Florence was to assimilate the most recent data concerning chemical carcinogens. This awareness was not complemented by focus on new treatment, let alone the well-being or otherwise of those diagnosed with cancer. I can’t reasonably assert that such matters were not mentioned, but they lacked the centrality now accorded to the burden that cancer diagnosis and cancer treatment inflicts on individuals, their families and their carers. Fortunately, awareness of these issues is not restricted to the health professionals directly involved; such awareness is the business of all involved in cancer control. This dimension, rather than any contrast between carcinogen-binding to DNA and genomics as currently understood, is the key development as I reflect on two World Cancer Congresses, 40 years apart.

Cancer Screening

PROGRESS IN CANCER SCREENING: WHERE ARE WE IN 2014?

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Abstract

Cancer screening aims to reduce overall mortality by prevention or early detection of invasive disease. This issue of *Cancer Forum*, launched to coincide with the 2014 World Cancer Congress in Melbourne, focuses on the latest developments in cancer screening. These developments include policy updates for the established screening approaches for prevention of breast, cervical and colorectal cancer. For example, in response to the rapid impact of HPV vaccination, Australia's established cervical screening program is now preparing to implement a major transition from cytology to primary HPV screening. National roll-out of two-yearly bowel cancer screening in people aged 50-74 years is underway and expected to be completed by 2020. Also discussed in this issue are the challenges in assessing the balance of benefits and harms of cancer screening (especially for breast screening and prostate specific antigen testing) and the future potential of screening more targeted populations for cancer, including screening high risk people for lung cancer, screening Indigenous populations for oral cancer and screening newly incident cases of colorectal cancer for Lynch Syndrome, so that at-risk family members can be identified. A common theme that emerges is the ongoing challenge as well as the opportunity posed by the introduction of new screening technologies, and the need to ensure that the benefits, cost-effectiveness and harms associated with use of these technologies are comprehensively evaluated and communicated effectively to clinicians and consumers.

Cancer screening aims to reduce overall mortality by prevention or early detection of invasive disease. This issue of *Cancer Forum* focuses on the latest developments in cancer screening, which include policy updates for established screening approaches (for cervical, breast and colorectal cancer screening), ongoing debates around the benefits and the harms of screening (especially for breast screening and prostate specific antigen (PSA) testing) and horizon scanning for screening more targeted populations for cancer.

In 1968, the World Health Organisation (WHO) formulated a set of principles for screening programs. These classic criteria, which now underpin screening policy in Australia, as in many other settings, include the requirement to adequately understand the underlying disease process, the availability and acceptability of a suitable screening test, the capacity to perform effective treatment for the condition, and the cost-effectiveness of the process. Over time, the criteria have been revised and extended to include a number of additional concepts, including equity of access and provision of informed choice in screening.[1] The WHO criteria form the basis of the population-based screening framework endorsed by the Australian Health Ministers' Council in 2008 (see box 1).[2] The Australian framework also emphasises the importance of a strong evidence base in making a decision about the introduction of a screening program and the requirement that the benefits of the screening program outweigh the potential harms.

Policy updates for established cancer screening programs

Australia has already established organised national programs for breast, cervical and bowel cancer screening. All three of these established programs have recently each undergone, or are undergoing, important changes.

Breast cancer screening

Australia's national breast cancer screening program, now known as BreastScreen Australia, was first established in 1991. Currently, women aged 40 years and older are eligible for two-yearly screening. Until 2013, recruitment strategies were targeted at women aged 50-69 years, but recently the Australian Government committed to expanding the target age range up to 74 years. In this issue, David Roder gives us an overview of the history of the program, the participation rates achieved, and a summary of the epidemiological data from local studies on program outcomes. He also provides an overview of the potential role of breast tomosynthesis as an adjunct to digital mammography, but notes that results from large scale overseas trials are awaited and that further evidence on its effectiveness and cost-effectiveness in Australia is required.[3]

To provide context for the Australian program, Julietta Patnick reviews the history of the UK Breast Screening Program, which invites all women aged 50-70 years for

three-yearly screening.[4] The UK program is currently conducting a major 'age extension' trial, which will involve cluster-randomising groups of women in the same geographical area to one of two groups i.e. either to include women aged 47-70 years or 50-73 years. Women will be randomised until at least 2016. The primary outcome will be mortality from breast cancer by age 60 years in women invited for an additional early screen before age 50 years, versus those not invited, and by age 80 years for women who have an additional late screen after 70 years versus those not invited.[5] This trial will provide critical new evidence on the optimal age range for breast cancer screening. As in Australia, the UK program is currently considering the evidence about introduction of tomosynthesis. Another major challenge at present is the workforce issues generated by the imminent retirement cohort of staff who were appointed at the start of the program.

Cervical cancer screening

Australia was the first country in the world to implement a national, publicly-funded vaccination program for the human papillomavirus (HPV), with the rollout of HPV vaccine starting in 2007, targeting females aged 12-13 years, and catch-up to 26 years to 2009. Young males were included in the program from 2013. The vaccination program has already had substantial effects on a number of HPV-disease related outcomes in young Australians - including reductions in vaccine-included HPV type-specific infections in females, reductions in anogenital wart presentations in both young females and heterosexual males, and reductions in high grade cervical precancerous abnormalities in young females. Megan Smith provides a comprehensive overview of the vaccination experience in Australia to date, including the coverage rates achieved and the many studies emerging on vaccine impact.[6] As discussed in her recent paper, new data indicate the vaccine is having a comparable impact in young Indigenous women to that in the general population. Indications are promising that vaccination will reduce longer term risks of anogenital warts and cervical cancer across the population.

Because current generation vaccines protect against two oncogenic HPV types (16/18, implicated in 70-80% of invasive cervical cancers), fully vaccinated women remain at some - albeit a substantially lower - lifetime risk of developing invasive cervical cancer. Although some form of cervical screening will thus likely be required for the foreseeable future, the rapid and substantial impact of HPV vaccination has been a driver for reviewing how screening is performed. A second driver has been a large body of emerging evidence on longitudinal outcomes after primary HPV DNA testing. Philip Castle gives us a comprehensive review of the rationale for HPV testing and the international evidence base currently supporting a major transition from cytology (Pap) screening to primary HPV screening in many countries.[7] A number of randomised controlled trials of HPV-based screening compared to cytology screening have now been conducted and a pooled analysis of data from these trials has demonstrated increased protection against the development of invasive cervical cancer in HPV-screened women.[8]

Marion Saville provides an overview of the policy context for cervical screening in Australia and the recent 'Renewal' review of the National Cervical Screening Program.[9] In 2014, the Australian Medical Services Advisory Committee, as part of the Renewal evaluation, recommended a transition from two-yearly Pap smears in women aged 18-20 to 69 years, to five-yearly HPV testing in women aged 25-69 years, with discharge from screening in their early seventies for women who have a negative HPV test. Pending final policy approval, changes are anticipated to be implemented from 2016 onwards. The transition will be associated with major challenges, including communication with women and their doctors about high negative predictive value of HPV testing, the safety of starting screening at age 25 years and moving to a five-yearly interval. However, there will be major benefits, including expected further reductions in cervical cancer incidence and mortality (of the order of a 15% or greater improvement) associated with the move to HPV screening.[10] A major trial of HPV screening being conducted in Australia in Victoria, 'Compass', which will eventually recruit over 100,000 women, is providing a sentinel experience for program transition in Australia.

Colorectal cancer screening

In the March 2014 issue of *Cancer Forum*, Graeme Young reviewed the evolution of technology for bowel cancer screening.[11] Randomised controlled trials conducted in the 1990s using guaiac faecal occult blood test technology, demonstrated a screening-associated reduction in colorectal cancer mortality of the order of 15% or more on an intention-to-screen basis.[12-16] The subsequent development of faecal immunochemical tests (iFOBT) further improved the sensitivity of detection of advanced precancerous adenoma as well as colorectal cancer.[17]

Bowel cancer screening has been shown to be cost-effective, both in the Australian context,[18,19] and internationally. The potential harms include the risks associated with undergoing colonoscopy after diagnostic referral of an individual with a positive FOBT test result. A number of peak bodies have concluded that the benefits of population screening for bowel cancer outweigh the harms.[20] In 2005, clinical practice guidelines endorsed by the National Health and Medical Research Council (NHMRC) concluded that "organised screening with FOBT, performed at least once every two years, is recommended for the Australian population over 50 years of age."[21] The rollout of the National Bowel Screening Program commenced in 2006, initially introducing tests to people age 55 and 65 years, and new age cohorts have been gradually added. In 2014, the Federal government announced the accelerated rollout of the final age cohorts such that by 2020, screening will be performed according to the NHMRC recommendation i.e. every two years in people aged 50-79 years. The program involves use of immunochemical FOBT kits, where eligible individuals are identified by Medicare and an iFOBT kit mailed to their homes. Participation rates are currently ~33% on average, but with even lower rates seen in men and in younger age cohorts,[22] emphasising the ongoing importance of awareness campaigns for bowel cancer screening.

Several efforts to develop new technologies for bowel cancer screening have been reported. Many of these have focused on molecular assays for markers of genetic and/or epigenetic abnormalities in either stool,[23] or blood samples.[24] An algorithmic approach may be taken to combine information from multiple molecular markers. However, before such tests can be used in population screening programs, a high quality evidence base (e.g. evidence from randomised controlled trials) will need to be available and acceptable test sensitivity for pre-invasive advanced colorectal adenomas and early stage cancer, as well as acceptable specificity and cost-effectiveness, will need to be demonstrated. This level of evidence is not yet available on any of the new molecular marker-based test technologies.

Balancing the benefits of screening against the harms

Although relevant to any prevention approach, over the past few years quantifying the magnitude of benefits in relation to harms has become the subject of particular focus for breast cancer screening and PSA testing.

Breast cancer screening

Julietta Patnick discusses the 2012 independent review of the UK breast screening program.[4] This review, prompted by an extensive and ongoing debate about the efficacy of screening and extent of overdiagnosis and overtreatment, concluded that the UK program saved about 1300 lives per year and should continue. It also provided an estimate of the extent of overdiagnosis, concluding for each life saved, three additional women were diagnosed with cancer who might not otherwise have had such a diagnosis. The potential harms of overdiagnosis include psychosocial distress, the need to undergo further diagnostic investigation, and overtreatment. Following the UK independent review, the information leaflet sent to women invited for screening in the program was revised to take account of the new calculations of benefits and harms.

Heather Bryant cautions us not to 'throw the baby out with the bathwater' when it comes to breast cancer screening.[25] She notes that population-based screening programs, and public messaging, must determine the best course of action based on a weighting of the risks and benefits for 'average' women in a specific population. She examines current information on the perceived benefits and risks and the recent move towards individualised decisions of risks and benefits. David Roder sets the international evidence for screening effectiveness in the Australian context, noting that Australian evaluation studies suggest a breast cancer mortality reduction from mammography screening in Australia that is at least as large as reported for the original international trials, which was of the order of 25-35%. He also notes that more research is needed to broaden the evidence on over-detection.

An upcoming development is that the International Agency for Research on Cancer will, late in 2014, convene a group of experts to consider updated recommendations for breast cancer screening for a new *Handbook for Cancer Prevention*. The brief of the agency working group is to "produce an up-to-date, objective, and independent evaluation of the benefits and harms of all modalities of screening in different age groups and different settings."[26]

PSA testing

Results from international randomised controlled trials conducted in the US and Europe have differed in terms of whether or not a mortality benefit is been associated with PSA testing in asymptomatic men.[27,28] The harms of testing may include referral for diagnostic evaluation, treatment and treatment-related adverse effects. However, PSA testing is still commonly used in Australia. In this issue, Bruce Armstrong and Anthony Lowe summarise an important ongoing process to perform systematic reviews of the literature for PSA testing, investigation of men with positive tests, and early management of test-detected prostate cancer, and to use the findings to develop national clinical practice guidelines.[29] NHMRC processes are being followed and NHMRC approval of the final guidelines will be sought. Public consultation on the draft guidelines is expected to commence at the end of 2014.

One of the difficulties in developing clinical practice guidelines for PSA testing is that high quality evidence is lacking in some areas. For example, it is possible that the balance between the benefits and harms of testing could be optimised by careful consideration of the testing interval, the populations, and triaging processes for men with elevated PSA. It is also possible that risk assessment tools, which use PSA level in conjunction with other patient information (such as comorbidities and life expectancy, or perhaps, validated measures of patient preferences) will have a future role.[30] It is not feasible to conduct large-scale trials of each potential approach. Furthermore, the benefits, harms and cost-effectiveness of testing in Australia depend on several factors specific to the local context, including testing uptake and the risk profile of the population. Michael Caruana and colleagues review the literature on mathematical models for simulating PSA testing in the population.[31] Carefully calibrated and validated models, which take account of existing levels of PSA testing uptake, have potential to provide useful information about the expected impact, as well as the costs, of different approaches to PSA testing. This will be an important tool to inform future revision of the clinical practice guidelines, as is needed in response to the emergence of new evidence.

Horizon scanning in cancer screening

New technologies are continually emerging, and they are sometimes publically promoted as cancer screening tests on the basis of early clinical results and/or regulatory approval, both of which are often obtained far in advance of the novel procedure's utilisation in an organised cancer screening program. Any changes to existing organised programs or implementation of new programs requires a substantial evidence base, generally identified via systematic review of the literature, involving extensive clinical trial evidence and cost-effectiveness modelling in the Australian setting. For example, before the Australian National Cervical Screening Program recommended a change from cytology to primary HPV testing, a major independent review process was conducted. The evidence

base underpinning decision-making included several large scale randomised controlled trials of primary HPV screening compared to cytology screening; meta-analysis of these trials involved data on 176,000 women.[32] This evidence was then synthesised in the Australian context to predict the future impact of primary HPV screening using a detailed model of HPV vaccination and screening in Australia.[10]

There are, however, some areas in which important new evidence is expected in the next few years. These include new data on ovarian cancer screening, as well as emerging evidence on potential new approaches for targeted higher risk populations including lung cancer screening, oral cancer screening, and screening for Lynch Syndrome in newly diagnosed colorectal cancer cases. Another important area of activity is the evaluation of prevention strategies for hepatitis-B related liver cancer in high risk communities.[33]

Ovarian cancer screening

The longitudinal outcomes from ongoing screening rounds of the UK Collaborative Trial of Ovarian Cancer Screening will provide important new evidence when this becomes available. The trial is evaluating annual screening with the CA-125 blood test (interpreted using a risk assessment algorithm) with transvaginal ultrasound as a second line test, as well as annual transvaginal ultrasound alone, compared to no screening in over 200,000 post-menopausal women. Findings from the prevalence screening round indicated encouraging sensitivity for primary ovarian and tubal cancers and primary epithelial invasive ovarian and tubal cancers.[34]

Lung cancer screening

Lung cancer is the leading cause of cancer death in both men and women in Australia,[35] and consequently the evaluation of lung cancer screening with low dose computerised tomography (LDCT) in high risk people has emerged as an important priority. Otis Brawley summarises the evidence from the US National Lung Cancer Screening Trial (NLST) and the resulting 2014 recommendations from the US Preventative Services Task Force.[36,37] The NLST, for the first time, demonstrated a mortality benefit in high risk individuals aged 50-74 years with 30 pack-years of smoking history.[36] However, although the NLST showed a 20% reduction in lung-cancer specific mortality and a reduction in all-cause mortality in this high risk group, it also showed that the harms of lung cancer screening are potentially substantial, with almost 40% of the screened group receiving a positive result over three tests, the majority of which were false positives. The US Preventative Services Task Force recommendation is for annual screening in adults, aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Although the task force emphasised that lung cancer screening is not an alternative to smoking cessation, it found adequate evidence that annual screening for lung cancer with LDCT in a defined population of high-risk persons can prevent a substantial number of lung cancer–related deaths.

The main issues that would need to be addressed, before lung cancer screening could be introduced in Australia include: achieving a balance of benefits and harms, costs and cost-effectiveness; the need to investigate and optimise the appropriate age range and screening interval; the need to define appropriate management/investigation algorithms for screen-detected nodules; defining referral pathways; and the need for credentialing of screening centres. In Australia, the Department of Health's Standing Committee on Screening has drafted an overview of the evidence and issues,[38] noting that "...there are still a number of issues that need to be investigated before the potential benefit can be properly assessed and weighed against the costs and potential harms..." in the Australian context. However, it is notable that a local trial, the Queensland Lung Cancer Screening Study, is currently ongoing,[39] and is expected to provide effectiveness and cost data to support a health economic evaluation of lung cancer screening in Australia. Modelling will be required to estimate the longer term mortality benefit and harms in the local context.

The potential harms of screening are one of the major issues to be addressed. Estimates of the overdiagnosis rate are up to 17-18% as a proportion of all screen-detected cancers.[40,41] Whether this rate will be applicable and whether it is compatible with a favourable benefit to harm ratio needs to be assessed in the Australian context. Since publication of the results of the NLST, further work has shown that using risk prediction tools in the general population to better target people for LDCT screening, can improve both the sensitivity and the positive predictive value (and hence reduce the harms) of screening. For example. Tammemägi and colleagues have developed and validated the $PLCO_M2012$ risk tool using data from the US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.[42] $PLCO_M2012$ uses data on socio-economic status, body mass index, ethnicity and history of chronic obstructive pulmonary disease, in addition to smoking history and age, to inform an assessment of the highest risk individuals to target for screening. The use of such risk assessment tools holds promise as a desirable future approach towards achieving a better balance of harms and benefits, and there is a need to prioritise the validation of such tools in the Australian population. While lung cancer screening is a promising approach, primary prevention via continuing efforts to prevent smoking uptake and to encourage smoking cessation remains the most important strategy for reducing the burden of lung cancer.

Oral cancer screening

Richard Logan reviews the emergent evidence on oral cancer screening involving visual examination.[43] The US Preventative Services Task Force recently conducted a review of international literature on oral cancer screening, concluding that there was inadequate evidence of diagnostic accuracy, and that the balance of benefits and harms of oral cancer screening for asymptomatic adults by primary care providers could not be determined.[44] However, Logan concludes that opportunistic visual screening opportunities should be part of general oral examinations for patients visiting dental practitioners.

There is evidence to support the mortality benefit of oral cancer screening in users of tobacco and/or alcohol,[45] and thus there is interest in the potential role of oral cancer screening in targeted high risk populations. Community-based screening programs targeting high risk males have potential to be cost-effective.[46] In Australia, a program involving Aboriginal and Torres Strait Islander communities might be considered in future, since these groups have a considerably higher incidence of oral cancer than in the general population.[47] However, the level of community acceptance, as well as the effectiveness and cost-effectiveness of such an approach, would again require consideration.

Screening for Lynch Syndrome

Lynch Syndrome is an inherited condition putting people at high risk of developing colorectal, endometrial and other cancers, often at a younger age than these cancers occur in the general population. Given that several constitutional genetic mutations associated with Lynch Syndrome have been identified, it is possible to genetically screen tissue from newly identified Lynch-associated cancers, and then offer testing to family members. In Australia, some centres routinely test all colorectal cancers, however there is currently no systematic national approach to screening. In this issue, Ian Frayling and Robyn Ward discuss a recent health economic evaluation in the UK, which found that this type of screening strategy applied to individuals under the age of 51 years was highly cost-effective.[48] They emphasise the importance of research into the determinants and barriers to uptake of genetic testing and the need for health economic evaluation in an Australian context.

Conclusion

As at 2014, Australian programmatic efforts in cancer screening are focused on increasing the age range for breast screening, implementing a major program transition to primary HPV testing for cervical screening, and on the completion of the full national roll out of two-yearly bowel cancer screening in people aged 50-74 years. In Australia, as elsewhere, the balance of benefits and harms, particularly for breast cancer screening and PSA testing, continue to be extensively debated, but one outcome is the consensus that screening participants should be fully informed about the potential outcomes following the decision to screen. A number of promising new cancer screening approaches are on the horizon, and many of these involve targeted higher risk populations. A common theme that emerges is the ongoing challenge, as well as the opportunity, posed by the introduction of new screening technologies, and the need to ensure that the benefits, cost-effectiveness and harms of these technologies are comprehensively assessed at the population level and communicated effectively to clinicians and consumers.

Conflict of interest statement

Karen is co-PI of an investigator-initiated trial of cytology and primary HPV screening in Australia ('Compass'), which is conducted and funded by the Victorian Cytology Service, a government-funded health promotion charity. The sevice has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. However neither Karen nor her institution on her behalf (UNSW Australia) receive direct funding from industry for this trial or any other project.

Box 1: *WHO screening criteria, as summarised for the Australian Population-Based Screening Framework.*

WHO principles of early detection

Condition

- The condition should be an important health problem.
- There should be a recognisable latent or early stage.
- The natural history of the condition, including development from latent to declared disease should be adequately understood.

Test

- There should be a suitable test or examination.
- The test should be acceptable to the population.

Treatment

- There should be an accepted treatment for patients with recognised disease.

Screening Program

- There should be an agreed policy on whom to treat as patients.
- Facilities for diagnosis and treatment should be available.
- The cost of case-findings (including diagnosos and treatment of patients diagosed) should be economically balanced in relation to possible expenditiure on medical care as a whole.
- Case-finding should be a continuing process and not 'once and for all' project.

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BREAST CANCER SCREENING: UPDATE IN THE AUSTRALIAN CONTEXT

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Abstract

The Australian mammography screening program was introduced as a joint Commonwealth and state/territory initiative in 1991. Australian evaluation studies suggest a breast cancer mortality reduction from mammography screening in Australia that is generally higher than estimated from the original field trials (reported by an International Association of Research on Cancer expert group to be about 35% for screening participants aged 50-69 years, and following a meta-analysis of data for all ages, to be about 25%). More research is needed to broaden the evidence on over-detection. Intervention research is also needed to determine the comparative effectiveness and cost-effectiveness of digital breast tomosynthesis in the Australian screening environment.

The Australian mammography screening program was introduced as a joint Commonwealth and state/territory initiative in 1991, following two-year pilot testing.[1] This followed field trials in North America, Scandinavia and the United Kingdom, where the collective data indicated a breast cancer mortality reduction from mammography screening.[1-3] The design features of those trials have been contested,[4] but a technical expert group, convened by the International Association of Research on Cancer, after re-assessing the trial evidence, concluded that a reduction of around 35% in breast cancer mortality was indicated in 50-69 year-old women who participated regularly in mammography screening.[2] A lower reduction of about 25% was suggested in a meta-analysis of trial data for women of all ages.[5]

The Australian program increased its coverage of the 50-69 year screening target group to about 55% by 1997-98, and this coverage has remained in the 55% to 57% range in the years since then to recent reporting periods.[6] Recently, the target age range was extended from 50-69 years to include 50-74 year olds, following recommendations of the National BreastScreen Australia Evaluation.[1] Older women over 70 years had been eligible for screening since 1991, but not as part of the target age range where active recruitment was practised.[1]

Mortality reductions from mammography screening should be weighed against negative effects, such as over-detection and over-treatment.[7] Trial evidence is often used to assess both the positive and negative effects of screening, due to the potential for confounding in observational research.[7] An important drawback of the trial evidence is that results apply to outdated screening technologies and protocols that would have uncertain relevance to contemporary screening settings.[2] It is important for this reason to consider more timely observational evidence, as well as the original trial evidence, when making a judgement about screening benefits and negative effects.

There have been four formal evaluations of the mortality-reducing effects of mammography screening in Australia. They comprised two ecological and two case-control studies.[8-12] Collective results point to a mortality reduction of about 45% from participating in mammography screening in the 50-69 year age range.[8-12] Estimates of breast cancer mortality reductions among screening participants in individual studies were estimated to be: national evaluation – 34% (method 1),45% (method 2),40% (mean, methods 1 and 2); [8,9] NSW - 43%;[10] SA - 47%;[11] and WA - 52%.[12]

These estimates generally are higher than indicated from the original field trials.[2,5] This may be real, due to advances in screening technology. Alternatively, it may be a result of confounding from an unequal distribution of breast cancer mortality risk factors between screened and unscreened women.[3] For example, if the quality of treatment had been better for screened than unscreened women for some reason, this could have contributed to lower mortality in screened women. In fact, both advances in screening technology and confounding could have had a combined effect. Despite potential for confounding, the evidence from the four evaluation studies is consistent and suggests a breast cancer mortality reduction from screening in Australia that is at least as large as reported from the original trials.[2,5,8-12]

One research team has interpreted secular mortality trends by age in Australia to indicate that the population-based reduction in breast cancer mortality has been mostly due to treatment.[13] By comparison, statistical modelling in the United States suggested that approximately half the mortality reduction was due to screening and half to treatment.[14] and similar results were evident from a UK study.[15] It is very likely that both screening and treatment are contributing significantly to breast cancer mortality reductions in Australia, but the respective proportional contribution of each is difficult to define.

Trial evidence also has been used to assess over-detection (often called over-diagnosis).[3,7] Again there is the question of whether trial results are relevant to contemporary Australian screening environments. Also, the trials were not designed to measure over-detection and only two of them have been used retrospectively for this purpose.[16-18] Results have been difficult to interpret due to under-powering and in one study, limited follow-up to clear the lead time effects post-screening,[16-18] although a recent 15-year follow-up of Canadian trial data reported that about 22% of screen detected invasive breast cancers in that trial were attributable to over-detection.[19] Little evidence was presented in the Canadian or other trial on engagement in privately conducted screening by women after they had left pilot screening, which could have extended lead-time effects,[16-19] although reference was made to the possibility of continued screening in one study.[18]

A plethora of observational studies of over-detection have been undertaken in many populations, yielding vastly different estimates, ranging from near 0% to over 30% of diagnosed breast cancers and ductal carcinomas in-situ.[3] They included a NSW study where the over-detection estimate was at the higher end of the range,[20] and a recent SA study where over-detection was estimated to be at the lower end of the range.[21] Additional observational research is underway in Australia to broaden the evidence base. Over-detection estimates may vary appreciably around the world due to differences in screening environments and differences in study design, especially whether study designs make adequate provision for differences in risk factors and lead time.[22] It will be important to assess the robustness of Australian estimates in the context of differences in study design.

Digital breast tomosynthesis is a new technology still in the testing phase as a screening tool.[23-25] Italian and Oslo trial data both showed an increased detection of breast cancer when tomosynthesis (3D mammography) was included in the screen reading to allow integrated 3D and 2D reading, as compared with digital mammography alone,[23,25] and a potential decrease in recall to assessment rates when using digital breast tomosynthesis.[23,25] A retrospective study of data from 13 North American breast centres has provided similar results.[26] It is not clear at present, however, whether the reported increase in detection sensitivity from tomosynthesis will translate to lower interval cancer rates and reduced breast cancer mortality, and whether the increased cost of this screening methodology will be worthwhile. The Oslo trial is expected to be complete in 2015 and results from another Malmo trial are expected soon.[25] The utility of this new technology needs to be tested in the Australian screening environment.

In summary, Australian evaluation studies suggest a breast cancer mortality reduction from mammography screening in Australia that is generally higher than reported for the original trials. More research is needed to broaden the evidence on over-detection. Intervention research is needed to determine the comparative effectiveness and cost-effectiveness of digital breast tomosynthesis in the Australian screening environment.

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BREAST CANCER SCREENING: THE UK INDEPENDENT REVIEW AND UPDATE ON BREAST SCREENING IN ENGLAND

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Abstract

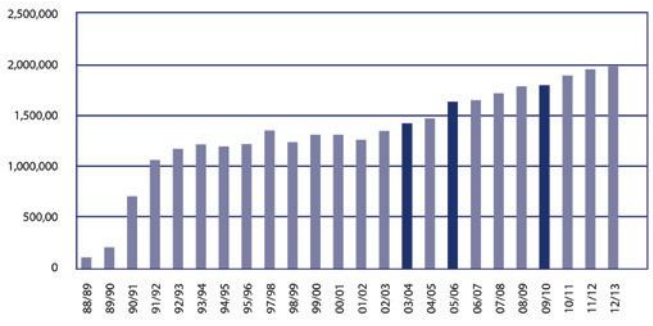
The National Health Service Breast Screening Program began operations in 1988. Good quality was achieved by the mid-1990s, by which time the program was screening one million women per year. Criticism of the program grew in the first decade of the 21st century. Originally it was alleged lives were not saved, but this moved on to alleging that only a few lives were saved, and that many more were damaged by overdiagnosis. In 2012, an independent review of the breast screening program was commissioned, which concluded that the program saved about 1300 lives per year and should continue. However, for each life saved, three women were diagnosed with cancer who might not otherwise have had such a diagnosis. Following the review, the information leaflet sent to women was revised to take account of the new calculations of benefits and harms. The program is now conducting a major trial of screening of women 47-49 and 71-73 years, involving sending additional invitations at each end of the routine 50-70 year age group. It is also considering the evidence about introduction of tomosynthesis and how to meet the challenge of the retirement of the cohort of staff who were appointed at the start of the program.

The National Health Service (NHS) Breast Screening Program commenced operations in 1988. At the time, the UK had the highest mortality rate in the world from breast cancer, although not the highest incidence rate. There were about 30,000 cases a year and 16,000 deaths. There is no reliable cancer stage data from the time, but the often expressed view was that this poor survival rate was due to British women presenting late.

The Swedish Two Counties trial of breast cancer screening published its results in 1985, showing a 31% fall in mortality among invited women.[1] Following this the Department of Health in the UK commissioned Professor Sir Patrick Forrest to lead a group of experts to examine the evidence and make recommendations.[2] They recommended three yearly screening for women aged 50-64 years. In 2004, this was expanded to women aged 50-70 years inclusive, but otherwise essentially this is the screening program which exists today. It was fully rolled out across England by 1990 and the first, prevalent, round of screening was completed in England in 1993.

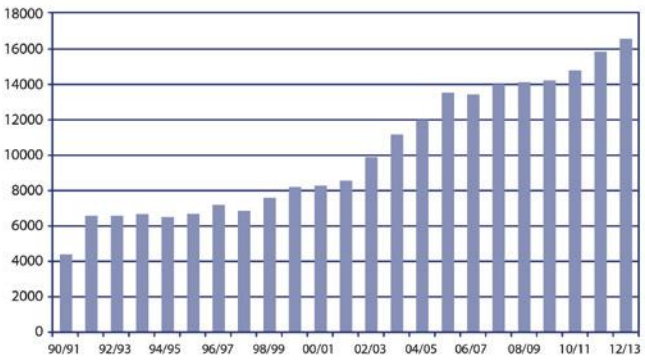
It took a number of years for the correct quality to be achieved, but by the end of the 20th century the program was working well. At the same time, mortality from breast cancer was falling dramatically as treatment improved, particularly with the introduction of tamoxifen, and the introduction of the breast screening program had hugely improved the infrastructure and techniques for breast cancer diagnostics for all women in the UK. Studies showed the greatest reduction in mortality was observed in the screened age group, but the effect was not as large as had been hoped for.[3,4]

***Figure 1**: Number of women screened annually in the breast screening program, England.*



Source: Department of Health and Health and Social Care Information Centre

***Figure 2**: Breast cancers detected annually in the breast screening program, England.*



Source: Department of Health and Health and Social Care Information Centre

The NHS Breast Screening program now screens nearly two million women a year and in the last year reported (2012/13) found over 16,000 breast cancers (see figures 1 and 2).

Criticism of breast screening

Criticism of breast screening for not achieving its objective of reducing mortality began in the 21st century. In particular, a paper from the Nordic Cochrane Group published in the *Lancet* caused a great deal of consternation. As time moved on, it was broadly accepted that there was some reduction in mortality, and the argument shifted to whether this was worth the price in overdiagnosis, but papers continued to appear regularly over the years which criticised mammographic screening and the NHS Breast Screening Program in particular. [6,7]

Overdiagnosis, that is the diagnosis of disease which would not be clinically relevant in the patient's lifetime, is a feature of all cancer screening programs. It is felt to be a particular problem in prostate cancer screening, but affects all programs to a certain extent. In breast screening, the diagnosis of a cancer which would never clinically present could lead to a mastectomy (i.e. overtreatment) and the concept of overdiagnosis leads often to a very emotional debate.

The problem is that those breast cancers which will never prove fatal to their host can generally not be distinguished from those that will. The introduction of mammography, whether for screening or investigation of symptoms, has led to a major increase in the proportion of ductal carcinoma in situ being found. But it is recognised that if this is not completely excised, some ductal carcinoma in situ will go on to become invasive and develop, in some women, to become a fatal cancer. Thus, the level of overdiagnosis can only ever be an estimate and to some extent is a function of when the time cut-off for analysis is set. Estimates vary from 1.7% to 54% for women aged 50–59 years, and 7% to 21% for women aged 60–69 years.[8]

The debate about breast screening continued. While in the UK, the stage moved from the *Lancet* to the *British Medical Journal*, it also raged around the world.[9,10,11] The information sent to women also became a topic of major discussion, as programs around the world moved to take better account of the concept of an informed choice and giving women information about the potential harms of breast screening, as well as the potential benefits. Many critics of breast screening, however, complained the information was still biased towards persuading women to be screened and that it deceived them about the true position.[12]

In the UK, new breast screening leaflets were commissioned in summer 2012 by the screening program, but the Department of Health felt something more than this was needed to deal with the criticism. Therefore, together with Cancer Research UK, the Department of Health decided to commission the UK Independent Review of Breast Screening in the autumn of 2012.[13] The work on the information was thus put on hold until the independent review reported its findings.

The UK independent review

The review team (the panel) consisted of two statisticians and two breast cancer clinicians, none of whom had ever published on breast cancer screening before. There was a female lay member who was an active patient advocate and the panel was led by Sir Michael Marmot, the Sydney-educated MRC Research Professor of Epidemiology and Public Health at University College, London. The panel embarked on the major task with the secretariat supplied by Cancer Research UK. The panel had a great deal to learn about breast cancer screening. Their reading list runs to 17 pages and would be helpful for anyone embarking on a master's degree in breast screening. They invited people prominent in the discussion to speak to them and held a discussion group to ascertain more closely the views of women eligible for the screening program.

The first finding related to a reduction in mortality. The panel concluded that a relative risk reduction of 20% was 'the most reasonable estimate of the effect of the current UK screening programs on breast cancer mortality'. The panel based this on randomised control trials (RCTs) and not observational studies, which they did not find particularly helpful. They noted considerable uncertainties in calculating the level of mortality reduction, but also noted that the findings of the observational studies were in the same direction as the trials.

Absolute mortality benefit was the next issue to be addressed. Using their own figure of 20% relative reduction in risk and calculating the benefit for women up to the age of 79 years (approximately 10 years after screening finished), the panel estimated that there was one breast cancer death prevented for approximately 250 women invited to breast screening. This contrasted with the range of one in 2000 used by some prominent critics of the program and translates into about 1300 lives a year saved by UK breast screening programs.

The issue of estimating the extent of overdiagnosis raised many difficulties. Once again the panel examined both RCT data and observational data. In the case of the latter, the most commonly used method to estimate overdiagnosis was examination of time trends in incidence rates of breast cancer for different age groups over the period that population screening was introduced. The panel however, commenting that estimates of overdiagnosis using this method varied from 0% to 36%, concluded that this method could give no reliable estimate of the extent of overdiagnosis and fell back on RCT data. Using RCT data, they estimated that "...the frequency of overdiagnosis was of the order of 11% from a population perspective, and about 19% from the perspective of a woman invited to screening...". Importantly, they also pointed out that a diagnosis of DCIS did not equate to an overdiagnosed case. Overall, the messaging resulting from this was that for every life saved, there were three diagnoses of breast cancer that might not otherwise have occurred. On balance, the panel concluded that the UK breast screening programs confered significant benefit and should continue.

The report was published 29 October 2012 in full with an executive summary. A paper was also published in the *Lancet*.[14] Predictably there was extensive coverage in the press the following day. Headlines talked of 'needless cancer therapy' *(Daily Mail)*. However, while there has been concern that falling participation rates might be attributed to falling confidence in the test, research has not yet shown any direct effect of the review on breast screening participation.[15]

Next steps for the NHS Breast Screening Program

With the independent review concluded, attention once more turned to the information sent to women with their invitation for screening. An independent research team from King's College, University of London, had been commissioned to do the work and relied on the new calculations about harms and benefits for the content of the leaflet. However, finding the best methods of communicating the issues proved difficult for an audience which include every woman over 50 years of age in the country. A number of ways to convey the information were tested out in opinion polls and with a citizens' jury. These steps in the process were all documented and the reports can be found online. Peer reviewed publications have been accepted and will appear shortly. The new leaflet was released in September 2013.[16,17,18] There is a commitment by the Department of Health to evaluate it, but this has not yet taken place.

The major development in the NHS Breast Screening Program through this period has been the instigation of what will be the largest trial in the history of breast cancer screening. The extension of the breast screening program from 50-70 to 47-73 years was announced in 2007. This is being implemented as a cluster-randomised controlled trial of an additional screening invitation for women about to enter the routine age group, those aged 47-49 years, and an additional invitation at the end of routine screening, at the age of 71-73 years.[19] The end points are death from breast cancer by the age of 60 years for the younger group, and death from breast cancer by the age of 80 for the older group. The trial will also be able to look at the issues of overdiagnosis and overtreatment in women, which were not specifically considered in the original breast screening trials which were instituted over 30 years ago.

The major technical issue currently facing the NHS Breast Screening Program is the evaluation of breast tomosynthesis. Digital breast tomosynthesis (DBT) uses multiple thin reconstructed slices to produce a 3D image and thus aims to avoid the problems of the 2D conventional image with overlapping tissues. It is to minimise overlapping tissues that compression is used, and this will still be needed. Overlapping tissues can mean small cancers are obscured behind normal tissue, or conversely that normal tissues superimposed one on another, can give the impression of an abnormality and lead to a false positive recall. Thus DBT has the potential to improve both the sensitivity and specificity of mammography. There has been a large trial examining its use for assessment of screen detected abnormalities and now the debate is moving on to the use of DBT for screening. Taking account of already published trials and observed data from both Europe and North America, is there a need for another trial focusing on whether to incorporate DBT in the initial screen or not?[20,21,22,23]

One factor which has always been a challenge for the screening program, although its manifestation has varied, is the need to develop and maintain sufficient and sufficiently skilled staff. When the screening program started, mammography was a rare skill in the NHS. Training radiographers to carry out the technique and radiologists to interpret the films consumed a great amount of energy and effort in the early years. Many new consultant posts were created at that time. Once this phase was over, increasing numbers of staff were needed to cope with the expanding eligible population. This expansion was caused by baby boomers hitting 50 and also by the slightly later expansion of the screening age group, adding two more screening rounds to the program. Training of radiographers to report films and to undertake biopsies in the assessment clinics relieved the radiologist staff of some of the pressure. Assistant practitioners were trained to take mammograms in order to release radiographers for these duties. Now another phase is coming upon the program, and that is the retirement of many of those people who were new consultants at the start and have been the leaders of the program through its first 25 years. It is not yet clear where their replacements will be found.

Some challenges remain the same as when the screening program commenced. Acceptance and participation rates need constant attention, and breast screening is still more likely to attract the affluent than the deprived.[24] The biggest challenge of all however, remains - to make breast cancer a curable disease by integrating early detection with ongoing improvements in treatment.

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OF BABIES AND BATHWATER: RECONSIDERING THE PUBLIC HEALTH APPROACH TO BREAST CANCER SCREENING

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Abstract

There are few topics in medical science that arouse as much controversy – and as much passion – as the role of mammography in breast cancer screening. Part of the reason for continued debate lies within the complexity of the audiences for any recommendations made. The recent emphasis has been upon the individual weighing personal benefit and risk. Public health recommendations however, are based upon the overall population-based estimates of risk and benefit. In particular, population-based screening programs and public messaging must, by definition, come to conclusions about the best course of action based on a weighting of the risks and benefits for 'average' women in a specific population. This overview provides a window into the current analyses of the risk and benefits of mammography screening, and of the impact of these debates on considerations of programmatic screening. It examines current information on the perceived benefits and risks, the recent move towards individualised decisions of risks and benefits, and the role of public health messaging and population-based programs within this context.

There are few topics in medical science that arouse as much controversy – and as much passion – as the role of mammography in breast cancer screening. Population-based recommendations have been in place for over 25 years; population-based programs were launched in the UK in 1988,[1] and subsequently in several countries.[2] With eight major randomised controlled trials dedicated to studying the efficacy of screening, most of which consistently found benefit in at least a subset of their participants, it is perhaps surprising to find that this degree of controversy still exists.

Part of the reason for continued debate lies within the complexity of the audiences for any recommendations made. The recent emphasis has been upon the individual weighing personal benefit and risk, and several excellent reviews exist that help to inform this.[1,3-5] Public health recommendations, however, are based upon the overall population-based estimates of risk and benefit. In particular, population-based screening programs, and public messaging, must by definition come to conclusions about the best course of action, based on a weighting of the risks and benefits for 'average' women in a specific population. Thus, there have also been recent reviews designed to assess whether current breast screening programs should be continued, and these have not always come to the same conclusion.[1,6]

This overview provides a window into the current analyses of the risk and benefits of mammography screening, and of the impact of these debates on considerations of programmatic screening. It will examine current information on the perceived benefits and risks of mammography screening, the recent move towards individualised decisions of risks and benefits, and the role of public health messaging and population-based programs within this context.

Development of recommendations and programs

The results of mammography screening studies were first published in the late 1980s, with a notable landmark being the publication of the results of the Shapiro study in 1977.[7] This US study enrolled women aged 40 to 64, and used annual mammography screening and physical examination as its screening interventions. When the study found a significant reduction in mortality, it was understandable that one result was population-based recommendations in US context based on annual screening for women over 40.

Subsequent studies, however, began to show a difference in results between those women who were under 50 years of age with those who were over 50 years, and several used intervals of two years or more between screens.[8] Thus, outside of the US, most recommendations for population-based screening put forward over the late 1980s and early 1990s, targeted women aged 50 to 69, with screening intervals of two years or more.[9] Many population-based programs used the Wilson-Jungner criteria to determine the value of instituting screening at a population level, which was of more interest in constituencies with publicly-funded health care systems than it was in the US.[10] In these jurisdictions, the focus was on the sustainability of providing mammography to a large segment of the population, the assurance of at least the same technical and interpretive quality as in the positive randomised trials, and on minimising the potential harm of false-positive results. In an effort to maximise the population impact of mammography screening, many programs set goals for participation rates, and used a combination of invitation letters and public health messages to encourage participation.

Recent estimates of potential benefits

Several recent meta-analyses and reviews have attempted to quantify the potential benefits of mammography. An independent review of the UK Breast Screening program concentrated on women aged 50 to 70 years, and arrived at a best estimate of a 20% reduction in breast cancer mortality with mammography in this age group.[1] The Canadian Preventive Services Task Force arrived at relative risk estimates of breast cancer death of 0.85, 0.79, and 0.68 for women in their forties, fifties and sixties respectively.[11] These are similar to those produced by a meta-analysis for the US Preventive Services Task Force (USPSTF) (2009), although the latter found slightly less benefit for women in their fifties (point estimate of relative risk 0.86).

All of the recent reviews are limited by the age of the studies (their start dates range from 1963 to 1982), and there has been some variability in which studies were included in various meta-analyses, largely due to different interpretations of the robustness of various study designs. Notably, a Cochrane review included only three of the eight available studies, and arrived at a relative risk estimate for the breast cancer mortality benefit of screening of 0.90, which was not statistically significant.[12] However, when the most recent Cochrane review included the studies that most other review groups found to be eligible for inclusion, their estimates of breast cancer mortality benefit were significant and consistent with the results of other meta-analyses (RR 0.81), although in conjunction with their finding the authors proposed that breast cancer mortality was an unreliable outcome that was biased in favour of screening, mainly because of differential misclassification of cause of death.[13]

While the USPSTF found similar relative risks for women in their forties compared to those in their fifties, they arrived at different recommendations for these two age groups. They recommended biennial mammography for women aged 50 to 74, while advising against routine mammography for women in their forties, stating that in this age group, women's own risks and preferences should be taken into account. This is consistent with the recent Canadian recommendations.

In arriving at these distinctions, the USPSTF noted that while they found the relative risks to be similar for women in the two age groups, the difference in the absolute risks for breast cancer resulted in quite different profiles of overall risk reduction.[14] They estimated that 1904 women in their forties would need to be invited to screening in order to avert one case of breast cancer mortality, but that this was reduced to 1339 for women in their fifties, and 337 for women in their sixties. The Canadian analysis looked at numbers needed to screen to avert one breast cancer death in the 40-49 year age group versus the 50-69 year age group, and arrived at estimates of 2108 and 721, respectively.[11] Again, these results are relatively consistent, and support the current differences in recommendations for the different age groups.

Recent estimates of potential harms

There are two principal areas of study in the category of potential harms associated with mammographic screening. Early estimates of harms focused on the potential detrimental effects of false positive results, which could generate additional imaging, consultation and potentially unnecessary benign biopsies. More recently, the potential for 'overdiagnosis', generally defined as

the discovery of a cancer that would not have become symptomatic or problematic in the absence of screening, has been a focus of study. Overdiagnosis has potential to cause harm via the psychosocial issues associated with the diagnosis, the need to undergo further investigation, and the impact of associated overtreatment.

The frequency of false positives is very sensitive to the practice setting in which screening occurs. A study by Hubbard et al. that contributed to risk estimates in the reviews, found that given screening over a period of 10 years, 61.3% of women could expect to be recalled for additional tests if the screening was done annually, and 41.6% if the screening was biennial.[15] However, this was based on an abnormality recall rate of 16.3% at first visit, and 9.6% in subsequent mammography. These recall rates are substantially higher than the target and reported abnormality rates within organised screening programs. In the Canadian breast screening programs, reporting on over two million screens done in 2007 and 2008, the abnormal recall rate for women aged 50 to 69 years was 12.6% at the first screening mammogram, and 6.0% for subsequent mammograms.[16] In Australia, for women aged 50–69 years, 12.2% of women screened for the first time were recalled to assessment, while 4.0% attending subsequent screens were recalled.[17] The UK screening program reports a recall rate of only 4%.[18] Thus, in the programmatic context, the risk of an abnormal mammogram can be reduced, which would also dramatically reduce the cumulative risk of being recalled for investigation of an abnormality over 10 years.

Studies examining the sensitivity and specificity of mammography and its relationship to reading volumes (i.e. the number of mammographic studies assessed by a radiologist in a year), have pointed to the need to focus on the optimisation of mammography as one route to maximising benefit while minimising risk,[19] and note that variability in recall rates among radiologists must be taken into consideration when calculating false-positive rates.[20] This is largely ignored in the meta-analyses however, and it would be valuable to have more realistic estimates of risk based on current organised program results, so that they could be compared with those that are commonly used, but which are based on other practice cohorts.

The majority of abnormal screening results are resolved with further imaging or ultrasound, but the potential for unnecessary biopsies exists and must be minimised. Again, these rates may vary by practice. In the Hubbard et al analysis, a false-positive biopsy rate of over 3% for the first visit in women 50 to 59 years was reported.[15] However, in Canadian programs in 2007 and 2008, the rate of biopsy with non-malignant result was 1.83% for women aged 50 to 69,[16] while the UK screening program reports a benign biopsy rate of only 0.05% (0.5 per thousand).[18] Programmatic attention to reporting and acting to minimise these rates can contribute to the limiting of negative impact from screening.

The most provocative issue in recent years has been the potential for overdiagnosis, and consequent overtreatment (i.e. treatment that ultimately does not provide a clinical benefit to the woman). The method to calculate the overdiagnosis rate is still under debate, and thus current estimates encompass a wide range. An early estimate used data from one randomised controlled trial, and arrived at an estimate of that 16% to 24% of cancers found could be considered as an overdiagnosis.[21] An analysis comparing historical and current rates in the US estimated that 31% of breast cancers diagnosed represent overdiagnosis.[22] However, based on actual follow-up data from the randomised controlled trials from Canada and Malmo, the UK Independent Review arrived at an estimate of overdiagnosis of 11% from a population perspective (the proportion of all cancers diagnosed in women invited to screening that are overdiagnosed), and 19% from an individual woman's perspective (the chance that a cancer diagnosed during her screening experience is, in fact, an 'overdiagnosis').[1] This probably represents the most realistic estimate to date, but further study is required and will need to include data from actual programmatic screening experiences.

Programmatic delivery considerations

With the number of randomised trials available, breast screening does not suffer from a lack of evidence on efficacy. Nevertheless, there are many different implementation decisions that need to be made in the provision of screening services, in order to deliver the maximal impact given constraints on resources and the local context.

One of the primary decisions to be made is whether screening should be offered opportunistically (through referrals from primary care physicians to existing specialists), or through organised programs, which involve centralised invitational and data collation systems. Canada, Australia and the UK have all moved forward with organised programs, although some mammography occurs outside of the programs to varying degrees in all three contexts. The Council of the European Union recommends that mammography occurs within the context of cancer screening programs, so that the entire population may be reached and appropriate quality controls are in place.[23] In a survey of 27 countries belonging to the International Cancer Screening Network in 2007–2008, all but two (US and Uruguay) reported the existence of programmatic screening.[2]

The continued debate on the efficacy, monitoring and appropriate targeting of screening, points to the need to achieve a critical balance between the reductions in breast cancer mortality with the risks of overdiagnosis and follow-up of false positives. As noted above, there is evidence that false positive results have been reduced in the context of existing high volume programs,[19] and routine outcome

monitoring, as occurs in most organised programs, is key to introducing quality improvement interventions to ensure this balance minimises known risks. On the other hand, the very visibility and transparency of organised programs makes them an easier target when renewed discussions of the harms and benefits of mammography arise. For example, in the companion commentary to the recent revision of the Canadian guidelines (which recommended screening in the 50 to 74 year age group), the following opinion was offered: "The best method we have to reduce the risk of breast cancer is to stop the screening program [12]".

In the UK, the ongoing debate led to a full independent review of the screening program, which included a careful consideration of the potential risks of overdiagnosis. While acknowledging that a woman who is screened beginning at age 50 years in the program would probably have an approximate risk of one per cent of having a breast cancer overdiagnosis, the review concluded that the program "...confers significant benefit and should continue".[1]

Recently, however, a review of Swiss screening programs resulted in a recommendation that no new systematic programs be implemented, and that existing programs should have a 'time limit' imposed upon them.[6] While it has been pointed out that the mortality reductions in Swiss cantons (regions) with breast screening programs decreased at about the same rate as in cantons without such programs,[24] it is acknowledged that there is active opportunistic screening occurring through private practice in other cantons. The Swiss Medical Board's additional recommendation, that the quality of all forms of mammography be evaluated, is in fact more difficult to carry out in the context of private practice, especially the evaluation of false-positive rates and overdiagnosis, and it is these harms, in fact, that are most under debate. While it is unclear whether the recommendations of the Swiss report will be adopted,[25] it will be of interest to follow whether any changes that are implemented as a result allow the evaluation of all mammography (not just programmatic screening), so that risks are minimised in whatever context screening is provided.

Decision-making considerations for individual women

Given the ongoing debate, there has been an emphasis in recent consensus processes on the need to refine our understanding of harms and benefits for individual women, and to involve each woman in decision-making around her own participation or non-participation in screening. At the proximate end of this process is the desire to arrive at more quantifiable estimates for women at lower or higher risk of developing breast cancer. For example, in the US, where public messages have targeted women in their forties for decades, modelling has been used to ascertain whether there is an identifiable sub-group of women in this younger age group whose elevated breast cancer risk profile may make the mammography benefit to harm ratio more favorable than for the average woman in her forties. One group determined that if breast cancer risk was doubled over that estimated to be the average or baseline risk, a woman in her forties may have the same benefit to harm ratio for screening as a woman in her fifties.[26] Based on this, it has been suggested that women in their forties with a first degree relative with breast cancer, or those with extremely dense breasts, may have this degree of sufficient excess risk of developing breast cancer.[14]

Any information on the benefits and risk of harm has to be explained in a way that is both comprehensible and salient to the woman considering screening. This is not straightforward, however. A truly transparent process necessarily involves the use of reasonably complex numbers. A study of numeracy and decisions about mammography found that even though 96% of the study subjects were high school graduates, few could provide correct answers to three simple numeracy questions – and there was a strong correlation with accuracy on these questions and the ability to correctly interpret information on mammography and breast cancer risk.[27] Thus, one cannot assume that simple presentation of the numbers will be sufficient to engage women in full decision-making.

Nevertheless, considerable effort has been put towards the development of relatively simple or complex decision aids to assist an individual woman in determining her preferences about whether to screen.[11,28] One cannot argue with the motivation to provide women with tools to sort through this complex information – although, as others point out, we have not successfully arrived at complete agreement among experts on how to interpret the data we do have, and it is acknowledged that the impact of decision aids in screening is not well quantified.[29] One study looking at the impact of a decision aid in assisting 70 year-old women to decide on mammography found that it did increase knowledge, but did not change women's decisions.[30]

Further, it must be acknowledged that a decision about screening is not a single life event, but will be revisited as a woman's perceived (and actual) risk changes, or as reports of emergent mammography studies change the available evidence base. Very little is known about the effectiveness of providing decision aid-based information over time. A Cochrane review of decision aids found that even when the individual's choice was towards a particular treatment course, there was no impact on adherence to that therapy over time.[31] Thus, while one cannot argue with the prudence of providing such tools, neither are they a panacea.

Finally, while the concept of shared decision-making implies a clinical context, most women receive much of their information about mammography from public messaging. It is true that we need to shift our efforts

toward educating the public, as distinct from earlier efforts to simply encourage women to be screened.[32] However, media reporting frequently emphasises the controversy rather than attempting to provide clarity; following the reporting on the USPSTF guideline changes in 2009, more women reported being more confused than helped by the information.[33] While we cannot change editorial policy or reporting style, as professionals must make the effort to be informative, rather than provocative, if we are going to discharge our responsibilities to the public we serve.

Conclusion

Most recent analyses find a favorable benefit to risk ratio for screening mammography in women aged 50 to 74 years. Estimates of the mammography-associated harms in many studies are based on community practice mammography, but it appears that the risk of false positives is much lower within the context of organised programs. Thus, the suggestion to discontinue programs while allowing continued opportunistic screening appears to be 'throwing the baby out with the bathwater'– and is unlikely to result in reduced risk to women. Consideration should be given to new analyses that reflect the lower false positive rates achieved in programmatic contexts, and of developing ways to explain this information to women and to policymakers to ensure that the highest quality screening is available for women who choose to be screened.

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UPDATE ON HPV VACCINATION IN AUSTRALIA

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Abstract

Australia implemented a national, publicly-funded vaccination program against human papillomavirus (HPV) in 2007. Initially the program targeted females aged 12-13 years, with catch-up of females aged 13-26 years to 2009. Since 2013, males aged 12-13 years have also been included in the program, with a two-year catch-up for males aged to 14-15 years. Three-dose coverage in 12-13 year-old females is approximately 71%, and estimated coverage rates over the female catch-up program were 70% in the school-based program (females 12-17 years) and ~30-50% in the primary-care-based program (female 18-26 years). Early data on cervical abnormalities, genital warts and HPV prevalence in cervical specimens suggest the impact of this program has been rapid and substantial, and that it also provided some indirect protection for young unvaccinated females and young males. Almost seven million doses of HPV vaccine have been delivered in Australia, and the vaccine safety profile remains favorable and comparable to that of other vaccines. Ongoing monitoring of coverage, impact and safety will be critical for the ongoing success of the program. It is important to emphasise that female cohorts offered vaccination should continue to attend cervical screening, since current generation vaccines do not protect against all types of HPV implicated in cervical cancer.

Australia was the first country to introduce a national, publicly-funded vaccination program against human papillomavirus (HPV), and the first country to fully fund HPV vaccination of males. The National HPV Vaccination Program (NHVP) was implemented in Australia from 2007, with routine school-based vaccination of 12-13 year-old females and catch-up in females aged 13-26 years to 2009, delivered through schools and primary care. The NHVP was extended to include routine school-based vaccination of 12-13 year-old males and a two-year catch-up program for males aged 14-15 years from 2013. The quadrivalent HPV vaccine (Gardasil®, Merck&Co., Whitehouse Station, NJ US) used within the program is delivered over a three-dose course, and provides protection against two oncogenic types (HPV 16/18),[1] estimated to be associated with approximately 78% of cervical cancer in Australia,[2] and two other types (HPV 6/11) associated with approximately 90% of anogenital warts,[3] and of juvenile-onset recurrent respiratory papillomatosis.

Coverage

Doses delivered through the NHVP are recorded on the NHVP Register, although completeness of recording is likely to be higher for doses delivered through the school-based program than through primary care.[4,5] Three-dose coverage in the school-based program as recorded in the NHVP Register ranged from 74% (females aged 12 years in 2007) to 62% (females aged 17 years in 2007).[6] Reported three-dose uptake in the catch-up program delivered through primary care was lower at 41% (females aged 18 years in 2007) to 17% (females aged 26 years in 2007), yielding 32% across this group,[5] although under-reporting to the NHVP Register is likely for this component of the program, and survey data suggest an overall coverage rate closer to 50% in women aged 18-26 years in 2007.[5] Early data suggest that uptake in the school-based program has been similar across different socioeconomic status strata.[7] This is encouraging in terms of increasing health equity, as cervical screening participation and cervical cancer incidence are known to vary by socioeconomic status in Australia.[8] National coverage data by Indigenous status are not available, but recent data from Queensland and the Northern Territory suggest that three-dose uptake is lower in Indigenous females (by 15% and 9% respectively).[6] Coverage data are not yet available for uptake in males.

While coverage in Australia is relatively high compared to many other countries, the most recent data available for the target age group suggests slightly lower coverage in the years since the commencement of the NHVP (71% in females aged 12-13 years, 2011).[9] Coverage in Australia has remained lower than for some other countries with similar school-based publicly-funded programs, such as England (three-dose coverage 86%) and Scotland (three-dose coverage 91%).[10,11]

Vaccine impact to date

Due to the comparatively early commencement of the NHVP and wide age range over which catch-up vaccination was offered in Australia relative to other countries, Australia has been the source of many population impact studies.[12] Since the commencement of the NHVP, substantial reductions have been documented in rates of anogenital warts in young females and young males in sexual health clinics and in national hospital data,[13,14] and in young females presenting to primary care,[15] and also in HPV prevalence,[16] and precancerous cervical abnormalities in young women.[8] HPV vaccination status has been found to be associated with a reduction in precancerous cervical abnormalities in Victoria and Queensland.[17,18] The impact of HPV vaccination on anogenital warts appears similar in young Indigenous and non-Indigenous females, based on the national hospital data.[14] There is some evidence of indirect protection for unvaccinated groups, including

an observed reduction in genital warts in young males attending sexual health clinics and admitted to hospital,[13,14] prior to their inclusion in the program, and also an observed reduction in the prevalence of vaccine-included HPV types in cervical specimens from unvaccinated females.[19] The extent and rapidity of impact are consistent with prior predictions made by epidemiological models.[20] Vaccination against HPV 6/11 also raises the possibility that future reductions may be observed in the rare but serious disease, juvenile-onset recurrent respiratory papillomatosis, due to reduced transmission of HPV6/11 from vaccinated mothers. Surveillance commenced for juvenile-onset recurrent respiratory papillomatosis, via the Australian Paediatric Surveillance Unit, in October 2011.[21]

However, a reduction in cervical screening participation has also been documented in young women in Australia.[8] In spite of consistent messaging that screening remains important for vaccinated women, since current generation vaccines do not protect against all oncogenic HPV types, recent data suggest that young women who are vaccinated are significantly less likely to attend for screening than young unvaccinated women.[22] There is also evidence that current cervical screening programs will become less efficient in the context of HPV vaccination.[23] Recently, the Medical Services Advisory Committee recommended that Australia adopt HPV-based cervical screening with partial genotyping and a call-recall invitation system, in order to provide a program which will be more effective, efficient and accessible to Australian women, both HPV vaccinated and unvaccinated.[24] A renewed invitation-based screening program, which involves direct testing for HPV, may motivate HPV-vaccinated women to attend for screening.

Safety

The safety profile of the HPV vaccine is good, and comparable to other vaccines.[25] Around seven million doses have been delivered to date in Australia, with adverse events reported in less than .05% of cases.[26] These adverse events have generally been mild and consistent with those recognised in clinical trials and recorded in product information.[26]

Conclusion

Australia has implemented a successful and equitable vaccination program against HPV. Early data suggest the impact of this program has been rapid and substantial. Ongoing monitoring of coverage, impact and safety will be critical for the ongoing success of the vaccination program. However, the success of the overall cervical cancer prevention program will also critically depend on cervical screening. It will be important to encourage and motivate female cohorts offered vaccination to attend for cervical screening, in order to achieve the maximum potential of the comprehensive cervical cancer prevention program in Australia.

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THE NEW ERA OF PRIMARY HPV SCREENING FOR PREVENTION OF INVASIVE CERVICAL CANCER

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Abstract

We now know that persistent cervical infections by certain types of human papillomavirus (HPV) designated as high-risk, carcinogenic or cancer-associated, cause virtually all invasive cervical cancer. The discovery of oncogenic HPV as the necessary cause of invasive cervical cancer has led to revolutionary advances in prevention, including the development of sensitive molecular HPV testing for cervical cancer screening. Using high-risk HPV testing for the primary screen shifts the use of the Pap test from the general population to those women at risk of cervical cancer, high-risk HPV positives. In high-resource settings, using high risk HPV testing as the primary cervical cancer screening test could increase the efficiency of current screening programs, more effectively identify women at risk for adenocarcinoma, and combined with self-collection, reach medically unserved populations that experience a disproportionate burden of invasive cervical cancer.

HPV natural history: rational basis for intervention

Since the discovery of human papillomavirus (HPV) in the tissue from invasive cervical cancer (ICC) by Harold Zur Hausen (2008 Nobel Laureate in Medicine) and colleagues 30 years ago,[1] there have been rapid advances in our understanding of ICC and its cause. We now know that persistent cervical infections by certain types of HPV, designated as high-risk, carcinogenic or cancer-associated, cause virtually all ICC everywhere in the world.[2] HPV also causes a significant number of vulvar, vaginal, anal, penile and oropharyngeal cancers.[3] Approximately 5% of the human burden of cancer is caused by HPV.[3] HPV16 is the most important HPV genotype, responsible for 55-60% of ICC.[4] HPV18 is the next most important HPV genotype, responsible for 10-15% of ICC, including 30% of adenocarcinoma of the cervix,[4] which is on the rise in western countries.[5,6] Together, HPV16 and HPV 18 account for approximately 70% of ICC and the same 12-15 HPV types cause 95-99% of ICC on all continents.[4] Thus, an important corollary of these findings is that HPV does not discriminate by race or ethnicity, and there is no evidence of significant genetic predisposition. Thus, the only two important causes of ICC are persistent cervical infections by high-risk HPV genotypes and a lack of access to preventive services.

The natural history of HPV and cervical carcinogenesis can be represented by a simple, causal schema, which is composed of four, reliably-measured stages: 1) HPV acquisition; 2) HPV persistence (versus clearance); 3) progression to precancer (CIN3, AIS); and 4) invasion.[2] HPV infection is a very common, perhaps universal exposure, among sexually active populations, but on a per infection event basis, is an uncommon cause of cancer. Most (~90%) HPV infections are benign and are cleared or controlled within two years. Although there is now evidence that some infections may become quiescent (latent) or undetectable,[7] the clinical importance of their re-emergence in peri- and post-menopausal women is uncertain and possibly lower because of the absence of hormones thought to contribute to the carcinogenic process.[8]

The key step in cervical carcinogenesis is overt, measurable high-risk HPV (hrHPV) persistence, which even after a year or two strongly predicts the development of cervical precancer, cervical intraepithelial neoplasia grade 3 (CIN3) or adenocarcinoma in situ (AIS).[9,10] Importantly, the longer an infection persists, the greater the risk for development of precancerous changes in the epithelium and for the development of frank malignancy. At some unknown average duration, HPV persistence becomes synonymous with cervical precancer and cancer, but the transition between the two states is imperfectly understood because of the less than perfect sensitivity of colposcopy and biopsy to detect errors in the pathologic diagnosis of cervical precancer, especially the earliest and smallest precancerous lesions with low malignant potential that must arise from the persisting infection.[11]

Finally, untreated precancerous lesions in older women (median age = 38 years), about 10 years after the earliest, smallest precancerous lesions can be found in the population by screening, have about a 30% risk of becoming invasive over the next 30 years.[12,13] The carcinogenic process for cancer to develop from incident HPV infection on average takes quite a long time, approximately 10 years at a minimum and 20-25 years on average, which makes it possible to successfully screen, diagnose, and treat most women with precancerous changes prior to invasion, even if with only moderately sensitive screening and diagnostic tests and procedures.

Targeting HPV

The discovery of hrHPV as the necessary cause of ICC has led to revolutionary advances in ICC prevention, including the development of prophylactic HPV vaccines and sensitive molecular hrHPV testing for cervical cancer screening. hrHPV testing is more sensitive and reliable for detection of CIN3, AIS or invasive ICC (≥CIN3) of the cervix than Pap testing.[14-22] The increased sensitivity of hrHPV testing over Pap testing for (≥CIN3) translates into two important benefits: 1) earlier detection of CIN3/AIS lesions that if treated, results in a reduced incidence of ICC within 4-5 years and related death within eight years;[23,24] and 2) greater reassurance against cancer (lower cancer risk) following a negative result for many years,[23-27] which permits screening at an extended interval of 5-10 years, depending on the acceptable minimum cancer risk. Thus, using hrHPV testing for the primary ICC screen, women would only need one to a few screens in their lifetimes to significantly reduce the burden of ICC.[28] hrHPV testing offers other important advantages, including easier implementation because these molecular tests do not require specialised medical training i.e. molecular tests are processed by machine and therefore do not require a large network staffed by cytopathologists. These advantages make the introduction of hrHPV testing for cervical cancer screening into low and middle income countries more feasible than cytology.

One of the important limitations of hrHPV testing is that it is less specific and therefore has a lower positive predictive value for cervical precancer and cancer than high-quality Pap testing. hrHPV testing detects 'clinically relevant hrHPV', equal or above a threshold that was established for one test and has become the benchmark for all tests.[29-31] However, clinical hrHPV testing does not distinguish between benign hrHPV infections that are destined to clear or be controlled versus those that have or will cause ≥CIN3. So although hrHPV testing detects 25-40% more ≥CIN3 than Pap in high-resource settings, in unvaccinated populations typically approximately twice the number of women will test hrHPV positive compared to Pap positive (atypical squamous cells of undetermined significance [ASC-US] or more severe cytologic abnormalities [≥ASC-US]).[14,32] While some of these additional pick-ups of CIN3/AIS by hrHPV testing represent true precursors to cancer, as evident by the reductions in ICC incidence and mortality when acting clinically to all hrHPV positives as discussed above, it may be impractical and/or unacceptable to send all these hrHPV-positive women to colposcopy or treat all of them using a screen-and-treat strategy.[33,34] In some settings, it may be desirable to use a secondary, triage test to 'rule in' hrHPV-positive women who need immediate follow-up and care. That is, hrHPV testing is used to 'rule out' ≥CIN3 in the generally health population, and a secondary, more specific test is used to 'rule in' those hrHPV-positive women who need colposcopy and biopsy or immediate treatment (figure 1A)

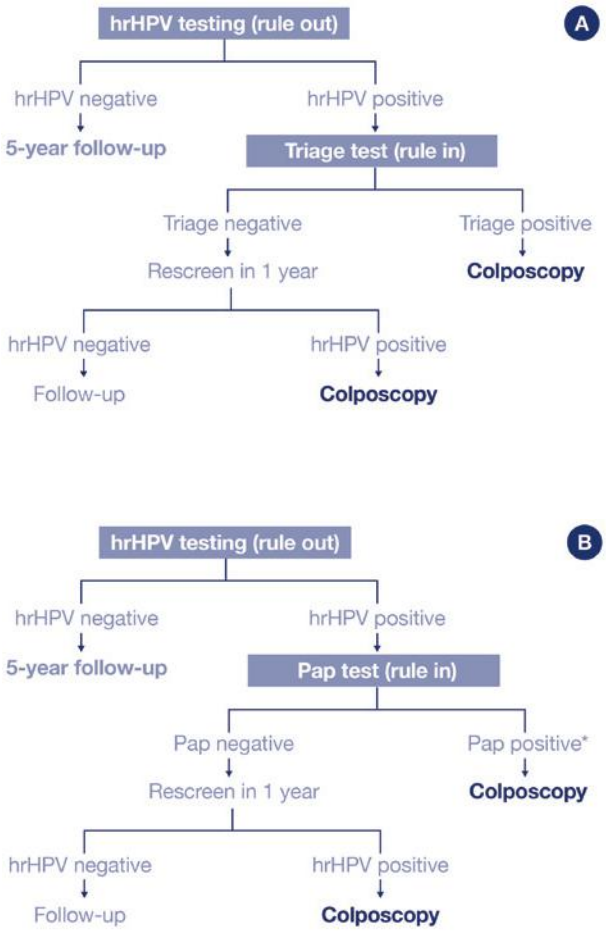
Paradigm shift from 'Pap on everyone' to 'Pap on hrHPV positives'

Pap is the obvious first choice as a triage test for hrHPV positives where good cytology is already available (figure 1B). Essentially, this shifts the use of Pap from the general population at short intervals to only the small fraction of those who have the necessary cause of ICC i.e. hrHPV, and women who are hrHPV negative are screened at longer intervals. Thus, there is a shift in focus and resources to those women who are truly at risk of ICC. However, Pap as a triage test still has limited sensitivity, unless the slides are more heavily scrutinised because they are hrHPV positive.

To glean more of the benefits of hrHPV testing, women who test hrHPV positive but Pap negative (hrHPV+/Pap-) should be followed more intensively than routine screening until there is evidence of persistent hrHPV infection, which even after a year or two strongly predicts the development of ≥CIN3,[9,10] or overt cytologic abnormalities. In the US, it is recommended that hrHPV+/Pap- return for re-screening

***Figure 1**: Algorithms for primary high-risk human papillomavirus (hrHPV) testing to 'rule out' cervical precancer and cancer and a secondary, triage test to 'rule in' cervical precancer and cancer among hrHPV-positive women. Shown are four different scenarios for triage: a generic algorithm with no specific triage test specified (A); Pap testing (B); detection of hrHPV genotypes HPV16, HPV18, and/or HPV45 (C); or combining HPV16, HPV18 and/or HPV45 detection and Pap testing (D).*

**Pap positive is the threshold of abnormality that is currently being used for referral to colposcopy in the Pap-based screening program.*



in a year.[35,36] Following a hrHPV+/Pap- result, the longer the interval, the lower the percentage of women testing hrHPV a second time and the greater the risk of CIN3+ and of frank invasive ICC among the repeat hrHPV positives.[37] Thus, in an organised screening program that can achieve excellent follow-up of patients, it may be desirable to extend the interval of rescreening hrHPV+/Pap-, but recognising that there naturally is a concomitant incremental increase in cancer with the longer surveillance interval.

Although, there has been a general agreement to limit hrHPV testing to women 30 or 35 years and older, there is no theoretical reason not to use hrHPV testing in women at any recommended age of screening, provided that clinical management is based on the triage test results and not on the hrHPV test results alone.

HPV tests

The available tests were previously reviewed, but the market and available products are rapidly evolving.[38] Currently, there are four US Food and Drug Administration (FDA) approved hrHPV tests: Hybrid Capture 2 (Qiagen, Germantown, MD, USA) (approved in 2003); Cervista (Hologic, Bedford, MA, USA) (approved in 2009); cobas4800 (cobas, Roche Molecular Systems, Pleasanton, CA, USA) (approved in 2011); and Aptima (Gen-Probe/Hologic, San Diego, CA, USA) (approved in 2011). The FDA recently approved one hrHPV test, cobas 4800, for primary cervical cancer screening.[39] A laboratory-developed preliminary chain reaction test based on GP5+/6+ primers meets the benchmarks of validity.[30,31]

A number of other tests have received CE marking and/or Chinese FDA-equivalent authority approvals, including a manual, lower-cost test developed for LMICs (careHPV, Qiagen), some of which are undergoing or will undergo pre-marketing approval evaluations for FDA approval. Speculatively, given the comparability of many of these assays, more tests will receive FDA approval for use in cervical cancer screening, and as the primary cervical cancer screening test or at least be accepted as comparable and therefore interchangeable by guidelines developed by professional medical organisations.

Adoption

The US was the first country to introduce hrHPV testing into routine screening, as hrHPV and Pap co-testing every three years for women aged 30 years and older, following FDA approval of the first clinical hrHPV test in 2003 and interim guidelines.[40,41] Kaiser Permanente Northern California, a managed care organisation that resembles an organised screening program in many aspects, was an early adopter, rolling out three-year co-testing in women aged 30 and older during 2003-4. The organisation has now screened over one million women 30 and older by co-testing. Some of the key observations from that real-world experience include: 1) although women could opt for annual Pap testing, there was a high degree of adoption (>90%) of triennial cotesting; 2) a negative hrHPV test was more reassuring than a negative Pap, as previously reported;[23,25,26] 3) a negative co-test (hrHPV-/Pap-) was not much more reassuring than a negative hrHPV test;[25,26] and 4) a high proportion of AIS and adenocarcinoma diagnosis was proceeded by hrHPV+/Pap-.

Numerous countries are now either implementing or planning to implement hrHPV testing as the primary screen for ICC in some or all of the country (e.g. Australia, the Netherlands, Argentina, Rwanda and Turkey) or undertaking evaluations (e.g. England, Norway, China, Vietnam, El Salvador and Colombia).[42] Importantly, the World Health Organisation has recently recommended the use of hrHPV testing for primary screening, especially for those places that have the resources to afford hrHPV testing and do not have a high-coverage, effective Pap program.[34] The challenge then, will be developing the financing for and tiered pricing to allow universal access to hrHPV testing and eliminate the historically large cancer health inequities in ICC burden between high-resource countries and low- and middle-income countries.

The introduction of hrHPV testing into high-resource settings, where there is an established and effective Pap test-based screening program, may still lead to some reductions in the burden of cervical cancer. More importantly, using hrHPV testing and extending screening intervals can potentially reduce the harms of screening by permitting newly acquired benign hrHPV infections and associated cytologic abnormalities to go away undetected and avoid triggering clinical action.[35] Screening at longer intervals may also be more cost-effective.[43]

hrHPV testing may address an important limitation of Pap testing, which is identifying women who have or are at risk of having AIS/adenocarcinoma, which has either not declined and in some high-resource settings has increased during the same period that squamous cell carcinoma incidence has declined dramatically.[5,44-46] Several studies have shown that hrHPV testing is more effective in identifying women at risk of AIS/adenocarcinoma than Pap testing,[27,47,48] and a case series report observed that most adenocarcinomas were preceded by hrHPV+/Pap-.[49] However, without good follow-up of hrHPV+/Pap- and concomitant improvements in the diagnosis of AIS and precursors of adenocarcinoma in the endocervical canal, the benefit of hrHPV testing for prevention of adenocarcinoma will not be fully realised.

As mentioned, in most high-resource countries, there is a segment (~20%) of the population in whom a significant fraction of its invasive ICCs occurs because women do not or cannot access routine medical care and are unscreened or under-screened. In fact, elevated ICC incidence and mortality is a general marker for health disparities.[50] hrHPV testing can potentially reduce these disparities because fewer screens in a lifetime will be needed to achieve effective prevention. hrHPV testing also allows for the effective use of self-collected cervicovaginal specimens,[51] which can address a number of barriers to participation including inconvenience, cost and geographical barriers of getting clinic-based screening.

Management of hrHPV-positive women

Although Pap testing of hrHPV positives is the first and obvious method of triage, as for primary screening, it has limited sensitivity for CIN2+ in routine practice. Pap testing with the knowledge that a woman is HPV positive could lead to more scrutiny of the slide and increase sensitivity,[52]

i.e. 'screening with prejudice', such an improvement has not been documented and almost certainly would be accompanied by a decrease in specificity.

Next generation hrHPV tests offer at least separate detection for HPV16 and HPV18, or HPV16, HPV18 and HPV45 in various formats (concurrent or sequential testing, individual detection or pooled detection), the three HPV genotypes that cause the most ICCs and have the highest ratio in cancers versus the general population.[4,53,54] There is significant evidence that one-time or two-time detection (persistence) of these types identify a subset of hrHPV-positive women at higher risk of CIN2+ and CIN3+ cross-sectionally and prospectively.[9,17,19,55-57]

The evidence for clinical utility for separate detection of HPV16 is the strongest.[35] HPV16 is the most carcinogenic genotype and identifying HPV18- and HPV45 related precancerous lesions appears to be more difficult than HPV16 related ones. So often HPV18 and HPV45 detections do not distinguish themselves as higher risk than other hrHPV genotypes when CIN2+ or CIN3+ is used as an endpoint.[58] Yet, HPV18 and HPV45 are the second and third leading causes of ICC and contribute a much higher proportion of adenocarcinoma and AIS, which are missed by Pap testing. HPV16, or HPV16 and HPV18 detection has been recommended for the management of hrHPV+/Pap- women in the US.[35] Individual detection of other HPV genotypes does not seem to provide important risk stratification, although several reports have suggested that HPV33 detection is comparable to HPV18 detection and might be useful, without accounting for the fact that HPV33-related precancer is common and probably has a lower risk of becoming invasive than HPV18 and HPV[45.54,59-62]

Thus, partial HPV genotyping could be used alone (figure 1C) or in combination with Pap testing (figure 1D) for the triage of hrHPV-positive women. The choice to use one, the other, or both depends on factors of cost, performance and follow-up rates of hrHPV-positive/triage-negative (e.g. hrHPV+/Pap) women.

New biomarkers

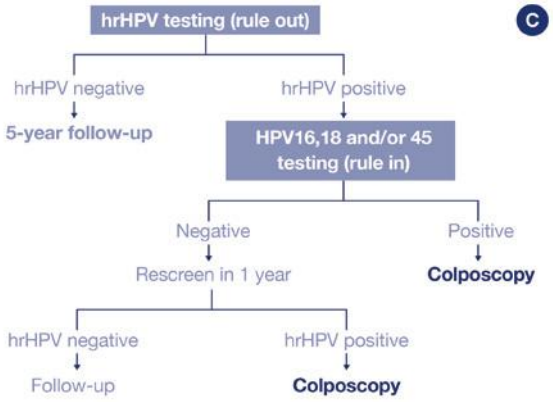
There are a number of promising new biomarkers that might achieve better performance as a triage for hrHPV-positive women than Pap and/or HPV genotyping for the riskiest HPV genotypes. The most advanced of these next-generation biomarkers with respect to validation and readiness for introduction into routine practice is $p16^{INK4a}$ immunocytochemistry. In a number of studies, p16 immunocytochemistry has demonstrated high sensitivity and specificity that is similar or better than Pap testing for CIN2+ and CIN3+ among hrHPV-positive women.[63-65] Ki-67, a cell proliferation marker, has been included with p16 immunocytochemistry as a dual stain to create a morphology-independent test.[65]

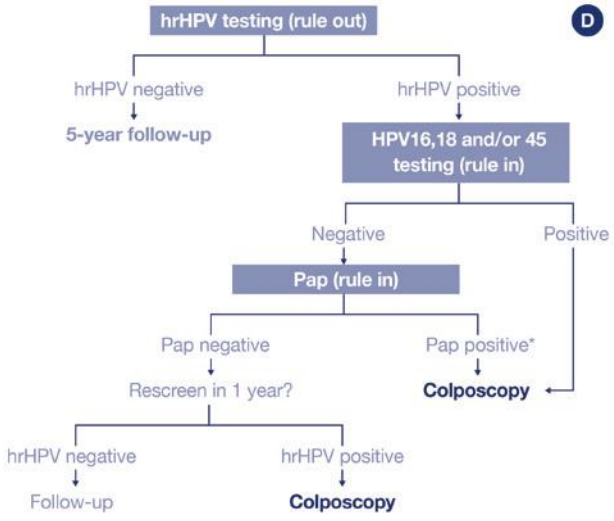
There are a considerable number of additional biomarkers that have not been fully validated. These include but are not limited to viral,[66-69] and host,[66,70-73] methylation, chromosome region 3q amplification,[74-79] and viral integration.[80,81] In addition to needing further validation and demonstration of performance and reliability, these biomarkers must be 'reduced to practice' i.e. translating from a promising biomarker to a test that can be readily used in the clinical laboratory setting.

Integration of HPV vaccination and screening

It is anticipated that in the absence of HPV16 and HPV18 due to HPV vaccination, the predictive values of hrHPV and Pap testing will decline because of a lower prevalence of CIN2+ in the population i.e. a negative test will be more reassuring and a positive test will be less predictive of CIN2+ and CIN3+.[82-84] This is due to approximately 50% of CIN2,[54] 60% of CIN3/AIS,[54] and 70% of ICC,[4,54] caused by HPV16 and HPV18 prevented, while hrHPV positives will only be reduced by 25-30%. In addition, largely due to the absence of HPV16, there will be fewer high-grade Pap results as specific indicators of the presence of cervical precancer or cancer.[85,86]

To adapt screening and maintain the balance of benefits and harms,[35] three strategies might be employed. Using





cancer risk to guide screening and management, as discussed below, HPV16/18-vaccinated populations might start screening later or be screened less frequently.[87] New biomarkers may be useful to increase the accuracy of cervical cancer screening now and in the future, when HPV16/18-vaccinated need to be screened to prevent the residual ~25-30% of ICC not caused by HPV16 and HPV18.

Final comments

In all likelihood, if we cannot prevent and control ICC on a global scale, given the robustness of the tools at our disposal, it seems unlikely that we will have a major impact on reducing the burden of any other cancer, except for those can be largely prevented through behaviour and environmental interventions (e.g. smoking cessation and reducing arsenic exposure, respectively). ICC prevention and control can serve as the flagship for the prevention and control of other cancers and more generally non-communicable diseases. Investment in ICC prevention and control will help build the capacities such as diagnostics, pathology, surgery and oncology necessary to impact these other non-communicable diseases. Specifically, hrHPV testing may be our best chance to reduce the burden of ICC now in both low- and middle-income countries and high-resource settings. In high-resource settings, using hrHPV testing as the primary cervical cancer screening test could increase the efficiency of current screening programs, more effectively identify women at risk for adenocarcinoma, and combined with self-collection, reach medically unserved populations that experience a disproportionate burden of ICC. In low- and middle-income countries, if made affordable and accessible, hrHPV testing could more rapidly reduce the burden of ICC in populations that experience 10-fold greater rates of ICC incidence and mortality compared to high-resource settings. Next generation hrHPV tests often are on testing platforms that include a menu of clinical tests for other medically important analytes (e.g. chlamydia and gonorrhoea, HIV, TB and genetic markers). As a result, on the same platform, hrHPV testing could be introduced where other clinical tests are already being provided or vice versa. Investment in delivery of cervical cancer prevention and control will strengthen the healthcare delivery and systems for other diseases that disproportionately burden these same populations. The challenge going forward is to make the new standard of care for cervical cancer screening, hrHPV testing, accessible to everyone.

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UPDATE ON CERVICAL SCREENING IN AUSTRALIA

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Abstract

The National Cervical Screening Program in Australia has been stable and successful for more than two decades. Nevertheless, the environment in which the program operates has been profoundly disrupted by the introduction of the equally successful National Human Papilloma Virus (HPV) Vaccination Program. The 'Renewal' (or review) of cervical screening is designed to ensure that the success of the screening program continues and that all Australian women, HPV vaccinated and unvaccinated, have access to a cervical screening program that is based on current evidence and best practice. Renewal has involved an assessment of the evidence for the benefits and harms of various screening pathways and a modelled assessment to inform the likely efficacy of the various proposed screening pathways in vaccinated populations. The findings indicated that the effectiveness of the program could be increased, while the expenditure could be decreased, if HPV tests were used in place of cytology. In April 2014, the Medical Services Advisory Committee recommended that Australia move to a five yearly screening program using an HPV test with partial genotyping for HPV16/18 as the primary screening test, commencing at age 25 and with an exit test between the age of 70 and 74. At a research level, a major trial, Compass, designed to evaluate primary HPV screening in a partially vaccinated population, will generate empirical evidence against which to test the modelled predictions of the Renewal. Together, the evidence review, modelling and ongoing research provide a framework for continuous improvement of the cervical screening program and the potential for further declines in cervical cancer in Australian women.

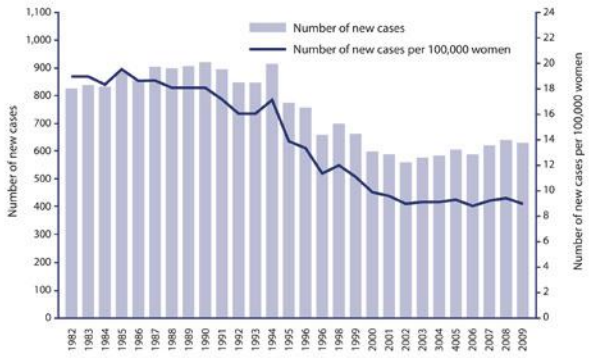
Cervical screening in Australia has been remarkably successful since the introduction of the *Organised Approach to Screening* in 1991, later renamed the *National Cervical Screening Program* (NCSP). There have been substantial reductions in the incidence and mortality from cervical cancer since the inception of the program (figures 1 and 2).

Impetus for change

Despite the incontrovertible success of the NCSP, there have been challenges with the declining trend in incidence and mortality having plateaued somewhat in recent years.

Additionally, there have been challenges in reducing the incidence of adenocarcinoma. The age standardised rate of cervical adenocarcinoma has been essentially stable over the last several decades (figure 3). Most importantly, cervical cancer disproportionately affects Aboriginal and Torres Strait Islander women, with the incidence of cancer being approximately 2.6 times that of other Australian women and the mortality 5.6 times greater than other Australian women (figures 4 and 5.)[1]

***Figure 1**: Incidence of cervical cancer in women aged 20-69, by year, 1982 to 2009.[1]*

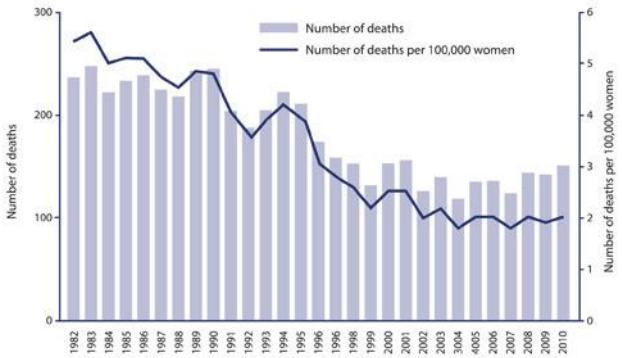


Notes:

1. Rates age-standardised to the Australian population as at 30 June 2001.
2. Bars on columns represent 95% confidence intervals.

Source: AIHW analysis of National Mortality Database.

***Figure 2**: Mortality from cervical cancer, women aged 20-69, 1982 to 2010.[1]*



Notes:

1. Deaths between 2006 and 2009 are derived from year of death; deaths in 2010 are derived from years of registration.Mortality data for 2009 and 2010 are revised and preliminary, respectively, and subject to further revisions
2. Rates age-standardised to the Australian population as at 30 June 2001.
3. Bars on columns represent 95% confidence intervals.

Source: AIHW analysis of National Mortality Database.

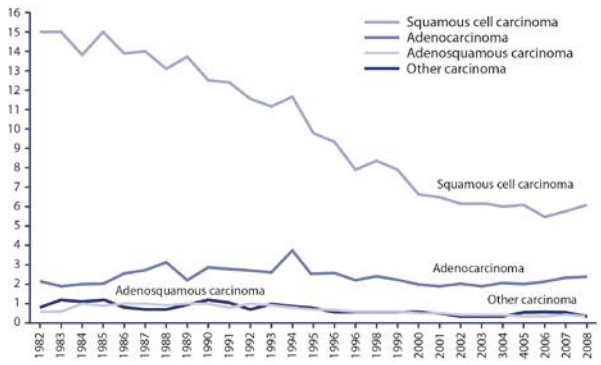
Cervical cancer also disproportionately affects economically disadvantaged women in Australia, with mortality being higher among women living in the most disadvantaged quintile (2.4 per 100,000 women) compared with women living in the least disadvantaged quintile (1.1 per 100,000 women).[1]

Overall however, the NCSP has been stable and successful for more than two decades. Nevertheless, the environment in which the program operates is in the process of being profoundly disrupted by the introduction of the equally successful National HPV Vaccination Program. This is because the National HPV Vaccination Program is already leading to substantial declines in the prevalence of cervical cancer precursors (CIN 2/3 and AIS), the targets of cervical screening. These declines will reduce the average risk of developing invasive cancer and consequently the cost effectiveness of the NCSP will be reduced. More importantly, it is anticipated that test performance characteristics of cytology, particularly the predictive values, will rapidly decline, notwithstanding the expertise and attention to quality seen in most Australian laboratories.[2]

Australian governments have initiated a process, the 'Renewal',[3] designed to ensure that the success of the NCSP continues and that all Australian women, irrespective of whether they are HPV vaccinated, have access to a cervical screening program that is based on current evidence and best practice. Phase one of the Renewal involved an assessment of the evidence for the benefits and harms of various screening pathways, including evidence regarding the screening test, the interval and the age range of screening.

***Figure 3**: Incidence of carcinoma of the cervix (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and other carcinoma) in women aged 20-69, by year, 1982 to 2008.*

Number of new cases per 100,000 women



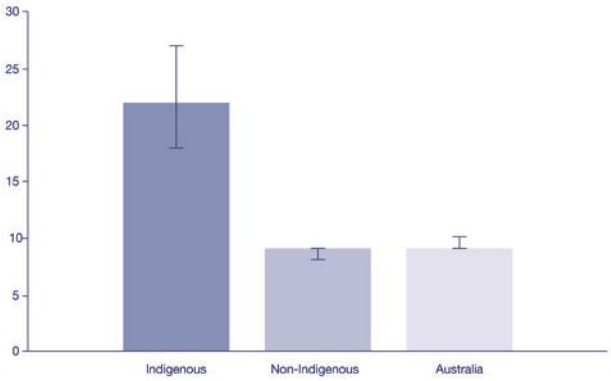
Source: AIHW analysis of National Mortality Database.

Following the evidence review, a modelled assessment was undertaken to inform the likely efficacy of the various proposed screening pathways in vaccinated populations and also to take account of more recently available updated HPV testing technology that had not yet been assessed in clinical trials. Modelling was also undertaken to understand the likely cost effectiveness of the various proposed pathways. The findings of the Renewal indicated that the effectiveness of the NCSP could be increased (in terms of cervical cancer prevention), while the expenditure could be decreased if HPV tests were used in place of cytology, as the primary screening test as compared with the current practice.

In April 2014, on the basis of the findings of phase one of the Renewal, the Medical Services Advisory Committee recommended that Australia move to a five yearly screening program using an HPV test, with partial genotyping as the primary screening test, commencing at age 25 and with an exit test between the age of 70 and 74. The new proposed 'preferred pathway' is shown in figure 6, but this is yet to be underpinned by a formal process of clinical guidelines development, which will be initiated in the next phase.

***Figure 4**: Incidence of cervical cancer in women aged 20-69 (New South Wales, Queensland, Western Australia, and Northern Territory), by Indigenous status, 2004–2008.[1]*

Number of new cases per 100,000 women

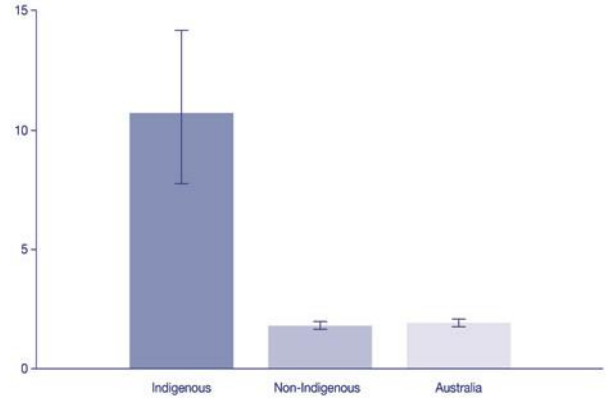


Notes:
1. Rates age-standardised to the Australian population as at 30 June 2001.
2. Bars on columns represent 95% confidence intervals.

Source: AIHW analysis of National Mortality Database.

***Figure 5**: Mortality from cervical cancer in Aboriginal and Torres Strait Islander women aged 20–69 (New South Wales, Queensland, Western Australia, South Australia and Northern Territory), 2006–2010.[1]*

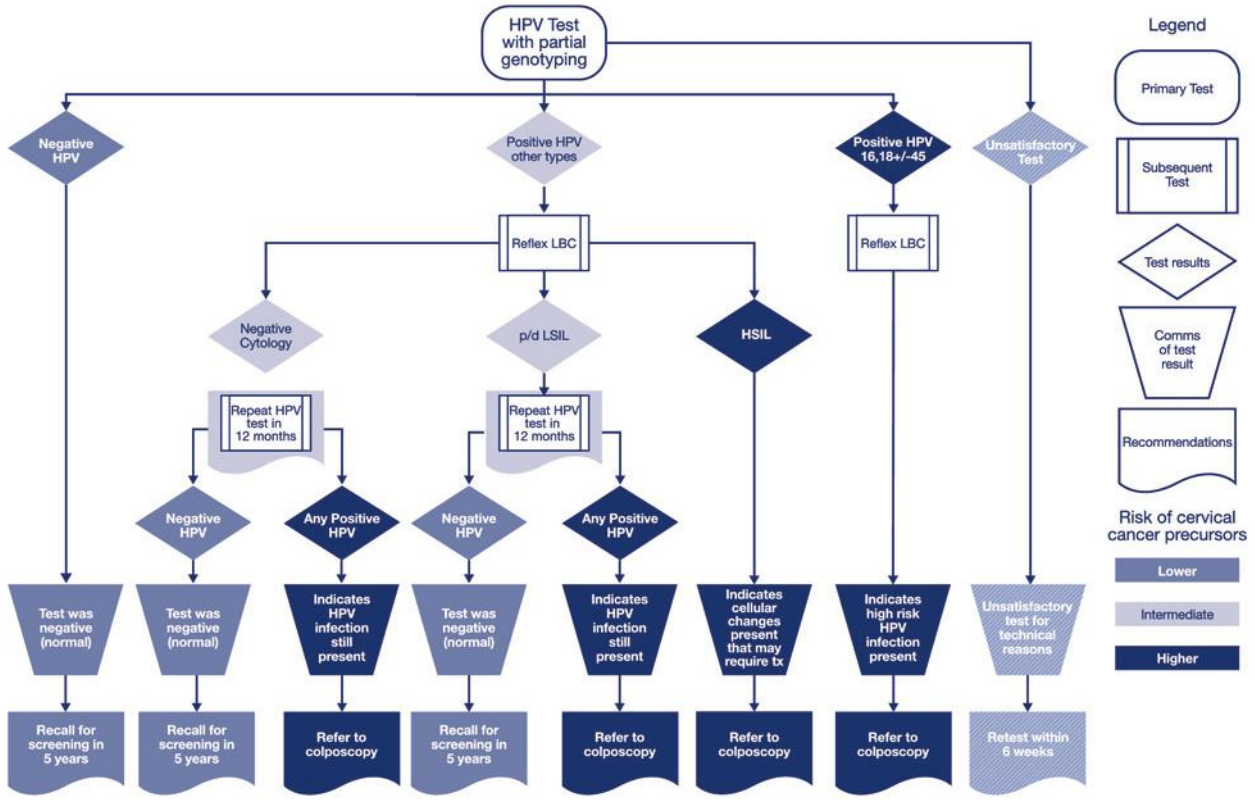
Number of deaths per 100,000 women



Notes:
1. Deaths between 2006 and 2009 are derived from year of death; deaths in 2010 are derived from years of registration.Mortality data for 2009 and 2010 are revised and preliminary, respectively, and subject to further revisions
2. Rates age-standardised to the Australian population as at 30 June 2001.
3. Bars on columns represent 95% confidence intervals.

Source: AIHW analysis of National Mortality Database.

***Figure 6**: Proposed Screening Pathway.*[4]



These recommendations are currently under consideration and it is anticipated that the Australian Health Ministers' Advisory Committee will endorse them later this year. Pending this endorsement, phase two of the Renewal will be initiated. This phase will examine national data collection systems and registry functions. It will also review quality frameworks and assess the feasibility and acceptability of the renewed NCSP to women and to practitioners.

At a research level, Australian investigators have initiated the Compass trial.[5] This trial is designed to evaluate primary HPV screening in a partially vaccinated population using updated HPV testing technology that enables partial genotyping. It therefore aims to generate empirical evidence against which to test the modelled predictions of the Renewal. The trial will also focus on the downstream management of women whose HPV screening test is positive. Compass is designed as an effectiveness trial and, as such, is being positioned as a sentinel experience of the renewed NCSP. Safety monitoring of women with a negative HPV test results is a key feature of the trial. A randomly selected sample of 5% of women with negative HPV results will be recalled at 30 months for cytology, in the expectation that the CIN3+ rate will be very low. Of course, this will be monitored by an independent data and safety monitoring committee, empowered to stop the trial and recall remaining women for earlier testing if necessary. In addition to managing the safety of women participating in the trial, this approach also provides a potential model for ongoing safety monitoring of the various HPV tests accepted for use within the renewed NCSP.

At the time of writing, recruitment of 5000 women into a pilot of the Compass trial had been completed and planning for the main trial, involving just over 100,000 women, was well advanced. It is anticipated that recruitment into the main Compass trial will commence in December 2014, and it is hoped that it can be completed in 18 to 24 months, before the roll out of the renewed NCSP.

Cervical cancer prevention in Australia has been very successful for a number of decades. The introduction of the HPV vaccine and the availability of new generation HPV tests are providing exciting opportunities to build on these earlier successes. The HPV vaccine and a screening program based on HPV testing together have the potential to at last reduce the incidence of adenocarcinoma of the cervix. The National HPV Vaccination Program, delivered in schools, is already showing signs of being equitable and it is to be hoped that in decades to come, the impact of this cancer on the most disadvantaged women in Australian society will be reduced as a consequence.

With these opportunities for improvement come the challenges of understanding the complex evidence and dealing with evidence gaps. Together, the evidence review, modelling and ongoing research provide a framework for continuous improvement of the NCSP and the potential for further declines in the impact of cervical cancer on Australian women.

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CLINICAL PRACTICE GUIDELINES FOR PSA TESTING AND EARLY MANAGEMENT OF TEST-DETECTED PROSTATE CANCER

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Abstract

There is a consensus among relevant peak professional bodies, government and non-government organisations in Australia, that Australian clinical practice guidelines for prostate specific antigen (PSA) testing and early management of test-detected prostate cancer are needed. Work is underway on systematic reviews of the evidence. Guideline development based on systematic review covers clinical questions relating to underlying risk of prostate cancer, PSA testing, investigation of men with positive tests and early management choices, the last relating particularly to choice among active surveillance, watchful waiting and immediate definitive treatment. National Health and Medical Research Council processes are being followed and the council's approval of the finished product will be sought. Public consultation on draft guidelines is expected to start in December 2014 and the council's approval is expected to be obtained in June 2015 or later. Planning for guideline dissemination and implementation is essential.

Over the 20 years to 2009, the number of newly-diagnosed prostate cancers in Australian men increased four-fold from 5311 in 1989 to 10,627 in 1999 and 21,808 in 2009.[1] While as much as half of this was due to population ageing, age-adjusted incidence rates also increased substantially, from 92.9 per 100,000 in 1989 to 194.3 in 2009, which 2010 figures (the latest publicly available) suggest may have been the peak year.

The beginning of this doubling in rates coincided with increasing use of prostate specific antigen (PSA) testing,[2] which by 2007-08 had reached annual levels of uptake in Australian men 45-74 years of age that were close to those attained by Australia's organised screening programs for breast cancer and cervical cancer.[3] Some 20% of PSA tests are done in men younger than 45 or older than 74, and research into community attitudes indicates there is widespread public confusion about the usefulness of testing.[4]

In late 2011, it became evident, from public statements made by the Urological Society of Australia and New Zealand, the Royal Australian College of General Practitioners, the Royal College of Pathologists of Australasia, Cancer Council Australia, Prostate Cancer Foundation of Australia (PCFA) and Cancer Australia, that there was a consensus in support of developing Australian guidelines for PSA testing for the early diagnosis of prostate cancer.[5]

In 2012, PCFA, in collaboration with Cancer Council Australia, undertook a consultative process that led, in November, to the first meeting of an expert advisory panel, chaired by Emeritus Professor Villis Marshall, which approved a series of clinical questions to underpin the development of *Clinical Guidelines for PSA Testing and the Early Management of PSA-detected Prostate Cancer.* The panel included experts in cancer control, consumer advocacy, epidemiology, general practice, medical oncology, nursing, pathology, psycho-oncology, public health, radiation oncology, rehabilitation and urology, who were nominated by the relevant Australian peak bodies. Panel members were appointed to guideline development groups for each clinical question. The need to maximise the potential benefits (reduced morbidity and mortality from prostate cancer) and minimise the potential harms of PSA-testing (resulting mainly from false positive and false negative tests and detection of prostate cancers that would not otherwise present during a man's lifetime),[6] were paramount in the panel's thinking.

In early 2013, Cancer Council Australia's Clinical Guidelines Network established a systematic review team, which PCFA funded, to undertake the literature reviews required to inform guideline development. These reviews use as a starting point, prior systematic reviews that underlie guidelines developed internationally with similar scope. In practice, however, few of the prior reviews have been found to have sufficient scope or to be sufficiently well done or up-to-date to facilitate the current process.

Clinical questions

The clinical questions the expert advisory panel agreed to and later refined are summarised in box 1.

***Box 1**: Clinical questions for Clinical practice guidelines for PSA testing and early management of test-detected prostate cancer*

Risk

What risk factors can identify Australian men who are at high risk of prostate cancer or death from prostate cancer?

Suggested risk factors include:

- family history
- genotype
- ethnic origin
- obesity.

Testing

In men without a prior history of prostate cancer or symptoms that might indicate prostate cancer, what should be the PSA testing strategies (age to start, level at which to declare a test abnormal and frequency of subsequent testing if the PSA level is normal) for men at average risk of prostate cancer and how should they be modified, if at all, for men at high risk of prostate cancer?

What variant of PSA testing is the best to use initially?

How best can digital rectal examination (DRE) be used, if at all, in association with PSA testing?

What age or health status criteria should be used to identify men who would be unlikely to live long enough to benefit from PSA testing and who, in consequence, would not be offered PSA testing?

What methods of decision support for men about PSA testing increase men's capacity to make an informed decision for or against testing?

What information should be given to men who are considering having a PSA test?

Investigation

What further tests for prostate cancer should be offered after an abnormal PSA test is obtained and before a prostate biopsy is offered?

Candidate tests include:

1. repeat PSA
2. % free PSA
3. rate of increase in PSA
4. magnetic resonance imaging
5. prostate health index
6. prostate cancer antigen 3 (commonly referred to as 'PCA3')
7. digital rectal examination.

What constitutes an adequate prostate biopsy?

If prostate cancer is not found in an adequate biopsy, what if any additional steps should be taken and what recommendations should be made regarding the strategy for subsequent PSA testing?

What constitutes an adequate repeat prostate biopsy?

Management

What should be the criteria for choosing active surveillance or watchful waiting in preference to definitive treatment to offer as primary management to men who have a positive prostate biopsy?

What is the best monitoring protocol for active surveillance and what should be the criteria for intervention?

What methods of decision support for men about active surveillance increase men's capacity to make an informed decision for or against it?

What information should be given to men who are considering having active surveillance?

What is the best monitoring protocol for watchful waiting and what should be the criteria for intervention?

What methods of decision support for men about watchful waiting increase men's capacity to make an informed decision for or against it?

What information should be given to men who are considering undergoing watchful waiting?

Developing the guidelines

Cancer Council Australia and PCFA are developing the guidelines in accordance with the Australian National Health and Medical Research Council's (NHMRC's) procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines outlined in box 2 (National Health and Medical Research Council. Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines – Summary for developers. Melbourne: National Health and Medical Research Council; 2011.). In addition, Cancer Council Australia and PCFA will seek NHMRC approval of the guidelines, which NHMRC will give subject to compliance with a range of process requirements and conformity with the standard.

***Box 2**: Requirements of the NHMRC standard for clinical practice guidelines development*

To meet the NHMRC standard, clinical practice guidelines must:

- provide guidance on a clearly defined clinical problem based on an identified need
- be developed by a multidisciplinary group that includes relevant experts, end users and consumers affected by the clinical practice guideline
- include a transparent process for declaration and management of potential conflicts of interest by each member of the guideline development group
- be based on the systematic identification and synthesis of the best available scientific evidence
- make clear and actionable recommendations in plain English for health professionals practising in an Australian health care setting
- be easy to navigate for end-users
- undergo a process of public consultation and independent external clinical expert review
- incorporate a plan for dissemination including issues for consideration in implementation.

We anticipate that the draft guidelines will enter the public consultation and independent external clinical expert review phases in early December 2014. Assuming they do, the earliest they can receive NHMRC approval is June 2015. Following approval, the guidelines will be published on Cancer Council Australia's cancer guidelines wiki platform (wiki.cancer.org.au) and be made available through NHMRC's clinical practice guidelines portal (clinicalguidelines.gov.au). It is anticipated that the wiki platform will be used to keep the guidelines up-to-date. Under present procedures, guidelines updated through the platform will not be NHMRC approved unless or until they go through the full NHMRC guideline development and approval process.

Implementation

The guidelines will do little to increase benefit or reduce harm if they are published but not used. The primary audiences for the guidelines are general practitioners advising men who are considering testing and urologists advising men who have either received a negative biopsy or who have been diagnosed with prostate cancer. While we sense relevant health practitioners are waiting for these guidelines, anticipation does not guarantee adoption in practice. Cancer Council Australia and PCFA must work with the relevant professional peak bodies, government and other non-government organisations to plan for wide dissemination and implementation as soon as the guidelines are approved.

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ESTIMATING THE BENEFITS AND HARMS OF PSA TESTING IN THE AUSTRALIAN CONTEXT

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Abstract

Results from international randomised controlled trials have been inconsistent as to whether prostate specific antigen (PSA) testing is associated with a mortality benefit. However, the PSA test is commonly used to test asymptomatic men for prostate cancer in Australia. The harms, including additional diagnostic evaluation and exposure to treatment regimens and their side-effects, may be substantial. It is possible that less frequent testing, a clearly identified target population and careful consideration of thresholds and triage protocols for men with elevated PSA could be used to achieve a more advantageous balance between the benefits and harms of testing. It is not practical to assess a wide range of potential testing strategies via clinical trials, since any testing-associated benefits for prostate cancer-specific mortality would take years to accrue and would also be logistically challenging. Furthermore, the benefits, harms and cost-effectiveness of testing in Australia depend on several factors specific to the local context, including testing uptake and the risk profile of the population. Mathematical modelling will therefore play an important role in synthesising the data from international trials with known local testing, disease and treatment variables. Here, we review the international literature on models of PSA testing and conclude that investment in a carefully calibrated and validated population model of prostate cancer in Australia will provide an important platform for estimating the impact of future candidate strategies for testing for prostate cancer.

Results from international randomised controlled trials have been inconsistent as to whether prostate specific antigen (PSA) testing is associated with a prostate-cancer specific mortality benefit. Although the European Randomised Study of Screening for Prostate Cancer (ERSPC) reported a significant 21% relative reduction in prostate cancer-specific mortality in men aged 55-69 years over 11 years of follow-up,[1] the US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial found no evidence of a mortality benefit for organised annual screening compared with opportunistic screening over 13 years of follow-up.[2] The National Health and Medical Research Council PSA Testing Expert Advisory Group recently prepared an evidence evaluation report based on a systematic review of prior systematic reviews, and concluded that "…the present evidence is inconsistent as to whether there is an effect of PSA testing, with or without digital rectal examination (DRE), on the risk of prostate cancer-specific mortality compared with no PSA testing, although the possibilities of no effect or a small protective effect cannot be excluded" and that "PSA testing with or without DRE has no discernible effect on all-cause mortality compared with no PSA testing."[3]

A study in NSW found that the annual number of PSA tests more than doubled between 1996 and 2006.[4] There was a sustained increase in prostate cancer incidence after PSA testing was introduced, presumed due in part to the effect of PSA testing uptake on increased detection. Although a decrease in incidence of advanced disease at diagnosis and a decrease in mortality from prostate cancer were also observed, factors other than PSA testing could not be excluded as potentially having an influence on these trends.

The harms of PSA testing, including additional diagnostic evaluation and exposure to treatment regimens and their side-effects, may be substantial. For example, an Australian study found that treatment for localised prostate cancer can have severe and persistent effects on quality of life, which, depending on treatment type, can involve sexual dysfunction, poor urinary function and compromised bowel function.[5] The balance of benefits and harms of any cancer testing or screening regime critically depends on several factors, including the characteristics of the test itself, the test threshold used, the frequency of testing, the age range of individuals tested (including setting a recommended upper age limit and/or using 'exit testing' to define a group at low risk of disease who do not require further testing), and the process for further triaging test-positive individuals before referring to further diagnostic evaluation. There are a range of other unanswered questions in relation to optimising prostate cancer detection, surveillance and treatment. It is possible that less frequent PSA testing

than would appear to currently exist, potentially combined with a more limited age range of screening and clearer recommendations for thresholds and triage protocols for men with elevated PSA, could be used to achieve a more advantageous balance between the benefits and harms of testing and its sequelae. There is also a potential independent role for DRE for screening, but this has not been examined in population-based studies. There are also a number of critical unanswered questions relating to the relative benefits of active surveillance compared to immediate treatment of men with a positive biopsy after an elevated PSA test, and the role and relative benefits and costs of various triage strategies for men with abnormal PSA tests (potentially including use of DRE, repeat PSA testing, assessing the rate of PSA increase, or use of magnetic resonance imaging). In addition, there are outstanding questions relating to the optimal testing and/or management of men with a family history of prostate cancer.

It is not practical to assess a wide range of potential PSA testing strategies via clinical trials, as any testing-associated benefits for prostate cancer-specific mortality would likely take years to accrue.[6] Furthermore, the benefits, harms and cost-effectiveness of testing in any particular context depend on factors specific to the local context, including testing uptake and the risk profile of the population. Therefore, mathematical modelling plays a key role in synthesising the data from international trials with local factors and simulating the effects of potential new strategies for testing or surveillance.

Models of PSA testing

Two international groups, the Fred Hutchinson Cancer Research Centre (FHCRC) and the Microsimulation Screening Analysis (MISCAN) group, have developed detailed population-based prostate cancer and PSA testing models for North America and the Netherlands, respectively. The FHCRC prostate cancer model is a comprehensive micro-simulation (individual-based simulation) of prostate cancer incidence and mortality. It has been used to evaluate the effectiveness of different PSA screening strategies in the US and the cost-effectiveness of PSA screening in British Columbia, Canada.[7,8] The disease natural history structure includes both preclinical and clinical states characterised by cancer stage and differentiation grade. The mortality component of this model uses age, stage and grade specific survival to model prostate cancer death; in the case of loco-regional cancers, survival also depended on primary treatment (radiation or surgery). PSA levels in simulated individuals are explicitly modelled as a continuous function, although other specific risk factors are not considered. Although the opportunistic PSA screening occurring in the US was taken into account when calibrating the model to US cancer incidence, realistic levels of PSA testing uptake rates (including less than 100% uptake at a distribution of times around the recommended interval) have not been used in the reported evaluations of PSA testing using the FHCRC model to date. Some of the specific harms of testing (short-term and long-term treatment effects) are taken into consideration.

In the FHCRC evaluation of PSA testing effectiveness in the US, the risk of prostate cancer death was estimated to be 2.86% in the absence of screening. A reference strategy that screens men aged 50-74 annually with a PSA threshold for biopsy referral of 4 µg/L was found to reduce the risk of prostate cancer death to 2.15%, with risk of overdiagnosis of 3.3%. A strategy that screens biennially with longer intervals for men with low PSA levels was predicted to achieve similar risks of prostate cancer death and overdiagnosis, but reduced total tests by 59% and false positive tests by 50%.[7] In the follow-up Canadian cost-effectiveness analysis, the incremental cost-effectiveness ratio of regular PSA testing was $36,300 per life-year saved, for testing every four years from ages 55 to 69 years, which indicates that this strategy is likely to be cost-effective. However PSA testing every two years, from ages 40 to 74, was associated with an incremental cost-effectiveness ratio of $588,300 per life year saved, which is very cost-ineffective. The findings were very sensitive to whether quality of life aspects were included in the evaluation, and if so, how these were weighted.[8]

The MISCAN prostate cancer model also involves a micro-simulation of prostate cancer incidence and mortality. It has been used to simulate health outcomes and corresponding costs for a cohort of men and to estimate quality of life effects for men with various PSA testing strategies.[9,10] The disease natural history structure includes both preclinical and clinical states, characterised by cancer stage and differentiation grade. Survival is modelled by age, stage and grade, and in the case of loco-regional cancers, as treatment-specific. No specific risk factors are included. In this model platform, PSA testing and biopsy are modelled as a single testing process with test characteristics (sensitivity and specificity) being stage and grade specific, and European Randomised Study of Screening for Prostate Cancer data used to inform modelling of PSA testing effectiveness. Again, realistic testing uptake assumptions have not been specifically taken into account to date, but specific harms (short-term and long-term treatment effects) are taken into consideration. Using the MISCAN platform, a recent evaluation found that PSA testing of all men between the ages of 55 and 74 would result in more life-years gained, however after the detrimental quality of life aspects were taken into account, would result in the same number of quality-adjusted life years.[10]

Two models have been developed in the Australian context.[11,12] A recently reported decision model used a Markov process to simulate health outcomes and estimate the net benefit and cost of four-yearly lifetime PSA screening in men aged 50 versus no screening, as a function of the mens' underlying risk.[12] For Markov models, all transitions depend only on the current state of the individual and so the model usually has limited ability to reflect different risk profiles or management strategies according to screening or treatment history. Men were classified as being at average risk (baseline rates), high risk (double the baseline rates) and very high risk (five times the baseline risk). The disease natural history structure included both preclinical and clinical states, but did not explicitly model cancer stages (local, regional, distant) or differentiation grade (Gleason score). The cancer incidence rates used in this model were obtained from ERSPC and adjusted to Australian age-specific rates. Prostate cancer mortality was calibrated to ERSPC data, however age, stage, Gleason score and treatment-specific survival or harms

from short-term and long-term treatment effects were not explicitly modelled, nor was a distribution of testing uptake behaviours considered. The evaluation found that PSA screening was not cost-effective for men at an average-to-high risk of prostate cancer, but may be cost-effective for men at very high risk. Although this provides important initial information, one difficulty in interpreting the findings is that the opportunistic PSA testing that has been taking place in Australia over the last two decades was not taken into account in model development and its calibration to observed Australian prostate cancer incidence and mortality data. Given this, and that the results modelled a single cohort of 50 year-old men through life, caution should be used in applying the results to the whole population of men in Australia.

Another study has used a Markov model to compare annual PSA screening with no screening for men aged 40, 50, 60 and 70 years who are at low, medium or high risk for prostate cancer.[11] Risk was defined according to family history. The disease natural history structure included both preclinical and clinical states (localised and non-localised), but age, stage, Gleason score and treatment-specific survival and harms from short-term and long-term treatment effects were not explicitly modelled. The objective was to develop a model of annual PSA screening that could help individuals make informed decisions regarding PSA screening. The evaluation found that for 1000 men screened annually from 40 to 69 years of age, there will be 30 prostate cancer deaths and 640 deaths overall by age 85 years compared with 30 prostate cancer deaths and 640 deaths overall in unscreened men.

In summary, two comprehensive models of natural history have been developed internationally and two further models have been developed for Australia. However, none of these important evaluations have yet taken into account realistic levels of PSA testing uptake or the full range of strategies of interest in the Australian context. The Australian models, while providing important information, have not been designed as fully calibrated, individual-based flexible simulation platforms for prostate cancer, and have not been designed to be capable of simulating a wide range of PSA testing strategies and population-based outcomes in Australia.

Development of a comprehensive Australian model

The Cancer Screening Group at University of NSW, together with Cancer Council NSW, are currently developing an Australian model for the ongoing epidemiologic and economic evaluation of changes in the detection, management and treatment of prostate cancer, and of the interactive effects of these changes on outcomes (including cancer incidence, mortality and treatment-related morbidity) and costs. The model will be developed on the POLICY1 microsimulation platform, a flexible model for cancer screening applications, which has already been used to simulate cervical cancer and colorectal cancer prevention. The development of POLICY1-Prostate is being funded by the Prostate Cancer Foundation of Australia and will use Australian data to model current levels of PSA uptake and calibrate outcomes to current Australian data on prostate cancer incidence, mortality and morbidity rates. Evidence-based quantifiable outcomes will be produced to support detailed recommendations for the optimal (most effective and most cost-effective) strategies for prostate cancer detection in Australia. The outcomes will include detailed predictions of prostate cancer incidence and mortality, effects on resource utilisation (such as the numbers of biopsies and specific prostate cancer treatments), and the cost-effectiveness and budget impact of a wide range of potential strategies.

POLICY1-Prostate will be readily usable for a range of future evaluations of new strategies for prostate cancer detection and management in Australia; these potentially include the role of specific testing strategies in men with a family history of prostate cancer, the role of new testing technologies, the effect of targeted efforts at testing men in low socio-economic groups and rural areas, future changes to diagnostic techniques or protocols, and the effects of changes in prostate cancer treatment patterns.

Conclusion

Investment in a carefully calibrated and validated disease model of prostate cancer development and PSA testing in Australia will provide an important platform for estimating the impact of various possible candidate strategies for PSA testing. The model, known as POLICY1-Prostate, will allow large scale simulations, at the level of the individual, of hundreds of thousands of men in the Australian population. This flexible tool will be designed to incorporate new data sources as they emerge and to evaluate new prostate cancer prevention strategies on an ongoing basis.

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LUNG CANCER SCREENING: SUMMARY OF THE EVIDENCE AND THE 2013 US PREVENTATIVE SERVICES TASK FORCE RECOMMENDATIONS

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Abstract

The United States Preventative Services Task Force is an independent panel of non-Federal experts in prevention and evidence-based medicine that reviews scientific studies and makes recommendations on screening and prevention interventions. The panel is widely respected for its rigour and basing its recommendations on the scientific evidence. In late 2013, the task force published a recommendation on screening for lung cancer using low-dose computerised tomography. They recommend annual screening in adults, aged 55 to 80 years, who have a 30 pack year smoking history and currently smoke or have quit within the past 15 years. They also recommend screening be discontinued once a person has not smoked for 15 years, or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. The statement also stresses the need for rigorous quality controls to minimise the harms associated with lung screening and resultant diagnostic procedure.

The United States Preventative Services Task Force (USPSTF or task force) is an independent panel of non-Federal experts in prevention and evidence-based medicine. The task force is composed of primary care providers (such as internists, pediatricians, family physicians, gynecologists/obstetricians, nurses and health behavior specialists). They conduct scientific evidence reviews of a broad range of clinical preventive health care services (such as screening, counselling, and preventive medications). The task force has made recommendations on interventions as varied as screening for sexually transmitted diseases and vitamin D deficiency, to counselling on weight loss and screening for cancer of the breast.[1]

USPSTF recommendations are intended as information for primary care clinicians and health systems. By their very nature, these recommendations are for asymptomatic patients, meaning those without signs or symptoms related to the disease in question.

The task force bases its recommendations on the evidence of both the benefits and harms of the intervention and an assessment of the balance between these. Indeed they are known for their rigour and insistence on evidence. The process used involves an extensive structured, often systematic review of the medical literature. A group of experts, usually from a school of public health specialising in medical outcomes, is commissioned to do the review. The task force then digests that review. In recent years, the task force has also commissioned epidemiologists to do population modelling when assessing some interventions.

The results of the structured literature review are ultimately made available to the public, along with a draft recommendation.[3] Public comment is taken into account and discussed as the task force writes a final recommendation.

The task force does not consider the costs of a service in its assessment, even though a recommendation can have substantial financial impact. The US Patient Protection and Affordable Care Act, enacted in 2010 and commonly known as 'Obamacare' or 'Healthcare Reform,' requires private US health insurance organisations pay for screening tests that the task force deems should be offered to patients. Interestingly, the legislation does not require the US Medicare program to reimburse for these services. Medicare insures most Americans aged 65 and over. The Medicare program is allowed to make its own decision regarding insurance coverage.

USPSTF and lung cancer screening

In December 2013, the USPSTF published a final recommendation on the issue of lung cancer screening.[2] The statement recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within

the past 15 years. 'Pack-year' is a way to measure the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.[3] They also recommend screening be discontinued once a person has not smoked for 15 years, or if a person develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

The 2013 recommendation replaced a previous recommendation from 2004, which stated the evidence was insufficient to recommend for or against screening for lung cancer in asymptomatic persons with LDCT, chest radiography, sputum cytologic evaluation, or a combination of these tests.[4]

The task force grades recommendations.[1] They gave the 2013 recommendation a 'B', meaning they advise the test be offered to eligible patients as there is moderate certainty that the net benefit of screening is moderate to substantial in the target population.[4,5] Of note, an 'A' recommendation means there is high certainty that the net benefit is substantial. More specifically, it was the opinion of the task force that LDCT is of moderate net benefit in asymptomatic persons at high risk for lung cancer based on age, total cumulative exposure to tobacco smoke and years since quitting.[2]

The phrase 'moderate to substantial net benefit' was chosen because the US National Cancer Institute Lung Screening Trial (NLST) is the only prospective randomised trial to date showing a life-saving benefit.[6] Several smaller prospective randomised trials are underway in Europe. To date they have not shown a benefit, but these studies are much smaller and some involve patients with a lower risk of lung cancer.[4]

National lung screening trial

The recommendation was heavily influenced by the results of the NLST.[6] The NLST began in 2002 and was conducted in 33 academic centres throughout the US. It randomised approximately 53,000 persons to three annual LDCT scans or single-view posteroanterior chest X-rays. Eligible participants were between 55 and 74 years of age at the time of randomisation, with a history of cigarette smoking of at least 30 pack years, and if former smokers, had quit within the previous 15 years.

After a median follow-up of 6.5 years, there were 13% more lung cancers in the LDCT arm and a statistically significant relative reduction in lung cancer mortality of 20% (95% CI, 6.8 to 26.7) in the LDCT arm compared to the chest x-ray arm.[6] It is of note that the 20% mortality reduction among the more than 26,000 randomised to LDCT translates into 80 to 90 lung cancer deaths prevented, with more than 320 still dying of lung cancer. It is also noteworthy that the NLST LDCT group also demonstrated a 6.7% (95% CI, 1.2 to 13.6) decrease in all-cause mortality.

NLST participants were at very high risk for lung cancer. Indeed, 25% of all participant deaths during the study were due to lung cancer. Further analysis of the NLST shows that screening prevents the greatest number of lung cancer deaths among participants who were at highest risk and prevented very few deaths among participants at lowest risk.[7]

Limitations of low dose computerised tomography

NLST was well designed and well conducted. It showed there were some limitations to LDCT. After three annual screens, 39.1% of participants had at least one positive screening result. Of those who screened positive, the false-positive rate was 96.4%.[6] The most common positive finding was a single pulmonary nodule and after thorough evaluation, the most commonly diagnosed cause was a non-serious fungal or mycobacterial infection. A final diagnosis for most nodules was never obtained, but they failed to progress over time.

For every 1000 persons in the NLST, 391 had a positive screen, and most of these were false positives. For most of those with a positive LDCT, the work-up was a conventional CT with higher radiation dose, but 25 out of every 1000 had a false positive conventional CT scan leading to an invasive test such as a transthoracic needle biopsy, bronchoscopy or thoracic surgery. These diagnostic procedures can cause anxiety and complications (e.g. pneumo- or hemothorax after lung biopsy). Indeed, 3 per 1000 had a major complication from an invasive procedure and there were 16 deaths within 60 days of an invasive diagnostic procedure. Six of these 16 ultimately did not have cancer. While it is not known whether these deaths were directly caused by the invasive procedure, such findings do emphasise the importance of considering the harms, as well as the benefits, of screening.[6]

Overdiagnosis is a particular concern in cancer screening. It is the finding of a cancer that is indolent to the specific patient. It can be a tumour that fulfills the histologic requirements of malignancy, but if left alone will either never metastasise and cause harm or if a malignant tumour, will never progress to clinical significance within the patient's lifetime. In either case, treatment and cure is not necessary. An overdiagnosed cancer is by definition asymptomatic.

Initial assessment of NLST suggests 18.5% of screen-detected cancers are overdiagnosed tumours.[8] This is consistent with long-term follow-up of the Mayo Lung Study, which estimated overdiagnosis at 17% of

diagnosed tumours.[10] The Mayo Lung Study began in 1971 as a prospective study of chest X-ray and sputum cytology screening in 9211 smokers, and it last screened participants in 1983. The USPSTF commissioned some recent population modelling, which estimated overdiagnosis at less than 17% of screen-diagnosed cancers.[10]

The long-term risk of radiation-induced cancers is also a concern. Although the long-term risk cannot be measured directly, LDCT lung screening exposes a subject to between 0.61 to 1.5 mSv per scan. Putting this in proper context, annual background radiation exposure in the United States averages 2.4 mSv, radiation exposure from mammography is 0.7 mSv, and radiation exposure from computed tomography of the head is 1.7 mSv. Those screened patients with a false positive will have additional diagnostic imaging and additional radiation exposure.

USPSTF recommendation and the screening population

While the USPSTF relied heavily on the NLST in making its recommendation, there are important differences.[2] These differences reflect the influence of findings from population modelling. The NLST evaluated persons at high risk 55 to 75 years of age and gave three screens, each a year apart. The task force recommends screening persons at high risk, aged 55 to 80 years. The task force also recommends that annual screening continue until the person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

The task force expanded the definition of high risk for lung cancer beyond age and smoking history, to include such risk factors as occupational exposure, family history, and history of other lung diseases. It also emphasised the need for screening to take place in a program that was carefully monitored to assure quality in diagnostic imaging and appropriate follow-up to replicate the benefits observed in the NLST in the general population. The task force also emphasised the importance of tobacco cessation as the primary way to prevent lung cancer deaths and noted that LDCT should not be used to discourage cessation efforts.

Applying LDCT to the US population

Recent estimates suggest that widespread high quality screening in the US has the potential to eventually prevent 12,000 lung cancer deaths per year.[11] However, there is uncertainty as to how many hospitals can provide the same high quality screening, diagnosis and treatment as was available in the NLST, which was performed at 33 centres with expertise in lung cancer diagnostics and treatment. Widespread screening may result in iatrogenic harm at rates significantly higher than in the NLST, and thus the balance of benefits and harms of screening on a widespread basis might be less favorable than suggested by the trial results.

Recommendations of other American organisations

The recent USPSTF recommendation is in general agreement with the recommendations of other American organisations. The American Cancer Society, the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network recommend that clinicians initiate a discussion about lung cancer screening with patients who would have qualified for the NLST, i.e. aged 55-74 years, at least a 30 pack-year smoking history, currently smoking or having quit within the past 15 years, and with relatively good health.[12,13]

Core elements of this discussion with the patient should include the benefits, uncertainties and harms associated with screening for lung cancer with LDCT. Adults who choose to be screened in the US setting should enter an organised screening program at an institution with expertise in LDCT screening, with access to a multidisciplinary team skilled in the evaluation, diagnosis and treatment of abnormal lung lesions. If such a program is not available, the risks of harm due to screening may be greater than the benefits.

All the above professional groups recommend annual screening, and the recommendations are not specific about when screening should cease.[12,13]

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ORAL CANCER SCREENING

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Abstract

The term 'oral cancer' encompasses neoplastic lesions involving the lip, oral and oropharynx. The vast majority of these lesions are squamous cell carcinomas. Risk factors include tobacco and alcohol use and, particularly for oropharyngeal cancers, exposure to human papillomavirus. Visual screening for oral cancers in the mouth necessitates an appreciation of the presentation of oral lesions that have an increased risk of malignant transformation. Recent evidence reviews by the US Preventative Services Task Force and the Cochrane Collaboration have concluded that at the current time, there is insufficient evidence to recommend oral cancer screening in the general population. However, because of the potentially serious outcomes for patients and impact on quality of life, opportunistic visual screening opportunities should be part of general oral examinations for patients visiting health professionals, particularly dental practitioners.

The general term 'oral cancer' encompasses neoplastic lesions involving the lip, oral cavity and oropharynx; the vast majority of these lesions are squamous cell carcinomas.[1] This neoplasm is the sixth most common cancer that occurs globally, however there is wide geographic variation with respect to numbers of cases and site of occurrence.[2] Worldwide, the majority of cases occur in South East Asia, Latin America and Eastern Europe.[2]

The risk factors for oral cancer are well characterised and include tobacco and alcohol use, as well as other factors in specific geographical areas such as areca nut.[3] Most importantly, tobacco in its various forms has been linked to an increased risk of oral cancer and this risk is potentiated by alcohol. Historically, most patients with oral cancer are in older age groups with a peak incidence between 64-70 years of age. Recently however, there have been increasing reports of patients less than 40 years of age presenting with oral cancer.[4] In Australia, the most common site for oral cancer to occur is the lip,[2] attributed to ultraviolet light exposure.

In the Australian Indigenous population, it has been reported that while the overall incidence of cancers is comparable to that of the general population, certain cancers, including oral cancer, have a significantly higher incidence.[5] It has been postulated that the reasons for the difference in this population are due in part to high tobacco smoking prevalence and increased alcohol consumption, and possibly diets low in fruit and vegetables.[5,6,7]

Recent reports have indicated that the overall incidence of oral cancer in Australia is stable, however the specific incidence of oropharyngeal cancer is increasing, particularly in males, and it has been suggested that this may be related to the effect of human papillomavirus (HPV).[8] In recent years there has been increased recognition for the role of HPV in the development of oropharyngeal cancers.[9] Clinically, the role of HPV is potentially significant, as there is evidence that HPV-related oral cancers may respond differently to treatment and may have better treatment outcomes.[9]

Potentially malignant disorders and clinical presentation of oral cancer

Visual screening for oral cancers in the mouth necessitates an appreciation of their presentation, as well as the presentation of oral lesions that have an increased risk of malignant transformation. These are referred to as potentially malignant disorders. The most commonly described potentially malignant disorders include leukoplakias and erythroplakias (figure 1).[10] Leukoplakia is defined as a "white plaque of questionable risk having excluded (other) known diseases or disorders that carry increased risk for cancer".[10] Erythroplakia on the other hand, is defined as a "fiery red patch that cannot be characterised clinically or pathologically as any other definable disease".[10] The malignant transformation rate of leukoplakia is approximately 1%, while it has been suggested that almost all erythroplakias will undergo transformation.[10] Other important potentially malignant disorders that have been discussed include lichen planus and oral submucous fibrosis, as well as other conditions such as actinic cheilitis and immune deficiencies. Oral submucous fibrosis is particularly a problem in South East Asia and is associated with chewing areca or betel nut.[11]

***Figure 1**: Clinical photographs showing examples of leukoplakia (A) on the anterior lingual aspect of the mandible and erythroplakia on the lateral border of the tongue (B).*

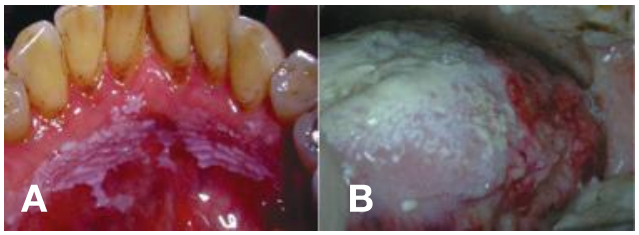
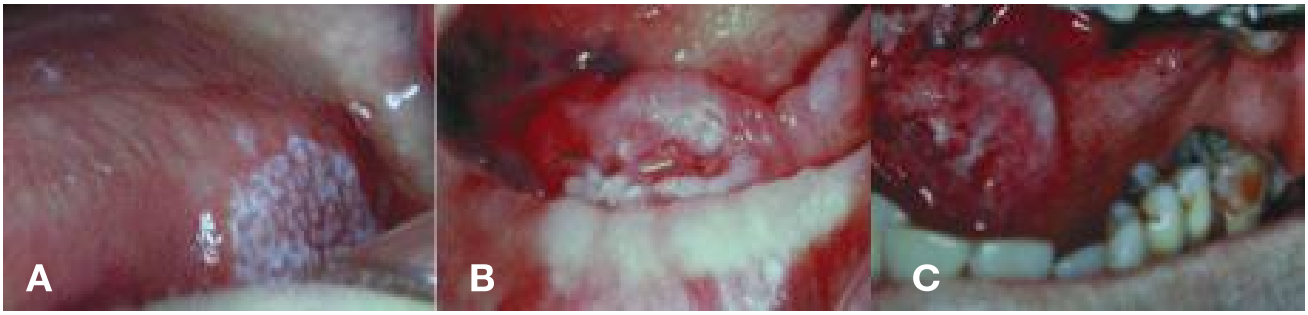


***Figure 2**: Variable appearance of oral cancer: (A) white patch, lateral border of the tongue; (B) chronic ulcer, edentulous mandible; (c) raised mucosal lump, floor of mouth.*



The clinical appearance of oral cancer itself can be varied and also depends on its anatomical location in the mouth and the stage at which it presents. Broadly, oral cancer can present as leukoplakias or erythroplakias, long-standing ulcers or lumps or swellings on the mucosa (figure 2).

Screening

Despite not being the most common cancer to affect the population in Australia, oral cancer is associated with serious outcomes for patients.[12] Furthermore, in those patients who do survive, there are often significant issues associated with quality of life as a result of debilitating surgery and long-term toxicities associated with treatment such as radiotherapy and chemotherapy.[13] Accordingly, there is a need to detect oral cancers early if their occurrence cannot be prevented by modification of risk factors. Despite this need, various evidence reviews, most recently the US Preventative Service Task Force and Cochrane reviews, have not been able to recommend large-scale screening programs for oral cancer.[14,15]

The evidence base for oral cancer screening largely consists of one randomised controlled trial conducted in Kerala, India.[16] This study included 191,873 participants, who were all older than 35 years, who were allocated to either an intervention or a control arm. In the intervention group, the participants underwent a visual examination by a trained examiner; the control group participants had no screening examination undertaken. Four rounds of screening occurred between 1996 and 2010.[17] A 15-year follow-up of the study concluded that there was a sustained reduction in oral cancer mortality, but this was statistically significant only in the participants who underwent all four screening rounds and who were users of tobacco and/or alcohol.[17] Given this result, the conclusions of the US Preventive Service Task Force were "…that the current evidence was insufficient to assess the balance or benefits and harms or screening for oral cancer in asymptomatic adults".[14] The Cochrane Systematic Review found "…that overall there is not enough evidence to decide whether screening by visual inspection reduces the death rate for oral cancer and there is no evidence of other screening methods. However, there is some evidence that it might help reduce death rates in patients who use tobacco and alcohol."[15] The Cochrane review noted that the Kerala study did demonstrate that screening produced a 'stage-shift' in that in the screened population, oral cancer was diagnosed at an earlier stage, which is an important factor in survival from cancer.[15] However, it was acknowledged that the Kerala study was undertaken in a population with high oral cancer incidence, which is very different from countries such as the United States, United Kingdom and Australia. The Cochrane review also indicated that opportunistic visual examination as part of a systematic oral examination by dentists and oral health practitioners was recommended for all patients, particularly those who used tobacco and or alcohol.[15]

Conclusion

There is no doubt that early detection of cancer reduces morbidity associated with the disease as a consequence of more conservative surgery and a reduced need for adjunctive treatment such as radiotherapy and chemotherapy. Despite the current lack of evidence to support population based screening programs for oral cancer, because of the potentially serious outcomes for patients and impact on quality of life, opportunistic visual screening opportunities should be part of general oral examinations for patients visiting health professionals, particularly dental practitioners.

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SHOULD WE CONSIDER INTRODUCING SYSTEMATIC SCREENING FOR LYNCH SYNDROME?

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Abstract

Lynch Syndrome is characterised by the development of colorectal, endometrial and other cancers, often at a young age. It is caused by constitutional mutations of DNA mismatch repair genes and cancers that arise in this setting are mismatch repair deficient, as demonstrated by loss of the relevant mismatch repair protein and microsatellite instability. In theory, universal screening of all index colorectal cancers for mismatch repair deficient should identify individuals who are at higher than population risk of carrying a constitutional mutation in the mismatch repair genes. A health economic evaluation in the UK found that this type of screening strategy applied to individuals under the age of 51 years was highly cost effective. In Australia, some centres routinely test all colorectal cancers for mismatch repair deficient, however there is currently no systematic national approach to screening. Given the cost effectiveness of universal screening is dependent on uptake of constitutional testing by the index case and their relatives, we suggest that research into the determinants and barriers to uptake of constitutional testing is a high priority. Further, given that the health care context can influence the assessment of cost-effectiveness, we propose that the UK economic evaluation also needs to be undertaken in an Australian context.

Lynch Syndrome (LS) is a familial cancer syndrome which predisposes to colorectal cancer (CRC), endometrial and other cancers, such as gastric and ovarian cancer. It is caused by constitutional mutations in the DNA mismatch repair (MMR) genes *MSH2, MLH1, MSH6* and *PMS2*. Rarely, some cases of LS are caused by constitutional methylation of the promoter of *MLH1* or *MSH2* rather than a constitutional sequence change.[1] Irrespective of mechanism, the normal cells of an individual with LS have proficient DNA repair despite containing a mutated allele (copy) of one of the mismatch repair genes. Once the remaining normal allele is mutated or lost, the cells accumulate a large numbers of mutations. It is unclear whether the increased mutation rate is, in itself, the driver to carcinogenesis, or whether this is a paraphenomenon and the driver is a reduction in apoptosis caused by an uncoupling of cell cycle control from recognition of DNA damage.[2,3]

The average age of onset of CRC in LS is about 40 years, but cases of teenage cancer have been described. While some individuals never develop any tumours, many patients develop more than one cancer, some many more. Previous studies overestimated the cumulative risk of cancer in individuals with LS, reporting cumulative colorectal cancer risks of 80%. Recent studies have estimated lower cancer risks and have also shown that cancer risk and type of cancer depends on which of the four genes is mutated. For instance, Bonadona et al estimated cumulative risks of CRC by age 70 years of around 40% for *MLH1* and *MSH2* mutation carriers, and 12% for *MSH6* carriers.[4] This study also showed that the risks of endometrial or ovarian cancer do not significantly increase until after the age of 40 years.

Identifying individuals with LS is important, since colonoscopic surveillance for both index cases and at-risk relatives reduces mortality from colorectal cancer. Biennial surveillance colonoscopy for LS patients is recommended because CRCs in LS appear to develop much more quickly than those in the general population.[5-7] The estimates of population prevalence of LS have steadily risen, in part because of programs for universal screening of incident cancers for the hallmarks of LS. Currently, it appears that ~1:1000 individuals have mutations in one of the four genes, giving a total population prevalence of ~1:250, thus accounting for approximately 2.8% of all CRCs.[8]

Tumour testing for LS

LS tumours are mismatch repair deficient (MMRD) and display microsatellite instability (MSI) and loss of the relevant mismatch repair (MMR) protein. The value of using MSI testing as a screening test for LS tumours is limited by the fact that 15% of sporadic CRC and some other cancers also display MSI as a consequence of

somatic inactivation of the *MLH1* gene. Another limitation of MSI testing is that the panel of MSI markers has been developed for colon cancers, and the testing is less sensitive when applied to endometrial and other cancers. Finally, the standard MSI markers often do not identify MMRD tumours, which arise in the context of an inherited mutation in *MSH6* or *PMS2*.[9]

The observation that a specific somatic mutation of *BRAF*, known as V600E, is not found in LS-associated colon cancers, but is found in a majority of sporadic colon cancers with loss of MMR, has now provided the means for restricting constitutional testing to those individuals with a high likelihood of LS.[10,11]

Expression of MMR proteins in tumours can be assessed by immunohistochemistry (IHC) and it is gene specific, however it is not a functional test, so expression of an MMR protein does not necessarily equate to MMR proficiency.[12] Also, as mentioned above, the most frequent cause of loss of MMR protein staining in CRC is somatic (acquired) methylation of the *MLH1* gene promoter. Both MSI and MMR IHC testing are included in some programs such as the UK National External Quality Assurance Service program.[13,14] As with all tests, they have finite sensitivity and specificity, and there is no single test which will indicate LS with complete accuracy.

Surveillance and treatment for LS-affected individuals

Biennial colonoscopy from around the age of 25 years is the mainstay of LS surveillance and treatment.[6,7] This allows identification and removal of premalignant lesions, and downstaging of cancers. However, it is acknowledged that even in the best hands, CRC mortality in LS can only be reduced by about half. There are no proven forms of effective surveillance for any other LS-associated cancers.[6,7] For this reason, total abdominal hysterectomy and bilateral salpingooophorectomy is recommended after childbearing is completed, or from age 40 years, to reduce the risk of gynecological cancers.[6,15] Nowadays, some surgeons recommend a total colectomy rather than a hemicolectomy as the preferred option for a LS patient with CRC. The rationale for the more extensive surgery relates to the high risk of cancer in residual colon and the reports of comparable quality of life following either type of surgery.[16]

Two other approaches to cancer prophylaxis for LS are on the horizon. Firstly, in one major placebo-controlled double-blind trial, daily aspirin reduced the relative risk of CRC by 37%.[17] In this study, the frequency and magnitude of side-effects was not high, in part because of the relatively young age of the participants. Given the high dose of aspirin (600mg) used in the CAPP2 study, a further dose determination trial (CaPP3) is planned. A second approach to cancer prophylaxis is currently being tested in a phase I/IIa vaccine trial of MicOryx, a vaccine directed at the specific abnormal proteins caused by loss on MMR in tumours with MSI.[18-20]

Current identification of LS

The Amsterdam Criteria were originally developed as a research tool to find the gene/s responsible for LS, rather than a clinical diagnostic aid in identifying such families.[21] With successful identification of the MMR genes and improved understanding of LS, the Amsterdam Criteria were subsequently modified in recognition that endometrial cancer was a major LS associated tumour. However, the custom and practice became established that LS was initially diagnosed by family history, and tumour testing was an aid once a putative family had been identified. Subsequently, much time and effort has gone into models which can be used in clinical practice to predict which families have a greater chance of having a LS gene mutation, but the fact remains that diagnostic laboratories only find mutations in about 10-15% of cases referred to them.[5]

Subsequently, as LS tumour testing came into routine practice, it was realised that incident tumours could be tested without a requirement for a family history, including cases of young-onset, multiple or co-occurrence e.g. colorectal and endometrial cancer in the same individual.[22] Thus, at an international meeting in Bethesda in 1996, criteria were drawn up to aid in selection of tumours for LS testing, the so-called Bethesda Guidelines.[23] As the variety of LS tumour types became apparent, so these were revised.[24] Although the Bethesda Guidelines in their various forms do somewhat improve the specificity of LS identification, they are not sensitive. It has also been recognised that the criteria vary widely in their performance depending on the underlying gene.[9,10] Additionally, it has been found that not only do healthcare professionals rarely ask about a family history of cancer, they struggle with recognising LS and referring cases to clinical genetics.[25,26]

Furthermore, individuals who have de *novo* mutations or are adopted have little, if any hope of being identified at risk of LS in a system based on family histories.

Universal screening of tumours for LS: international overview and cost-effectiveness

In response to the realisation that ascertaining LS by means of family histories had distinct limitations, the International Society for Gastrointestinal Hereditary Tumours produced a position statement on the identification of LS in Europe, in which systematic testing of LS-associated tumours was proposed. Simultaneously, a number of countries were endeavouring to institute such programs, either nationwide (notably Denmark) or in individual regions (Australia).[5,27]

In the UK, the Peninsula Technology Assessment Group (PenTAG),[28] was contracted by the National Health Service National Institute of Health Research to undertake a health technology assessment on the diagnostic utility and cost-effectiveness of genetic testing for LS in index cases of CRC under the age of 50 years of age.[29] The PenTAG group built an economic model applicable to the National Health Service system. The model incorporated all test performance characteristics and costs, a full range of health (e.g. clinical genetics, oncology, surgery) and social care costs. Six different combinations of tumour tests (immunohistochemistry, MSI and/or BRAF) were evaluated and all were evaluated in comparison with no intervention. Also evaluated was the benefit of taking a family history and acting upon it, if it fulfilled the Amsterdam Criteria, and simply testing for constitutional mutations without tumour

testing. The PenTAG model showed that all colorectal tumour testing-based strategies up to age 50 years offered the National Health Service good value for money versus no testing, with all incremental cost-effectiveness ratios below the National Institute for Health and Care Excellence threshold of <£20k(AU$36k) per quality adjusted life year (QALY) gained. The model predicts an expected average gain in longevity of 1.3-1.7 years for probands, and 1.1-1.4 years for relatives. Moreover, cost-effectiveness was positive even if only the proband was identified with LS, albeit that identifying relatives, up to a point, is more cost-effective. Interestingly, family history as a 'test' is more cost-effective than doing nothing, but not as cost-effective as tumour testing, and simply sequencing all probands was also found to be cost-effective, although less so than tumour testing strategies. Furthermore, the model shows that it would still be cost-effective to test all tumours up to age 70, with incremental cost-effectiveness ratios <£20k(AU$36k)/QALY.

While tumour testing strategies which include MSI followed by *BRAF* testing appeared to give the best incremental net health benefit, all six tumour testing strategies are predicted to be effective and cost-effective. Thus there is little to choose between the available options and no justification to change current practices of universal screening for LS through tumour testing. A sensitivity analysis conducted as part of the modelling showed that the following factors had a substantial impact on cost-effectiveness: CRC incidence for individuals with LS; the mean number of relatives per proband (0 – 12; base = 5); the effectiveness of colonoscopy in preventing metachronous CRC; the cost of colonoscopy; and the psychological disutility associated with prophylactic total abdominal hysterectomy and bilateral salpingo-oopherectomy disutility. Thus, the model usefully predicts areas requiring careful attention and further exploration.

Implementation of LS screening

Implementation of a LS screening program should necessarily fulfill the requirements for any screening program, including that there should be: a detectable disease marker; a simple, safe, precise and validated test; and an effective treatment with evidence of early treatment leading to better outcomes than delayed treatment. Value for money is also an important consideration, specifically the opportunity cost of the screening program (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole. Moreover, assessment against these criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resources.[30] In addition, there should be a plan for managing and monitoring the screening program and an agreed set of quality assurance standards, from which no doubt, the experience of other countries who have successfully implemented such programs will be germane.[13,14]

Given that universal screening for LS theoretically satisfies the requirements for adoption into routine practice, it is important to consider the possible barriers to implementation. One barrier is the behavior and circumstances of clinicians and patients. In one study of population-based universal screening for LS, over half of the individuals identified did not take up constitutional testing or refused to be informed of their results. As a consequence, one third of LS cases were missed.[31] Another barrier is the capacity of clinical genetics and thence to colonoscopic surveillance services to accept new referrals. To accommodate the additional LS patients, it may be necessary to make changes elsewhere in the system, for example changing the approach to surveillance for those at moderately increased risk of CRC.[32,33]

There are concerns that implementation of universal tumour testing amounts to genetic testing without consent. However, the situation is analogous to one where patients with polyposis are able to be diagnosed on sight and they and their relatives benefit from life-saving prophylaxis. Should those with LS be denied such a diagnosis simply because the tests they warrant are microscopic or molecular? In effect, their cancers are unanswered referral letters. We require LS families to recognise they have a family history of a complex disorder, and we require doctors to be similarly skilled, but the evidence shows that such a pathway amounts to an unfair obstruction to a diagnosis which may save lives. In any event, such a testing program does not force a diagnosis of LS on an individual – reporting pathologists merely need to say in their report: "Testing shows that this cancer may be due to an inherited syndrome. Referral of the patient to clinical genetics is strongly indicated."

Current status of universal tumour screening for LS in Australia

There is currently no consistent national approach to testing for LS in Australia. Although immunohistochemistry in tumour samples is rebatable by Medicare,[34,35] molecular MSI and BRAF mutation testing in CRC is not (although testing for BRAF mutation status is approved for other indications).[36] Genetic testing for constitutional mutations in *MLH1, MSH2, MSH6 and PMS2* is also not Medicare-reimbursed, although the State Health Departments in Victoria and Western Australia fund these tests.[37] However, two Australian LS testing experiences have been reported.[27,38,39] In an evaluation of routine screening of incident CRC in South Eastern Sydney,[27] participating cases with MMRD tumours were triaged into low- and high-likelihood LS cases based on IHC and *BRAF* mutation testing. Constitutional mutations were reported in ~7% (95%CI:3-18%). In WA, screening for LS has been in place since 2008 as part of the familial cancer program, which was established in several steps. A 2006 evaluation of the cost-effectiveness of screening CRC tumours in WA found that offering genetic testing to first-degree relatives, followed by intensive surveillance for cancer of the colorectal, endometrium, ovary, stomach and urinary tract, or prophylactic colorectal surgery, was cost-effective, incurring a net cost <$13,000 for a gain of eight CRC-free years.[40] A pilot involving retrospective testing of CRC cases <60 years diagnosed from 2000-2006 using MSI and molecular *BRAF* mutation testing was performed; high MSI tumours without *BRAF* mutation were further investigated using IHC, which led to the identification of previously unrecognised cases of LS.[41] Routine screening targeting incident CRC cases aged <60

years has been established and a recent report concluded that the program has resulted in identification of two-thirds of the expected LS cases among CRC cases aged <60 years in WA.[38]

Prior work suggests that uptake may be one of the major practical limitations of an LS screening process. In the South Eastern Sydney experience,~50% of MMRD CRC cases did not wish to proceed with further testing for LS.[27] A systematic review reported that only 52% of first-degree relatives of identified LS cases chose to receive genetic testing.[42] However, once genetic testing has been performed, surveillance uptake may be relatively high.[15,43,44] In an Australian study of confirmed LS carriers, all had undergone colonoscopy by three years after testing and 69% of the female carriers had undergone gynaecological screening in the previous two years.[43]

Conclusion

Given the inconsistencies in current approaches to testing in Australia and the potential difficulties in achieving high uptake of testing if it were to be systematically offered, we suggest that research into the determinants and barriers to testing uptake is a high priority, as is performing a national assessment of the effectiveness and cost-effectiveness of systematic screening for LS in Australia.

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LETTER

CELEBRATING 20 YEARS OF THE AUSTRALIAN CANCER CONSUMER ADVOCACY MOVEMENT, 1994-2014

Sally Crossing

Convenor, Cancer Voices Australia, Chair, Cancer Voices NSW, Australia.

The independent cancer consumer advocacy movement in Australia has a proud record, one we think deserves to be noted by cancer professionals. A hallmark of our achievements has been sharing with health professionals the common goal of working in the interests of improving things for people affected by cancer.

Consumer advocacy allows us to make a real and visible difference to the cancer experience of many, making sure the informed view of people affected by cancer is part of the decision-making mix. Some call this adding the 'essential perspective'. And the evidence shows meaningful consumer engagement is a win-win for all, with improved outcomes and experiences for those affected by cancer and more trust and confidence in the health service.[1]

Consumers working with cancer professionals

Cancer Forum readers who have been around as long as I have, will know of cancer consumer organisations popping up when and where we felt the consumer voice needed to be heard, or when you felt it should be. Many in the Clinical Oncology Society of Australia have welcomed our contributions to discussion and debate through a range of interfaces. These include conferences, committees, boards, consumer advisory groups and peer reviewed journal papers. You may also have worked with us when: we offer the consumer perspective to researchers seeking grants and on the 14 Clinical Trials Groups; collecting and presenting our research priorities; visiting politicians with you or joining debate in the general media. We thank you for your inclusiveness and for listening to us as the ultimate beneficiaries of all your work. It's been a great and productive partnership.

Twenty unbroken years of cancer consumer advocacy is worth celebrating. It all began in Melbourne in 1994, and has diversified and flourished since then.

First steps to take-off

The Breast Cancer Action Group began it all and shaped the Australian model of volunteer, survivor-led cancer consumer advocacy. In 1994, Marcia O'Keefe, an engineer diagnosed with secondaries, wrote a passionate letter to *The Age*, calling on other women to join her. Founder of Breast Cancer Network Australia, Lyn Swinburne, remembers they agreed a support group was not for them: "We wanted action to make the system more responsive to our needs." They developed a vision for getting consumer input into decision-making and the concept clicked.

As a harbinger of things to come, Breast Cancer Action Group's first and very successful campaign was to get Taxol for breast cancer on to the Pharmaceutical Benefits Scheme. After Marcia's death, Lyn and Sue Lockwood promoted the new concept, making sure people who would benefit were heard. They also realised that being up to speed and capable, networked with others in the same boat and independent, all led to credibility. Crediblity is essential if the consumer voice is to be taken seriously by stakeholders – government, cancer professionals, cancer charities, etc.

In 1995, the new National Breast Cancer Centre established a Consumer Advisory Group, inviting representative women form all states and territories to give them advice on their programs and resources. The centre later gave seed funding to help establish a nationwide organisation which could advocate for the issues and needs of women with breast cancer. The Breast Cancer Network Australia grew from a few in 1998 to 90,000 supporters today.

Meanwhile (1997), a group was set up in NSW, which became the Breast Cancer Action Group NSW, based on the Victorian model and sharing newsletters. Heady days for us all – topped by a memorable trip to Washington DC in 1998 to learn how it was done, with encouragement from Hillary Clinton.

If the medical community was not fully convinced of the latent power of consumer advocacy, all that changed in 2001 when Breast Cancer Network Australia led a campaign to have Herceptin made available without cost to women (HER2 positive) with advanced disease. The sponsor's bid had failed the Pharmaceutical Benefits Advisory Committee process three times. It took the combined efforts of women around Australia to rally support via MPs, the media and people of influence to ensure access to this new drug.

Then in 2007, a record seven week campaign led by three passionate Breast Cancer Action Group NSW members successfully spearheaded a change in federal superannuation legislation, to allow access to superannuation tax free for people dying, at any age, of a terminal illness.

Consumer voice expands

This model was influential in how other cancer consumer groups came into being. Recognising most people with cancer faced similar issues, the Cancer Voices movement took off in 2000, initially in NSW and soon after in other states. In 2005, the movement established Cancer Voices

Australia to provide a voice on national issues. Funded and housed by Cancer Council Australia until 2012, it is now independent. Cancer Councils have assisted consumer groups of various kinds and to varying degrees to find their feet, recognising the intrinsic value to their own work, as well as for the cancer and wider communities. For this the movement is very grateful.

A much larger group of organisations, the Australian Cancer Consumer Network, will be launched at Parliament House, Canberra on 26 November. The network will share information and ideas, alerts about Pharmaceutical Benefits Advisory Committee and Medical Services Advisory Committee agendas, and opportunities to participate in national cancer related inquiries. Most importantly, it will be able to muster an even louder voice on national issues if and when necessary.

Most Cancer Consumer Network groups are survivor-led, voluntary and represent a range of cancers, common and rare. A few come under the umbrellas of foundations and institutes with their own roles and funding sources, but which also facilitate a consumer voice. These differences need to be recognised. Fully independent consumers, financially and in purpose, cannot be accused of vested interests, except that they want the best for people with cancer. Strength through independence has proven very compelling, especially when talking to government politicians.

What have we achieved?

From the beginning, the movement's objectives have been clear to improve the cancer journey and outcomes in the areas of diagnosis, information, treatment, research, support and care. We have worked in partnership with decision makers and service providers, ensuring the patient perspective is heard from planning to delivery.

Achievements have included improvements in:

- access to multidisciplinary cancer treatment and care
- the range and quality of information for cancer patients, including guidelines and directories of specialists
- support and survivorship services
- the direction and value of research
- funding for new comprehensive cancer centres
- programs for nominating capable consumer representatives
- capacity building through training in advocacy, representation and research
- access to superannuation tax free for all people dying of a terminal illness
- free matching service to researchers to help meet the requirements for consumer involvement of many cancer research funders.

Some priorities for 2015

Priorities are built on what people affected by cancer see needs to be addressed. They are regularly reviewed. For example, a national priority is working for better coordination of care. To reach this goal, we are advocating for guidelines or best practice statements, and to encourage jurisdictions to earmark funding for coordination services to help cancer patients to navigate the system's maze. To help both clinicians and their patients, we would like to see the Australia-wide adoption of the Radiation Oncology Clinical Practice Standards, and their development for medical oncology. We are also working with the Cancer Drugs Alliance 'think tank' about how to arrive at the most effective health technology assessment system, especially for cancer.

What do we put in and get out?

We put in our passion, commitment, persistence and expertise (as consumers) – probably in equal quantities, well mixed to achieve a sum greater than its parts. Using our skills and personal experience, doing our homework, building partnerships and adding some effective training, we can and do build the capacity of our voices. In return, we reap the rewards of successful giving back, of improving the cancer journey for others like ourselves. There is a strong sense of camaraderie in working together for our common cause.

The nature of our disease means that we have lost a number of our best along the way. Improvement in cancer diagnosis and treatment over these 20 years has also meant that some of us gain more time, adding to experience and corporate memory. A challenge we must meet each year is to harness the commitment, passion and persistence of younger cancer consumers so the essential perspective continues to be heard.

Lastly, heartfelt thanks to the many supportive cancer professionals who have helped us along the way. We could not have grown and prospered without you. And thanks to all those people affected by cancer, the consumer side of the equation, who have given so much to our common cause since 1994. And now for the next 20 years – let's keep on making a difference together!

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AWARD



CANCER COUNCIL AUSTRALIA'S STUDENT ESSAY COMPETITION

Cancer Council Australia's annual essay competition is open to Australian residents enrolled in a medical course in an Australian university. Students are required to submit an essay on an issue related to cancer control. In 2014, the topic was 'Ageing and Cancer'. The essays are judged by members of Cancer Council Australia's Oncology Education Committee.

The winning essay in the 2014 Student Essay Competition was submitted by Emma Maloney. Emma attended the summer school in Groningen, The Netherlands from 30 June-11 July.

AGEING AND CANCER: A COMPLEX RELATIONSHIP

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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.[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.[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.[4] In spite of this, by 2025 it is predicted that the number of cancer diagnoses in Australia will further increase by 60%.[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.[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.[2] 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.[6,7]

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.[2] 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.[6,8] Additionally, it is speculated that the accumulation of senescent cells with age creates a tissue environment permissive to cancer.[9] 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.[6] 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.[2,7] Other age-associated genetic modifications, including DNA hypermethylation, point mutations and chromosomal translocation are thought to groom ageing tissues for neoplastic development.[3,7]

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.[7] This may promote the growth of immunogenic tumours.[3] 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.[7]

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.[10] 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.[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.[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.[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.[7,15] However, discussing such information with elderly patients can be difficult in the context of cognitive and sensory deficits.[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.[14] Additionally, it is reported that doctors do not spend as much time communicating with elderly cancer patients.[12] These factors potentially contribute to issues of delayed diagnosis and incomplete workup, which have been reported in an older patient cohort.[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.[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.[1,16,17] Both reduced hepatic and renal clearance may affect loading doses, maintenance doses and dosing intervals of many drugs.[17] However, it is reported that both elective cancer surgery and radiotherapy are well tolerated by most older patients.[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.[5,18] 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.[19] 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.[20] Research initiatives such as the CLEAR (Cancer, Lifestyle and Evaluation of Risk) study, conducted by Cancer Council NSW, will direct future prevention strategies.[21]

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 Screening Programs to individuals between 50 and 74 years.[22,23] 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.[7] Randomised controlled trials assessing mammography and faecal occult blood tests have suggested benefit of screening for individuals with a life expectancy of at least five years.[3]

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.[24]

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.[24] 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 aged 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.[20]

The geographical distribution of the older population within Australia impacts upon the provision of cancer services. High mobility rates are recognised among older age brackets, particularly in the 85-94 age group, as people relocate to be close to family and support services.[25] Additionally, the 'sea change phenomenon' sees the migration of older people from larger metropolitan areas to smaller coastal towns.[25] By 2025, it anticipated that 22% of the Australian population will reside in non-metropolitan areas. 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.[17] Initiatives such as the Cancer Service Networks National Program and telehealth programs are seeking to resolve such disparities.[26] Projects like '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.[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 permits relatively healthy older adults to be included.[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.[11,15] However, it is tenuous to extrapolate these findings to guide the management of frail, elderly patients with multiple co-morbidities.[11]

Given the rapidly ageing population, there is a priority to conduct high-quality research in geriatric oncology.[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.[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.[16]

It is hoped that focused 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.[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.[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 assumption 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

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.

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.

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BEHAVIOURAL RESEARCH AND EVALUATION UNIT (BREU), CANCER COUNCIL SA

Sun protection practices and policies implemented by small outdoor workplaces in South Australia: Facilitators and barriers to adherence

Cancer Council Australia's position statement regarding sun protection in the workplace recommends that workplaces have a comprehensive sun protection program in place. Outdoor workers are identified as an 'at risk' group for the development of skin cancer due to high levels of UVR exposure. However, recent systematic reviews have reported that outdoor workers generally do not engage in adequate sun protection. Research further suggests that employees of smaller-sized businesses in the building and construction sectors are least likely to follow sun-safe guidelines.

In view of these indications, Cancer Council SA's Behavioural Research and Evaluation Unit undertook a qualitative study to document knowledge, attitudes and behaviours related to skin cancer and sun protection among employees, contractors, employers and managers of small outdoor building and construction businesses in South Australia. The principle objective of the investigation was to identify ways in which Cancer Council SA might assist small businesses with sun protection policy implementation, monitoring and adherence.

Semi-structured interviews were undertaken with participants recruited from various businesses across the Adelaide metropolitan region. The findings of the investigation indicated that many participants did not engage in effective sun protection and did not routinely use sun protective measures. The research highlighted that use of sun protection by outdoor workers is influenced by a complex interplay of workplace and individual-level factors, including knowledge and beliefs about sun exposure and skin cancer, subjective perceptions of skin cancer risk and workplace cultural norms related to sun protection practices. A number of misconceptions among outdoor workers were identified, including a prevalent view that sun protection is primarily warranted to minimise the effects of heat stress and a perception that there are limited benefits of using sun protection when working outdoors for extended periods of time. Awareness of the consequences of skin cancer and of workplace sun protection policy requirements among participants was generally poor, and workplace cultural norms related to sun protection appeared to play a significant role in determining individual sun protection practices, personal awareness of skin cancer risk and concern about sun protection.

An encouraging observation from the findings was that both outdoor workers and employers acknowledged the importance of workplace sun protection policy, and perceived a need for this policy to be effectively communicated and enforced, along with education about the risks of skin cancer. The research highlights that there is considerable scope for health promotion initiatives targeting sun protection specifically aimed at workers and owners of small outdoor businesses, including engaging industry stakeholders to facilitate coordinated efforts to support both workers and owners of small outdoor businesses to comply with sun protection policy.

CENTRE FOR BEHAVIOURAL RESEARCH IN CANCER (CBRC), VICTORIA

Self-sampling for human papillomavirus: Could it overcome some of the barriers to cervical screening?

Self-sampling for human papillomavirus (HPV) is an alternative to conventional cervical screening. This study, led by Robyn Mullins, examined which groups of Victorian women would be most likely to participate in self-sampling, and its perceived benefits and barriers. A random sample of 3000 women aged 18-69 years were interviewed by telephone for a general cervical screening survey, and 2526 answered the questions about self-sampling. The terminology 'taking their own Pap test' was used, due to the low understanding of HPV and its link to cervical cancer. One-third of women (34%) indicated they would prefer to self-sample, 57% would not and 9% were unsure. Preference for self-sampling was significantly stronger among women who hadn't had a Pap test for more than three years (65%) or had never had a Pap test (62%), compared to up-to-date women (27%). Convenience was a key benefit (38%), as was less embarrassment (32%). For those who did not want to self-sample or were unsure, professionals being more skilled (53% and 29%), and doubts about being able to do it properly (29% and 26%) were key barriers. These findings indicate that self-sampling was most popular among women who needed a Pap test, and it has potential to reach women who are not participating appropriately in cervical screening. Key participation barriers could be addressed in communication materials which provide information about the test being for HPV, and it being easier to do properly than a Pap test.

Food marketing with movie character toys: Effects on young children's preferences for healthy and unhealthy fast food meals

Movie tie-in premiums are a pervasive method of targeting children with fast food advertising. CBRC is conducting an experimental study to test whether premiums accompanying fast food meals influence young children's meal choices and their perceptions of these meals. Via an online questionnaire, ~800 Melbourne grade 1 and 2 students will be randomly assigned to one of four conditions: (i) unhealthy v healthy meals (control – no premiums); (ii) unhealthy v healthy meals (both with premium); (iii) unhealthy meals (with premium) v healthy meals (without premium); or (iv) unhealthy meals (without premium) (v) healthy meals (with premium). Students will be shown a short promotional trailer for the children's movie 'How to Train Your Dragon 2,' followed by an associated fast food advertisement (conditions 2-4) or an advertisement for a children's leisure activity (control condition). Participants will then be shown four meal options (2 unhealthy and 2 healthy) and asked to choose their preferred meal. They will also complete detailed ratings of one healthy and one unhealthy meal. Analyses will test for differences in meal choice and ratings as a function of the inclusion of the movie tie-in premium. Results will inform a potential regulatory model, whereby movie tie-in premiums would not be permitted to accompany any fast food meals, or the potential for premiums to only be permitted to accompany healthy fast food meals.

NEWCASTLE CANCER CONTROL COLLABORATIVE (NEW-3C), NSW

Improving patient-centred care for lung cancer patients

Patient-centred care is the hallmark of quality health care. However, the delivery of patient-centred care to lung cancer patients is challenging due to a number of factors. Lung cancer patients experience poor prognosis and significant physical and psychosocial burden. Support persons (SPs) of patients are also faced with increased burden and poorer outcomes compared to SPs of other cancer types. There is an urgent need to develop innovative solutions to improve patient-centred care and reduce psychosocial burdens placed on lung cancer patients and their SPs. With funding from the University of Newcastle and the Hunter Medical Research Institute, we are undertaking a cross-sectional study to examine the preferences and experiences of lung cancer patients and their SPs in relation to patient-centred care. Participants are recruited in outpatient clinics and asked to complete a survey of: (i) preferences for involvement in decision-making; (ii) quality of life; (iii) views on discussing life expectancy and end of life care; and (iv) views on research and methods of receiving information. Given the growing contribution of lung cancer to burden of disease, there is a need to re-design health care systems to meet increasing demand and ensure health care providers and organisations are equipped to provide equitable cancer care. This study will provide much needed data about who is most at risk for poorer outcomes, and inform future studies to improve service delivery for lung cancer patients and their SPs.

Patient perspectives on quality of care: A cross cultural comparison

Little is known about cross cultural differences in patients' views about and experiences of cancer care and patient psychosocial outcomes. New-3C is conducting a study to compare experiences of care and psychosocial outcomes of cancer patients' receiving radiotherapy in Japan, South Korea, Australia and Vietnam. Cancer patients who were attending radiation oncology clinics to receive treatment completed a cross-sectional pen-and-paper survey (Japan, South Korea, Australia) or a face-to-face structured interview (Vietnam only). Survey items explored i) patient views across the Institute of Medicine's (US) six domains of patient-centred care; ii) patients' perceptions of life expectancy discussions with their healthcare provider; iii) congruence between preferred and perceived involvement in medical decision making; iv) patients' views about the causes of their cancer; v) the frequency with which providers initiated discussions about their physical and emotional symptoms; and vi) their current levels of anxiety and depression (as assessed by the Hospital Anxiety and Depression Scale). A forwards and backwards survey translation process was undertaken to ensure cultural relevance and consistency across international study sites. To date, data collection has been completed in Vietnam (n=300), South Korea (n=299) and is nearing completion in Japan (n=259). Australian data collection is currently in progress (n=77) and is expected to be completed by December 2014. This project will produce new information about cross-cultural differences in cancer patients' views and experiences of patient-centred care. Exploring how experiences vary across countries will enable a coherent framework of patient experiences to be developed, and assist in informing improvements in care.

CANCER COUNCIL AUSTRALIA

Cancer Council welcomes new bowel cancer screening and medical research investment

The Federal Government committed to a $95.9 million, four-year plan to finalise Australia's National Bowel Cancer Screening Program in the 2014-15 budget, preventing at least 35,000 Australian bowel cancer deaths.

Cancer Council Australia CEO, Professor Ian Olver, applauded the Minister for Health, Peter Dutton, for committing to the completion of the program, which was introduced 10 federal budgets ago.

"Bowel cancer is the second-largest cause of cancer death in Australia, yet most cases can be cured if detected early," Professor Olver said.

"Our research shows the Government's commitment to bring the program's full implementation date forward by 14 years will prevent at least 35,000 bowel cancer deaths over the next 40 years.

"By filling in additional gaps in the bowel cancer screening program from July next year, the benefit in lives saved will be maximised while full roll-out occurs."

Cancer Council calls on GPs to support first ever bowel cancer screening TV campaign

Cancer Council called on GPs in June to encourage patients aged 50 and over to screen for bowel cancer with a faecal occult blood test, as part of a campaign to promote the National Bowel Cancer Screening Program.

Developed by Cancer Council with funding from the Australian Government, the campaign followed a federal budget announcement that the free screening program would be fully implemented by July 2020 and offered to everyone aged 50 and over, every two years.

Professor Olver said GP support was critical to boosting participation in the program and to getting people not yet eligible for the program to screen.

"Screening for bowel cancer with FOBT is one of the most clinically and economically effective public health measures available to Australians," Professor Olver said. "Support from GPs has great potential to increase the number of Australians taking the test, particularly when the campaign is running.

"While the screening program is based on participants taking their FOBT at home, GPs nonetheless have a critical role – in referring patients who test positive, in assisting with follow-up and in encouraging patients to take the test in the first place."

Tobacco industry misinformation aims to undermine success of plain packaging

Cancer Council spoke out in June against the tobacco industry's efforts to undermine the effectiveness of plain packaging through ongoing misinformation about tobacco sales in Australia.

Professor Olver said independent tobacco sales figures published by the Department of Health showed tobacco consumption in Australia in the March quarter of 2014 was at an all-time low.

New Treasury figures were further indication of a decline in smoking, with tobacco clearances (including excise and customs duty) falling by 3.4% in 2013 relative to 2012 when tobacco plain packaging was introduced.

"The so-called data being spun by the tobacco industry to claim that plain packaging has not worked is plain wrong," Professor Olver said.

"If we used tobacco industry claims to guide health policy, life expectancy in Australia would be much lower than it is today."

New data shows 643,000 Australians binned lifesaving test in 2012-13

Cancer Council has urged eligible Australians to participate in the National Bowel Cancer Screening Program, following the release of data in June that showed around 643,000 Australians threw away a free kit in 2012-13 that could have saved their lives.

The National Bowel Cancer Screening Monitoring Report 2012-13 shows that participation in the program fell to 33.5% of the 964,000 Australians invited to screen for the disease over the period.

Cancer Council Australia's Advocacy Director, Paul Grogan, said the low screening rate reflected a lack of awareness of bowel cancer. "People don't talk about bowel cancer, they do not realise it is the nation's second biggest cancer killer and they do not appreciate that a simple test for the disease can mean the difference between life and death," Mr Grogan said.

"On average, every 2½ hours another Australian dies of bowel cancer. Yet around 90% of cases can be cured if detected early."

Mr Grogan said that while participation was low, the good news was that the program was still saving lives and reducing unnecessary treatment costs.

"Thanks to the program, 400 Australians were diagnosed with a confirmed or suspected cancer that was twice as likely to be cured than someone who presents with symptoms and another 730 Australians had advanced adenomas removed that were at high risk of developing into bowel cancers," he said. "By increasing participation, we can build on these successes."

Cancer Council urges food industry to embrace Health Star Rating system

Cancer Council has congratulated Australia's food policy ministers in June for reiterating their support for the Health Star Rating system on front-of-pack food labels and called on the food industry to embrace the voluntary scheme.

Cancer Council spokesperson, Clare Hughes, congratulated the intergovernmental Legislative and Governance Forum on Food Regulation for announcing their renewed support for the Health Star Rating system, which will help Australians who want to improve their diets to make more informed choices about the packaged foods they purchase.

"We are facing a significant increase in cancers associated with poor nutrition and obesity, unless Australians make much healthier choices about the foods they purchase and consume," Ms Hughes said.

"Individual choices are only as good as the information on which they're based. The Health Star Rating system helps consumers identify healthier packaged foods at a glance. Healthier food choices translate to improved cancer outcomes across the population."

Ms Hughes said the level of take-up for the scheme would be reviewed in two years and, if it was not voluntarily adopted by the industry, a mandatory code would be introduced in five years.

Australian smoking rates at record lows

Cancer Council has announced that new data released in June showing a record fall in smoking rates confirms that Australia is on track to achieve major reductions in smoking-related diseases.

Chair of the joint Cancer Council/Heart Foundation Tobacco Issues Committee, Kylie Lindorff, said the new data, published by the Australian Institute of Health and Welfare, showed that only 12.8% of Australians aged 14 and over smoked daily in 2013.

The new data says that the proportion of Australians who smoke has dropped by 15% since 2010.

"These figures are a triumph of evidence-based public health policy, especially when you compare them with data from previous generations," Ms Lindorff said. "In the 1960s, more than half of all Australian men were smokers and nearly a third of women. Even in the mid-1990s, smoking rates were around double what they are now.

"This result is a tribute to successive Australian governments and to non-government health organisations that we have been able to reduce the proportion of smokers so dramatically with effective policies."

Ms Lindorff said that although the figures were welcome news, more than 2.4 million Australians continued to smoke daily, increasing their risk of developing 15 cancer types caused by smoking, cardiovascular disease and other potentially fatal conditions.

"We still have a lot to do before smoking is no longer the main preventable cause of cancer death in Australia, but these figures confirm we are heading in the right direction."

New report shows cancer one of the leading causes of alcohol-related deaths

A new report released in July showing that cancer was one of the leading causes of alcohol-related deaths in Australia, should help raise public awareness of alcohol as a significant cancer risk factor according to Cancer Council.

Professor Olver said the new report, *Alcohol's burden of disease in Australia*, published by the Foundation for Alcohol Research and Education and VicHealth, added to the growing evidence base that showed alcohol consumption was one of the most preventable causes of cancer.

"We have long known that alcohol causes as many cancer deaths in Australia as melanoma, yet the level of public awareness is low," Professor Olver said. "Australians who choose to drink should try to stay within the National Health and Medical Research Council guidelines and have no more than two standard drinks a day.

"There are plenty of good reasons to moderate consumption – and preventing cancer is one of the most significant.

"Today's report adds a new and alarming perspective by calculating that cancer is the cause 25% of all alcohol-related deaths in Australian men and 31% of alcohol-related deaths in Australian women – making cancer one of the leading causes of all alcohol-related deaths."

CLINICAL GUIDELINES NETWORK

Cancer Council Australia aims to produce concise, clinically relevant and up-to-date electronic clinical practice guidelines for health professionals. All guidelines are available on Cancer Council Australia's Cancer Guidelines Wiki platform (wiki.cancer.org.au).

Newly published guidelines

Clinical practice guidelines for the diagnosis and management of Barrett's Oesophagus and Early Oesophageal Adenocarcinoma

Following review of public submissions, the Barrett's Oesophagus Guidelines Working Party has finalised these guidelines, which were launched in September.

Guidelines in development

Clinical practice guidelines for PSA testing and management of test-detected prostate cancer

Cancer Council Australia, together with the Prostate Cancer Foundation of Australia, are planning to release the draft guidelines for public consultation at the UICC World Congress in December 2014.

Clinical practice guidelines for the prevention, diagnosis and management of lung cancer

Cancer Council is currently developing prevention and diagnosis guidelines for lung cancer to complement the treatment guidelines. The Lung Cancer Screening Guidelines Working Party has defined the guideline scope, formed topic groups and finalised the key clinical questions. The systematic reviews for the lung cancer screening guidelines are about to commence

Clinical practice guidelines for the management of melanoma

Planning for the revision of the 2008 melanoma guidelines began earlier this year, with guideline scope focusing on treatment of melanoma (including diagnosis and follow-up).

For this iteration of the melanoma guidelines, our Melanoma Management Committee is planning to adapt and update existing systematic reviews for all applicable clinical questions of the German S3 Melanoma Guidelines.

Guidelines on the wiki

Cancer Council's Cancer Guidelines Wiki (wiki.cancer.org.au) features the following cancer-based guidelines:

- *Clinical practice guidelines for the diagnosis and management of Barrett's Oesophagus and Early Oesophageal Adenocarcinoma*
- *Clinical practice guidelines for the treatment of lung cancer*
- *Management of apparent early stage endometrial cancer*
- *Clinical practice guidelines for surveillance colonoscopy*
- *Clinical practice guidelines for the management of adult onset sarcoma*
- *Clinical Practice guidelines for the management of locally advanced and metastatic prostate cancer*
- *Cancer pain management.*

Clinical Oncology Society of Australia guidelines on the wiki

- *NETs guidelines*
- *Head and neck cancer nutrition guidelines*
- *Early detection of cancer in AYAs*
- *AYA cancer fertility preservation*
- *Psychosocial management of AYA cancer patients*

For more information regarding the clinical practice guidelines program at Cancer Council Australia contact the Head, Clinical Guidelines on 02 8063 4100.

CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA, COSA

Annual Scientific Meeting (ASM)

The COSA ASM is upon us and has provided a unique collaboration with the Union for International Cancer Control (UICC). Staging our ASM with UICC's World Cancer Congress in Melbourne has presented many opportunities for both COSA and the UICC.

Our shared theme (which we adopted from the UICC) 'Joining Forces – Accelerating Progress' emphasises the impact that can be realised by consistently and energetically applying what we know, and what better way to do that than by coming together, sharing knowledge and learning from our peers.

It's important that we hear from our members so we can truly understand the success of the conference, therefore we look forward to the delegate evaluation. Feedback from delegates helps us plan for future conferences and provides COSA with valuable information about how we can support our members both in and outside the ASM.

I am pleased to announce that the 42nd COSA ASM will be held at the Hotel Grand Chancellor Hobart, 17-19 November 2015. The last time the ASM was held in Hobart was in 1997, so we are overdue for a visit to the Apple Isle. Drs Louise Nott and Allison Black, medical oncologists at Royal Hobart Hospital, have kindly agreed to act as convenors and are in the process of convening

their organising committee. We are also considering rare cancers as one of the ASM themes – a new but emerging area for COSA. This will likely be complemented by presentation on more common cancers to ensure the ASM program appeals to the broad COSA membership.

COSA Strategic Plan – July 2014 to June 2019

The new COSA Board has achieved a great deal in its first year of operation. In July 2014, we launched a new strategic plan to guide our activities for the next five years and enable us to report back to the members on our achievements.

Vision: Quality multidisciplinary cancer care for all.

Mission: To improve cancer care and control through collaboration.

Our four key strategic directions are:

1. Advocate for matters affecting cancer service delivery, policy and care.
2. Meet the educational needs of COSA's multidisciplinary membership.
3. Promote and facilitate cancer research.
4. Ensure the sustainability of COSA.

Guiding principles for COSA activities

As a membership organisation, COSA activities are driven by the needs of our members. The following guiding principles are intended to provide an overarching direction for all COSA activities

- COSA activities should have a multidisciplinary focus.
- COSA activities should have a clinical focus.
- COSA activities should have outcomes relevant to its members, patients and carers.
- COSA will act as a hub and facilitator for idea generation.

For more information about COSA activities and to view our strategic plan in full visit www.cosa.org.au

Marie Malica, Executive Officer

MEDICAL ONCOLOGY GROUP OF AUSTRALIA, MOGA

Oncology drugs, treatments and advocacy

The recently announced *Post-market Review of Authority Required Public Benefits Schedule (PBS) Listings* was identified in the Review of Chemotherapy Funding Arrangements, where it was found Authority Required listings caused significant regulatory burden to prescribing medical oncologists. There are 447 phone or complex authority required listings on the PBS, most relating to oncology. The review is considering criteria to determine, as well as reviewing all listings to reduce the administrative burden on prescribers and dispensers.

Key stakeholders include the Australian Medical Association, Royal Australian College of General Practitioners, Royal Australasian College of Physicians, Pharmacy Guild of Australia, Medicines Australia and MOGA. A/Prof Gary Richardson has been appointed to the Review Reference Group representing MOGA.

2014 and 2015 Annual Scientific Meetings

Integrating Molecular and Immunologic Advances into Practice was the theme of the 2014 MOGA Annual Scientific Meeting (Sydney Hilton, 6-8 August), which explored contemporary challenges and advances in medical oncology research, discovery and clinical practice. The meeting's focus on immunology, immunotherapy, biomarkers and genomics provided an opportunity for Australian medical oncology practitioners to review their role in managing cancer patients and how they guide drug development, as well as impact on targeted therapy. Professor Alison Stopeck (US) and Professor Klaus Pantel (Germany) provided perspectives on molecular and immunologic advances and related scientific and research trends. Sessions on specific tumour types include a symposium on lung cancer with Professor Ramaswamy Govindan (US). A highlight of the meeting was the launch of our Young Oncologists Group as part of a special education program.

The 2015 Annual Scientific Meeting (Hobart, 5-7 August) will be convened by Dr David Boadle, Staff Specialist in Medical Oncology at Royal Hobart Hospital. The theme is *Pathways in Medical Oncology - the path less travelled* and the program will focus on lesser covered areas of medical oncology practice and research, such as rare tumours and haematological malignancies.

ACORD and international activities

The Association received record applications for the 10th Anniversary *Australia and Asia Pacific Clinical Oncology Research Development Workshop (ACORD).* Seventy-two oncology professionals from the region have been selected to join the workshop (14-19 September, New South Wales Central Coast). The faculty of 25 Australian and international oncology professionals includes leaders in research and clinical practice from the American Association for Cancer Research, American Society of Clinical Oncology, NSW Cancer Institute and Clinical Oncology Society of Australia. Faculty and participants worked through an intensive program covering the design and conduct of clinical trials.

The Association recently signed a *Memorandum of understanding for co-operation in cancer research* with the Centre for Global Health at the National Cancer Institute (NCI) in the US. The agreement will foster collaboration in clinical research and development of health care

systems globally through exchange of knowledge, skills, technology, training programs and other activities.

The Association is pleased to have secured Professor James L. Gulley, Chief, Genitourinary Malignancies Branch Director, at the NCI as a guest speaker for the 2014 Annual Scientific Meeting.

Associate Professor Rosemary Harrup, Chairman

FACULTY OF RADIATION ONCOLOGY, RANZCR

RANZCR's 'Radiation Oncology: Targeting Cancer' campaign is progressing well. Targeting Cancer is an education campaign that seeks to improve the profile of radiation as a sophisticated cancer treatment.

We aim to ensure patients are aware of their treatment options, that primary care providers have all the information when referring a patient and that politicians and policy makers understand the importance of better funding for radiation therapy services.

Our website (www.targetingcancer.com.au) has patient and health practitioner resources, including information about the specialty, FAQs and a search function so patients can find their nearest treatment centre.

The Faculty will conduct information evenings for GPs, focusing on common cancer management issues.

You can support the campaign by:

- visiting our website and registering your support
- following on Twitter (@TargetingCancer)
- liking on Facebook (Radiation Oncology: Targeting Cancer)
- connecting via LinkedIn (Radiation Oncology: Targeting Cancer)
- requesting a resource pack through our website
- emailing us ideas and stories at info@targetingcancer.com.au.

Funding for radiation oncology services

In 2012, as part of the development of the Tripartite National Strategic Plan for Radiation Oncology, Allen Consulting was commissioned to undertake projections of the radiation oncology workforce in Australia.

The Faculty recently updated these projections, based on the recently revised target utilisation rate of 48.3% and data collected from our 2013 facilities survey. If the target utilisation rate is to be achieved by 2022, the model projects a shortfall of 10 full time equivalent radiation oncologists.

The 'A Career in Radiation Oncology Project', which promotes the roles of radiation oncologists, radiation therapists and radiation oncology medical physicists, was completed in May 2014. The project, funded by a Federal Government grant, was a great success in raising the profile of radiation oncology as a career option.

Regional radiation oncology services

Over the last decade, as a result of advocacy efforts by the sector, several regional cancer centres have been established in Australia. Although well received, there have been challenges – including workforce attraction and retention, ongoing education and research capabilities, quality treatment delivery, timeliness and availability of treatment options, and patients' perceptions about services they receive.

Through a comprehensive literature review and semi-structured interviews with staff from a number of regional centres, common core issues were identified and collated into a draft discussion paper, to be presented at a regional workforce workshop at the Combined Scientific Meeting in Melbourne in September 2014. With input from members of the three professions, we should be able to develop strategies to address some of these challenges.

Dr Dion Forstner, Dean, Faculty of Radiation Oncology



CALENDAR OF MEETINGS

AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
November			
8-11	15th Biennual Meeting of the International Gynaecological Cancer Society (IGCS)	Melbourne, Victoria	International Gynaecological Cancer Society Website: www.igcs.org Email: adminoffice@igcs.org Phone: +61 502 891 4575
11-14	Australasian Leukaemia & Lymphoma Group (ALLG) Annual Scientific Meeting 2014	Sydney, New South Wales	Australasian Leukaemia and Lymphoma Group Website: www.allg.org.au/events.html Email: dilupa.uduwela@petermac.org Phone: +61 9656 9011
16-19	Australian Health and Medical Research Congress	Melbourne, Victoria	ASN Events Pty Ltd Website: www.asnevents.net.au Email: eg@asnevents.net.au Phone: +61 3 5983 2400
26-28	Sydney Cancer Conference 2014	Sydney, New South Wales	Cancer Research Network Website: www.sydney.edu.au/cancer-research/SCC2014/ Email: merilyn.heuschkel@sydney.edu.au Phone: +61 2 8627 1532
December			
2-4	Clinical Oncology Society of Australia's (COSA's) 41st Annual Scientific Meeting	Melbourne, Victoria	ASN Events Pty Ltd Website: www.asnevents.net.au Email: eg@asnevents.net.au Phone: +61 3 5983 2400
4-6	Union for International Cancer Control (UICC) World Cancer Congress	Melbourne, Victoria	Union for International Cancer Control Website: www.worldcancercongress.org Email: congress@uicc.org Phone: +41 22 809 1834
2015			
February			
6-7	Flinders Survivorship Conference 2015	Adelaide, South Australia	ASN Events Pty Ltd Website: www.asnevents.net.au Email: eg@asnevents.net.au Phone: +61 3 5983 2400
March			
15-18	Australian Pain Society 35th Annual Scientific Meeting 2015	Brisbane, Queensland	DC Conferences Pty Ltd Website: www.dcconferences.com.au/aps2015/ Email: aps2015@dcconferences.com.au Phone: + 612 9954 4400
25-28	Australia New Zealand Gynaecological Oncology Group (ANZGOG) Annual Scientific Meeting 2015	Gold Coast, Queensland	ANZGOG Website: www.anzgog.org.au Email: enquiries@anzgog.org.au Phone: +61 2 8071 4880
April			
11-14	Urological Society of Australia and New Zealand (USANZ) 68th Annual Scientific Meeting	Adelaide, South Australia	To be announced

May			
4-8	Royal Australian College of Surgeons Annual Scientific Meeting 2015	Perth, Western Australia	*Royal Australian College of Surgeons* *Website: http://asc.surgeons.org/* *Email: asc.registration@surgeons.org* *Phone: +61 3 9276 7431*
24-27	13th National Rural Health Conference	Darwin, Northern Territory	*National Rural Health Alliance* *Website: http://www.ruralhealth.org.au/* *Email: conference@rural health.org.au* *Phone: 02 6285 4660*
November			
17-19	Clinical Oncology Society of Australia's (COSA) Annual Scientific Meeting 2015	Hobart, Tasmania	*ASN Events Pty Ltd* *Website: www.asnevents.net.au* *Email: eg@asnevents.net.au* *Phone: +61 3 5983 2400*

INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
November			
6-7	2nd Breast Cancer in Young Women Conference (BCY2)	Tel Aviv, Israel	European School of Oncology Website: www.eso.net Email: efiore@eso.net Phone: +39 02 85464529
December			
9-13	37th Annual San Antonio Breast Cancer Symposium	San Antonio, United States	Rich Markow, Director Website: Email: sabcs@uthscsa.edu Phone: 210 450 1550
12-14	4th International Gastrointestinal Cancer Conference	Istanbul, Turkey	Serenas Tourism Congress Organization and Hotel Management Co. Website: http://igicc2014.org/ Email: betul.cucen@serenas.com.tr Phone: +90 312 440 50 11
2015			
March			
23-4	Pain and Palliative care for Patients with cancer training	Monastir, Tunisia	To be announced
September			
16-19	18th Reach to Recovery International Breast Cancer Conference	Beijing, China	Reach to Recovery International Website: www.reachtorecoveryinternational.org/ Email: info@reachtorecoveryinternational.org Phone: +61 7 3634 5100

CANCER COUNCIL AUSTRALIA

Cancer Council Australia is the nation's peak independent cancer control organisation.

Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.

MEMBERS

Cancer Council ACT
Cancer Council New South Wales
Cancer Council Northern Territory
Cancer Council Queensland
Cancer Council South Australia
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia

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Ms O Stagoll OAM
Prof G Yeoh

CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA

The Clinical Oncology Society of Australia (COSA) is a multidisciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.

It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with Cancer Council Australia.

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MEMBERSHIP

Further information about COSA and membership applications are available from:

www.cosa.org.au or cosa@cancer.org.au

Membership fees for 2014
Medical Members: $170
Non Medical Members: $110 (includes GST)

COSA Groups

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Neuroendocrine Tumours
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Nutrition
Paediatric Oncology
Palliative Care
Psycho-Oncology
Radiation Oncology
Regional & Rural Oncology
Social Work
Surgical Oncology
Survivorship
Urologic Oncology

Information for contributors

Cancer Forum provides an avenue for communication between all those involved in cancer control and seeks to promote contact across disciplinary barriers. To this end, articles need to be comprehensible to as wide a section of the readership as possible. Authors should provide sufficient introductory material to place their articles in context for those outside their field of specialisation. *Cancer Forum* is primarily a review journal, with each issue addressing a particular topic in its 'Forum'. The Forum topic and appointment of Guest Editor(s) are determined by the Editorial Board, which welcomes suggestions. Proffered papers containing primary research findings will be considered for publication in *Cancer Forum* in limited circumstances. Articles will be considered by the Editorial Board and then published subject to two peer-reviews. Generally speaking, authors are encouraged to submit their primary research findings to established cancer research or clinical oncology journals. The following information is provided for contributors invited to prepare manuscripts for *Cancer Forum*.

Format

Prospective authors are encouraged to examine recent editions of *Cancer Forum* for an indication of the style and layout of Forum papers (www.cancerforum.org.au). All manuscripts should be submitted by email to the Forum's Guest Editor(s) and Executive Editor (rosannah.snelson@cancer.org.au) as MS Word documents.
Length: 2000-2500 words.
Font: Arial - 20pt and bold for title, 12pt and bold for headings, 12pt and italics for subheadings and 10pt for text.
Following the title, include your full name, organisation and email address.
Include introductory headings and sub-headings that describe the content.
Number pages in the footer.

Abstract

All manuscripts must include an abstract of approximately 200 words, providing a summary of the key findings or statements. No references or abbreviations should be included in the abstract.

Abbreviations and acronyms

Abbreviations and acronyms should only be used where the term appears more than five times within the paper. They must be explained in full in the first instance, with the abbreviation in brackets.
The Editorial Board reserves the right to remove the heavy use of abbreviations and acronyms that may be confusing to the diversity of our readership.

Photographs, tables and graphs

Photographs and line drawings can be submitted via email, preferably in tiff or jpeg format. If images are not owned by the author, written permission to reproduce the images should be provided with the submission. A maximum of five illustrations and figures and three tables can be submitted with the manuscript. Inclusion of additional items is subject to approval by the Editorial Board. Unless otherwise specified by the authors or requested by the Editorial Board, all images, graphs and tables will be printed in black and white. All figures – including tables and graphs – will be reproduced to *Cancer Forum's* style. Figures containing data (eg. a line graph) must be submitted with corresponding data so our designers can accurately represent the information. Figures and images should be labelled sequentially, numbered and cited in the text in the correct order e.g. (table 3, figure 1). Tables should only be used to present essential data. Each must be on a separate page with a title or caption and be clearly labelled.

Referencing

Reference numbers within the text should be placed after punctuation and superscripted. The maximum number of references is 75. Only papers closely related to the subject under review should be quoted and exhaustive lists should be avoided. Only one publication can be listed for each number. Citation of more than one reference to make a point is not recommended. The Editorial Board prefers a focus on more recent references (in the last 10 years). The list of references at the end of the paper should be numbered consecutively in the order in which they are first mentioned and be consistent with the National Library of Medicine's International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals. i.e. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.

A full guide is available at www.nlm.nih.gov/bsd/uniform_requirements.htmlA guide to abbreviation of journal names can be found at https://www.library.uq.edu.au/faqs/endnote/medical_2010.txt

The Editorial Board will make the final decision on inclusion of manuscripts and may request clarifications or additional information.

For further information or confirmation of the above, please contact:

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