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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