NATIONAL BREAST CANCER FOUNDATION
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Challenging Breast Cancer:

A National Action Plan for Breast Cancer Research and Funding

October 2004

Challenging Breast Cancer: A National
Action Plan for Breast Cancer Research and Funding.
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Foreword

In 2002, the National Breast Cancer Foundation (NBCF) organized a series of national consultations as the first step in setting priorities for research into breast cancer. The resulting document *Breast cancer research in Australia: Meeting the challenges*[1] identified several important issues – in particular, the lack of a national cancer research strategy, the lack of connection between funding policies and research goals, and the inability to monitor progress. Many of the findings and recommendations in the NBCF document are similar to those of two other reports produced by other organizations *"Breast cancer research in Australia: Current research and future priorities"* (NHMRC National Breast Cancer Centre 1996)[2] and *Cancer research in Australia – A survey of cancer researchers* (2004)[3] (National Cancer Control Initiative). All three publications describe in considerable detail both the achievements and strengths as well as the gaps and impediments to Australian cancer research in general and breast cancer research in particular.

An important goal of NBCF is to ensure that, as a community, we utilise and build on Australia's unique strengths to take breast cancer research forward as rapidly and efficiently as possible. Consequently, following the publication of *Breast Cancer Research in Australia: Meeting the Challenges*[1], the NBCF decided to develop and promote a National Plan for breast cancer research.

Challenging Breast Cancer: a National Action Plan for Breast Cancer Research and Funding, drawn up by a group of experts in fields across the breadth of the breast cancer continuum, is a far-reaching document that defines priorities, sets goals and suggests structural changes that will accelerate and enable Australia's effort in breast cancer research. The plan focuses on actions that will, if realistically resourced, have a significant impact on our understanding of the causes of breast cancer and thus lead to strategies to prevent, detect and treat the disease. A key proposal is the formation of an alliance of Australia's breast cancer funders to act as an umbrella to implement the plan and be responsible for its ongoing development, for continued funding and for monitoring the national effort in breast cancer research. The plan therefore issues a challenge to Australia's cancer funding agencies to commit to and sustain a national, collaborative approach that NBCF believes also has the potential to inform research into other types of cancers.

Despite the talent and enthusiasm of the Australian research community, it is clear that this country is not in a position to lead the world in all aspects of breast cancer research. We must concentrate on what we are well placed to do and we must do it better. We believe that this plan tells how these goals can best be achieved.

Jenni Neary
Chair

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PHOTOGRAPHY
Naomi Eddy

6 Executive Summary

The purpose of this plan is to determine how best to facilitate research that will generate the knowledge necessary to reduce the burden of breast cancer in Australia. Breast cancer prevention remains the ultimate goal. However, until that is achieved, more sensitive approaches to detection and more effective treatment are necessary to improve prognosis and survival. Moreover, with the increasing numbers of women diagnosed with and surviving breast cancer, research into subsequent recovery and quality of life has become paramount.

The more we find out about breast cancer, the more complex the disease appears. Despite the appearance of similar clinical symptoms, the heterogeneous nature of the underlying biology suggests that breast cancer arises as a consequence of multiple causes and that very specific treatments may be necessary to most effectively control disease. This requires a different approach to research, with an emphasis on larger numbers and greater coordination to capture and adequately characterise the diversity of disease pathways that comprise breast cancer. Massive advances in molecular biology and associated technology during the past few years have supplied a range of tools to make this research possible. However, it is very difficult in Australia to take full advantage of current research opportunities due to our system of managing and funding research.

Progress in breast cancer research is hampered by the absence of strategic planning and coordination among funding agencies, health service providers, consumers, and researchers. This conclusion has been endorsed in reports produced by the NHMRC National Breast Cancer Centre, the National Cancer Control Initiative, and the national consultation process sponsored by the National Breast Cancer Foundation (NBCF) in 2002. Moreover, Australia lags behind the USA, UK, and Canada, all of whom have developed more coherent cancer research policies in recent years. The NBCF therefore invited a group of experts across the spectrum of breast cancer research to produce an action plan that defines priorities, sets goals, and suggests structural changes that would enable and enhance Australia's efforts in breast cancer research.

Due to the multidisciplinary nature of breast cancer research and competing priorities across the continuum of the disease process, it was simply not possible to generate a list of research projects that, if implemented, would lead to certain prevention or cure. Instead, it became apparent that modifications to the way breast cancer research is funded, implemented, and monitored would facilitate strategic thinking, optimise use of available resources and expertise, and accelerate progress toward understanding the disease and ultimately eliminating breast cancer. Proposals were articulated by the Expert Advisory Committee, circulated to the research community and other stakeholders for comment and discussion, and subsequently revised.

Twelve specific actions have been put forward, as follows:

A1 Establish an alliance of breast cancer funders, which would create opportunities to attract new funds, eliminate donor confusion, monitor progress in breast cancer research, improve accountability and communication between researchers, serve as a political advocate for breast cancer, and potentially generate and implement research policy

B1 Sustain and create long-term, large-scale projects that are national in scope and character, take advantage of Australian strengths, are internationally competitive, address questions relevant to prevention or cure of breast cancer, and have the ability to generate many add-on or downstream research projects

C1 Establish and maintain a national bank of comprehensively annotated breast tumours and relevant normal tissues, available for ethically-approved, peer-reviewed research

C2 Create a database of breast cancer research and funding that classifies grants by internationally-recognised coding systems and includes project goals, summaries, timelines, outcomes, and publications

C3 Distribute a biennial report on the status of breast cancer research in Australia that measures past progress against pre-determined milestones and recommends changes in strategy or priorities for future progress

C4 Implement a program to fund research projects addressing truly novel ideas that, even if considered high risk, have the potential to produce important new insights or approaches that could change the course of breast cancer research

C5 Facilitate national and international research collaborations by providing short-term support for travel and living costs

C6 Expand the number of fellowships to alleviate the shortage of researchers in key areas and to encourage early-career researchers to consider a career in breast cancer research

C7 Develop a more coherent community of breast cancer researchers by promoting a biennial national meeting designed to bring together researchers across the continuum for presentation and discussion of projects and findings and by facilitating other means to enhance communication and exchange ideas

C8 Establish two grant review cycles per year to increase the responsiveness of the granting process and speed delivery of benefits to the Australian community

C9 Facilitate translation of research into practical outcomes, including development of new models to improve implementation of clinical trials and to accelerate production of evidence-based clinical guidelines

C10 Simplify access to biospecimens and medical information by streamlining the processes of informed consent and ethical review and by harmonising legislation governing access to data from cancer registries

We believe that implementation of the changes and actions proposed in this plan will not only bring pivotal advances in fundamental knowledge but will also achieve significant improvements in breast cancer prevention and treatment.

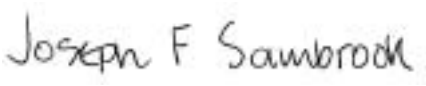
8 Discovering What is Not Yet Known

Breast cancer is a disease driven by hormones – that much has been known since the days of George Beatson more than 100 years ago.[4] It took a further 50 years of careful work to show that ovarian hormones not only promote growth of breast cancers but also influence many other aspects of the disease: its etiology, its treatment and its prevention. But by the early 1970's, when the modern era of biological research into cancer began, breast cancer was still a blank slate in molecular terms and we lacked the fundamental knowledge necessary to reduce the impact of the disease on women's lives. The only sensible course was to invest heavily in basic research, driven by the imaginations of individual scientists and clinicians, whose aim was to discover the magnitude, dimensions and major features of the unknown.

These people did their work well. We now know a great deal about the lifestyle and genetic factors that influence the risk of developing breast cancer, the disruptions in cellular processes that contribute to the development and progression of the disease, and why some breast cancers respond to drugs and others do not. We are having increasing success in translating these discoveries into tangible benefits for women: better prevention, more accurate diagnosis and prognosis, improved therapies, more effective psychosocial support, and extended cancer-free survival for those continuing to live with the disease.

Breast cancer however, continues to strike the Australian community indiscriminately and often. It robs families of their mothers, daughters, sisters, aunts, and wives; it kills fathers and sons; it affects women of all ages, races, and socio-economic groups. In 2002, 11,314 Australian women developed breast cancer and 2,521 died of the disease, despite improvements in survival following diagnosis. The best efforts of researchers notwithstanding, breast cancer remains the most common form of cancer in women. Researchers now need to ask what it will take to finish the job. Is our depth of knowledge still so shallow that we should continue to emphasize basic research? Do we know enough to begin to chart a course towards a more certain cure?

As this plan says, the answer to both questions is yes. We may already know a great deal, but no-one would pretend that we understand enough to offer women certain protection from the disease, nor a certain return to health should they develop breast cancer. Consequently, we need to sustain and, if possible, expand our investment in investigator-initiated basic research. But we must also use the explosive advances in laboratory technology of the last 10 years to test the value of our accumulating knowledge in larger-scale research projects with defined goals and end-points. To pursue both strategies effectively will mean changes to the ways that breast cancer research is planned, funded, performed and monitored in Australia. We believe that the changes and actions proposed in this plan should be welcomed both by researchers and by the wider community. They will not only bring pivotal advances in fundamental knowledge but will also achieve the significant improvements in breast cancer prevention and treatment that until now have been beyond our grasp.



Joseph F Sambrook PhD FAA FRS
Chair
Expert Advisory Committee

9 Introduction

Few would dispute the importance of breast cancer as a major source of morbidity in Australia. Despite over 100 years of research and continuous improvements in detection and treatment, this disease remains an important challenge to women and health professionals alike. A review of statistics quantifying the burden of illness provides convincing evidence of the undiminished need for ongoing research.

In 2000, Australia's incidence of breast cancer was ranked 5th in the world, following The Netherlands, USA, Denmark, and France[5]. Currently, women in Australia have a 1 in 11 risk of developing breast cancer before age 75 years[6]. Thus, each year over 11,000 women and their families are confronted with the dreaded news of breast cancer. Friends, colleagues, employers and others in the community are inevitably touched by the diagnosis. Men also can develop breast cancer, but the risk among women is 100-fold higher than among men. Yet, we still do not fully understand how breast cancer develops in women nor what we can best do to prevent it.

Breast cancer is the fifth leading cause of death among Australian women, accounting for over 2,500 deaths in 2000. It is the leading cause of death for women aged 45-64 years and third among women 25-44 years[7]. Annually, these deaths account for a cumulative 28,305 years of life lost (before age 75)[8]. In the absence of prevention, improvements in our ability to detect breast cancer early, particularly among younger women, and more effective treatment are the best options for preventing this premature mortality.

Despite this substantial loss of life due to breast cancer, prospects for survival are better than ever. Currently in Australia, over 90% of women diagnosed with breast cancer will survive for at least 2 years, and 84% will survive for 5 years or longer[8]. Although this accomplishment is worthy of celebration, breast cancer survivors often encounter problems ranging from physical limitations to psychosocial difficulties following their diagnosis and treatment. Only recently have researchers begun to systematically study the recovery pathways experienced by women. Additional attention is also warranted to develop effective means for rehabilitation and for enhancing health-related quality of life following breast cancer.

Although risk is higher in developed nations, the numbers of women diagnosed with breast cancer and dying from the disease are also substantial in developing nations. Worldwide, over 7.1 million deaths were attributed to cancer in 2002[9]. Among women, breast cancer is the leading cause of cancer death, accounting for 1.05 million new cases and 373,000 deaths in 2000[5]. With economic development, the rate of breast cancer is anticipated to increase further. Hence breast cancer clearly represents a health problem of significant international importance.

This action plan was commissioned by the National Breast Cancer Foundation to determine how we might best proceed in Australia to facilitate much-needed research into the causes, diagnosis, treatment, and outcomes of breast cancer. The scope of research across the breast cancer continuum crosses disciplinary boundaries and hence we invited a range of scientists and clinicians to assess the status of research in their areas of expertise, as well as strengths and limitations to conducting future research in Australia. Concurrently, a critical appraisal was conducted to identify the most productive areas of research in Australia based on publications in the scientific literature.

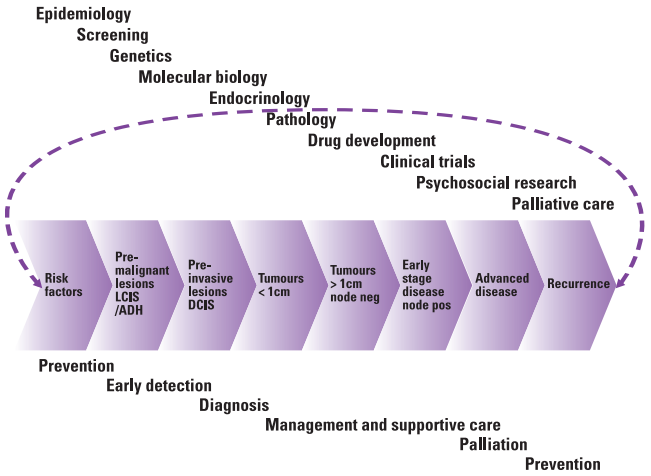
It would be everyone's hope that we could set a course that would lead to certain prevention or cure of breast cancer. In reality, however, our current state of knowledge of the disease is not yet sufficiently deep or extensive to allow us to do so. Breast cancer takes many forms and we now understand that a single solution for such a complex disease is unlikely. Research has already brought us far but the challenges ahead are formidable. So instead of generating the usual lists of specific research projects, the Expert Advisory Committee decided to take a bolder course and to recommend structural changes and reforms to the way that breast cancer research in Australia is organized, implemented and monitored. We believe that these structural changes, many of which have already been set in place in other countries, will enable Australia to use its scientific and medical strengths to best advantage, will benefit all aspects of breast cancer research and, most importantly, will accelerate progress towards prevention and cure of a disease that we all want eliminated from our lives.

10

Dr Nik Zeps

The Breast Cancer Continuum: A Survey of Research

RESEARCH



As the illustration of the breast cancer continuum shows, breast cancer research encompasses a broad range of disciplines with multiple areas of overlap. While research focused specifically on the breast has been with us for about 100 years, the major growth in this area has been over the last three decades. During this time there have been major advances including advances in surgical techniques, the introduction of breast cancer screening (mammography) and effective new treatments with cytotoxic and endocrine drugs. In addition, our understanding of the cellular biology and molecular genetics of breast cancer has expanded exponentially with global advances in understanding how breast cells function and how disruption of these functions can lead to cancer. Importantly we also have a better comprehension of public health issues related to increased risk of developing breast cancer, and insights into the psychosocial well being of women are providing real improvements in our community health. The combined effect of these advances has been a decline in the mortality from breast cancer, first evident in the 1990s.

As a consequence of the dramatic increase in the complexity and power of the tools available to probe human biology at its most fundamental level, the research landscape has changed irreversibly. Breast cancer research is now done on a scale, and at a speed hitherto unimaginable, by research teams that span the globe and encompass all components of the breast cancer continuum. Australia's contribution to the world-wide effort to understand the fundamental biology of breast cancer has been in proportion to the number of researchers involved and the comparatively low amount of available funding. Australian-initiated publications on laboratory-based breast cancer began in the 1980s, and over the course of the following 25 years, Australian researchers have added significantly to the international body of knowledge on the modes of action of ovarian hormones, on cell growth and immortalization, on cell-cycle regulation of breast cancer cells and on the epidemiology of breast cancer. In addition, during the last two decades, Australian researchers have pioneered new areas that include, for example, the psychological and social welfare of women affected by breast cancer and the genetic epidemiology of the disease. However, fundamental breast cancer research is now a world-wide effort and each major step forward inevitably reflects the sum of many individual contributions. Defining Australian-specific research contributions within a global context is no easy task and may well be undesirable.

In the following pages, members of the Expert Advisory Committee and invited contributors survey the current state of research in various components of the breast cancer continuum. The survey consists of twelve brief documents, beginning with a description of research into the epidemiology and etiology of breast cancer, proceeding along the continuum and ending with a discussion of research into palliative care aspects of the disease. Although not exhaustive, this cross-section of research foci illustrates the diversity of important issues still requiring resolution.

Australian breast cancer research draws much strength and encouragement from the dedicated involvement, political activism and unstinting support of the community of women and men who have been affected by the disease. However, the opportunities for this community to participate in policy decisions and strategic planning of research have been limited. The membership of the Expert Advisory Committee included two consumer representatives who, in the final segment of this survey, suggest ways in which the breast cancer community can have a stronger voice in the future in both the planning and execution of research.

A table summarising the strengths, weaknesses, goals and priorities for each area of breast cancer research in Australia (including consumer involvement) may be found at the end of this section of the report (pages 38 – 43).

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Professor Beth Newman

Epidemiology and Prevention

The long-term goal of epidemiological research must be to reduce the burden of breast cancer by linking women's exposure histories to their underlying physiological and genetic make-up and hence to develop effective strategies to prevent disease, delay mortality, reduce disability, and enhance quality of life among survivors.

Epidemiology traditionally focuses on etiology, or identifying the causes of disease. The incidence of breast cancer differs among subgroups of women, defined by age, ethnicity, race, reproductive history and a range of other characteristics. These differences can be exploited to probe the underlying physiological, genetic and environmental interactions central to breast cancer risk. While these factors are associated for the most part with only modest increases or decreases in lifetime risk, and have so far failed to yield concrete advances in the primary prevention of breast cancer, there are reasons to be optimistic about the future.

Over the past five years, data from available studies worldwide have been pooled analytically to provide more robust estimates of risk associated with various exposures and to allow more systematic exploration of subgroups of women. As a consequence, we now have better ideas than ever about the extent to which family history of breast cancer, reproductive history, body size, use of exogenous hormones, and alcohol consumption contribute to breast cancer risk. Similar approaches are starting to clarify the roles of diet, tobacco, medications (including vitamin supplements and non-steroidal anti-inflammatory drugs), endogenous hormonal status and physical activity. Although some new risk factors are under study, an encouraging development is the initiation of intervention studies to reduce the occurrence of breast cancer (eg, diet, physical activity, use of NSAIDs).

Importantly, the etiologic heterogeneity of breast cancer is now recognised in that many factors confer varying degrees of risk depending on the women's status, for example, whether they are pre- or post-menopausal or whether their tumours contain oestrogen and progesterone receptors. Other tumour markers also have begun to be evaluated. This has reinforced the potential importance of inherited genetic susceptibility in determining the subsequent influence of environmental and behavioural exposures. Few people doubt that interactions between genetic and environmental factors may be the key to the etiology of breast cancers. In recent years, large numbers of candidate genes with relevant biological function have been catalogued. The challenge is to understand how the expression of these genes and the activity of their protein products are modified by environmental factors.

Epidemiology is equally useful to explore the natural history of disease, including pre-clinical stages and the recovery process following diagnosis and treatment. Increasingly, interest is shifting to the study of precursor states before the development of invasive breast cancer. Several studies currently focus on the interplay of environmental and genetic factors in the development of breast carcinoma *in situ* – both ductal and lobular. Perhaps of more significance has been the attention paid to the breast's composition of glandular, stromal, and fatty tissue, which can be measured from the image taken during mammography. This characteristic, known as breast density, is now recognised as one of the strongest risk factors for breast cancer. The genetic and lifestyle factors that influence breast density are currently the focus of intense investigation.

A relatively new area in breast cancer epidemiology addresses the period following diagnosis and treatment. This research describes the nature and extent of disability, functional impairment, psychosocial distress, and health-related quality of life among breast cancer survivors. These findings provide important information for future rehabilitation programs and support services.

Strengths and weaknesses of epidemiological research in Australia:

The results of epidemiologic research can be transposed in a reasonably faithful fashion between economically-developed countries. Although there may be some environmental/lifestyle exposures that are idiosyncratic to Australia, most risk factors are comparable to those of other westernised populations. However, questions related to the natural history of disease are sensitive to the social and health service context, including the delivery of interventions, and hence require work specific to Australia. In addition, Australia has resources/settings that offer the best opportunity of solving wider epidemiologic questions. These include:

- *Population-based studies* (ABCFS/BCFR, Melbourne Collaborative Cohort Study, etc) of environmental, genetic and physiological factors affecting the broad range of breast cancers

- *KConFaB* – for analyses of environmental and physiological influences on women who are at very high genetic risk of developing breast cancer
- *BreastScreen (the national mammographic screening program)* – for a variety of questions related to carcinoma in situ, assessment of risk and detection of interval cancers, and determinants of breast density.

Australia has demonstrated past success and is exceptionally well-suited to long-term, multi-disciplinary studies of this type because:

- It has population-based cancer registries and concentrated sources of medical care that enhance the possibilities for recruitment into studies
- There are cadres of well-trained, internationally-recognised epidemiologists and molecular biologists who are convinced of the benefits of working across disciplinary lines; and
- The practice of not requiring investigator salaries from research grants means that research can be carried out more cheaply in Australia than in other westernised countries.

Goals and Priorities

Understandably, most epidemiological research in Australia has sought to establish *causal relationships* between environmental, behavioural and genetic factors and the incidence of breast cancer. That remains a high priority. However, the value of epidemiology has begun to expand in a variety of ways by searching for factors, both environmental and genetic, that inform strategies for earlier detection of breast cancer and that influence prognosis and health-related quality of life. Because these large-scale epidemiological projects require easier and seamless access to cancer registries, medical records, death records and archival pathological samples, they would be best implemented as part of a National Plan to translate the results of epidemiological research into clinical and public health practice.

Professor Alan Rodger

13 Screening for Breast Cancer

Population-based breast screening has an established, evidence-based place in screening women from age 50-69 years. This evidence base from randomised controlled trials (RCTs), meta-analyses and systematic reviews has reached varying conclusions. However, several consensus and overview groups have confirmed the value of mammographic screening if at least 70% of the target population can be screened. The benefit is a 30% reduction in mortality from breast cancer.

There are now screening programs in a number of countries, including Australia. These programs vary in a number of ways:

- Funding
- Frequency of screening
- Number of mammography views
- Number of readers of mammograms
- Target age group(s)
- Recall to assessment criteria
- Assessment processes
- End-point of the screening program process e.g. diagnosis or treatment.

Many of the decisions that have caused these variations are arbitrary and are often based on political and/or financial issues and/or acceptability to the stakeholder groups such as medical practitioners. However, while RCTs have produced the evidence that supports such programs in women over 50 and under 70, the variations have not been fully tested.

LOWER AGE OF SCREENING TARGET GROUP

There are RCTs, for example in the UK, researching the value of mammographic screening in those aged 40-49. Other prospective studies may be useful to complement these. They could be based on audit of current Australian programs, which can include this age group.

This group may also be amenable to technology assessment (see below).

UPPER AGE OF SCREENING TARGET GROUP

There are probably no RCTs investigating the value of screening in those over 70 yet the Australian program accepts such women. This group will increase as more women 50-69 are screened and choose to remain in the programs. Again, high quality prospective audit of this increasing cohort should address the issue of acceptability, detection rate and outcome in terms of survival/mortality.

THE HIGH RISK GROUP

As more evidence accumulates to identify and assess women in high risk groups due to family history (or previous benign disease) studies are required to determine the most appropriate surveillance. While it is possible at present to screen for BRCA1 and BRCA2 mutations (and no doubt others in due course), the best and most effective surveillance program for those shown to be at high genetic risk remains unknown . The situation of those at highest genetic risk brings both practical challenges and research opportunities. While the sensitivity and specificity of mammography may be less in this generally younger age group and the dangers of ionising radiation are potentially higher, this cohort offers opportunities to consider evaluating the place of nonionising radiation e.g. MRI or ultrasound.

ACHIEVING PARTICIPATION TARGETS

From the results of RCTs and meta-analyses, it is generally accepted that a participation rate of 70% in the prime target age group (50-69 years) is essential if the mortality reduction of 30% that has been delivered in those trials is to be achieved. The breast screening registry reports from around Australia would suggest that target has not been achieved. Because of Australia's many demographic and geographic variations (Indigenous, migrant, non-Indigenous Australian-born, non-English speaking, metropolitan, suburban, regional city, rural) there is enormous scope for research studies to address this question. Thus, while participation across these spectra can be measured from BreastScreen Australia's state and federal registries, variations in uptake of screening and the reasons for such can be explored in detail. The aim, of course, is to explore ways to improve participation.

IMPROVING IMAGING SENSITIVITY, SPECIFICITY AND ACCEPTABILITY

Mammography has been the mainstay of breast screening for over half a century. Other methodologies have been explored in prospective studies and in RCTs. Thus clinical examination and breast self-examination have been shown to be inadequate in terms of breast screening where the aim has been to reduce mortality from breast cancer. Attempts to avoid ionising radiation with relatively cheap and accessible technologies have also failed. Thus, thermography

has failed to show the required benefits. Ultrasound has a role in breast screening but only, to date, as a complement to mammography to assist or clarify diagnosis.

Medical Resonance Imaging (MRI) is being studied particularly in younger women who are known to have dense breasts. The whole area of investigation of breasts with radio-dense parenchyma (e.g. younger women, those on hormone replacement therapy) is ideal for further research – of MRI (a relatively costly and less accessible format) and of digital radiography (itself using ionising radiation). The technology of digital radiological imaging allows many possibilities of image interrogation and should be examined urgently for breast screening.

Mammography is generally uncomfortable and can be painful because of the compression required to ensure adequate imaging of as much breast tissue as possible. Techniques that could minimise pressure and hence pain should be explored.

OPTIMAL PROGRAM PROTOCOL

As stated above many aspects of a breast screening program protocol have developed not from best evidence but from financial and/or political considerations. While it is crucial to research the target age groups and the technology questions listed above, the Australian programs could lend themselves to study of:

- Number of views, especially if better imaging technologies can be explored
- Who read mammography images and how many readers are optimal
- Criteria for recall to assessment
- Linkages with the rest of the healthcare system.

BREAST DISEASE IN THE SCREENED POPULATION

Those who attend for screening are well-women. A small percentage will become patients as a result of the screening process. Those agreeing to screening do not, by definition, also agree to become subjects of research. Nevertheless, data are collected with patient consent. That process is an essential element of outcome audit. However, it is appropriate to approach the women in the screened population and particularly those diagnosed with breast cancer to allow the study of epidemiological and aetiological and other factors that may affect screening specificity/sensitivity or prognosis.

Strengths and weaknesses

- There are no current RCTs in Australia. In the UK RCTs are exploring the younger age group (less than 50 years of age) and the role of MRI in high-risk groups
- Research initiatives are often haphazard, with no direct planning or organisation by breast screening programs
- There may be a tendency to rivalry between groups, specialties or programs within a state or between states
- Consumer advisors to screening programs are often considered to be overly protective of well-women and, hence, are perceived to inhibit research initiatives
- The corollary is that consumer advice often ensures that any research is likely to be acceptable and ethical and achievable and desirable
- The registry databases of the breast screening programs are comprehensive and offer a wealth of already agreed data for analysis
- There is general enthusiasm among program staff to engage in both research and audit
- Some programs may have inadequate levels of statistical advice systems and staff.

Levels and sources of funding

There are minimal, if any, ring-fenced monies available to screening programs in Australia for research. State programs allocate to individual program budgets for screening, assessment, administration, preparation for accreditation, audit and equipment replacement. State governments have not seen it as their role to finance, in addition to this, a research component.

Funding, therefore, is "available" to researchers from both within and outside the programs through the peer-reviewed competitive grant system of such bodies as:

- NHMRC
- NBCF
- State Cancer Councils
- VicHealth and similar bodies in some other states.

Competition for grant support, a lack of a planned, agreed collaborative research program at either state or federal level and a lack of insight by governments in valuing and prioritising this research mean that what money is allocated may not be used to its best advantage.

Impediments to progress

The following are some of the impediments to progress:

- There is no program with clear priorities for research agreed by those involved in breast screening and the state programs
- Outside the program there is a similar lack of coordination of research
- The lack of dedicated funding and the need for all researchers to compete for those grants that are available will impede research in this field
- Governments seem content to have addressed the public health issue of providing funds for the screening program. Perhaps because there is no further political gain and because there is generally cross-party support for these programs, governments at both state and federal level – and their officials – seem disinclined to direct and fund and encourage research into areas that may either increase the target population (as it would cost more money) or to improve the quality by technological advance, which will also cost more. They also seem oblivious to the fact that such research could lead to a better, leaner program that costs less
- The clear impression the federal health department does not wish to be involved in directing and supporting the program.

Comparisons with other countries

The UK established the first national and nationally-funded mammographic breast screening program in the world. It had funded 2 trials and assessed the results of trials from other countries. Since implementing the program, the UK has instituted RCTs addressing the place of screening in younger women; the role of MRI in high risk women; and through the program, major outcome reviews. The latter has led to changes in the program across the UK.

Sweden has delivered several RCTs in screening and they continue to address the value of screening in various age groups. Outcomes continue to be measured in a variety of prospective and retrospective studies involving the screened population.

By comparison, in Australia the research that occurs is small, meagrely funded and researcher-driven rather than health department or screening programs directed.

Goals and priorities

1 National five year strategy to be agreed by all stakeholders in breast screening in Australia

2 State programs also to agree with their stakeholders a five year prioritised program

3 Agreement by all state programs to publish annual data. One model is those of the Victorian and South Australian programs. These data reports to be linked to Cancer Registry and national death data to ensure full evaluation of outcomes

4 A national strategy of funding should be agreed. Audit of such a high profile, high cost, flagship national public health endeavour must be a priority and that requires both structure and funding

5 Regular – at least biennial – national scientific meetings on screening results in Australian programs

6 State programs should fund staff adequately to attend appropriate international meetings. Staff should be encouraged to present local and Australian data at such conferences

7 Some of the items of possible research are listed in this paper. It is up to the public health community (in government, service and academic institutions), the breast screening community and the appropriate medical royal colleges to identify the key issues that Australia can address and to prioritise these issues

8 Where possible, programs should seek to collaborate with international groups.

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Professor David Ravine

Breast Cancer Genetics and Inherited Risks

No woman is entirely free from genetic risk of developing breast cancer. But the degree of risk varies by at least an order of magnitude between different women. The goal of research on breast cancer genetics is to identify all the genes involved in inherited predisposition to breast cancer; to measure the risk conferred by each of these genes, singly and in combination; to identify environmental and physiological factors that modify inherited risk of breast cancer; and to seek effective solutions to the array of practical challenges facing members of high-risk families.

Women who inherit a deleterious mutation in genes such as BRCA1 and BRCA2 are more likely than not to develop breast cancer over the course of their lives. But only 30-40% of hereditary breast cancer cases result from mutations within these two genes. The majority of families with multiple cases of breast cancer in successive generations are likely to carry mutations in other genes that are as yet unknown. The identification of these genes is one of the goals of kConFab – the Kathleen Cuningham Consortium for Research into Familial Aspects of Breast Cancer. During the past five years, kConFab has created a valuable resource of genetic, medical and epidemiological data and of biological samples (tumours, prophylactic specimens, DNA and RNA) of hundreds of families with intensely strong histories of breast cancer. After these families have been followed for several more years, kConFab investigators should have sufficient statistical power to, for example: compare the efficacy of interventions such as intensified surveillance, chemoprevention and prophylactic surgery; to define more precisely the appropriate forms of psychosocial support; and to classify the risk conferred by specific types of mutations.

Until very recently, Australia played a minor role in gene discovery efforts, mostly because of geographic fragmentation of scarce human skills and poorly-developed infrastructure. kConFab has shown that this history can be overcome and has pointed to the benefits arising from a nationally-coordinated approach, drawing patient resources and scientific skills required to achieve international competitiveness from across Australia. kConFab's success has come from its catholic membership, which spans disciplines across the entire continuum of breast cancer research and treatment and is drawn from every region of Australia; from its policy of open access to data and biospecimens for any researcher with an ethically-approved and peer-reviewed project; and especially, from its close connections to family cancer centres in each of the States and Territories. Welding a national research project directly to clinical service has brought intellectual and practical benefits to both sides and has created opportunities for families to become involved in a wide variety of research projects.

Several thousand families in Australia carry mutations in high-risk genes. A much larger number of families have more moderate histories of breast cancer, in which the incidence of disease is elevated and its pattern of inheritance is irregular. So far, these families are a genetic enigma. Most likely, their increased incidence is the result of the interaction between as yet unidentified moderate-risk genes and environmental exposures, both endogeneous and exogenous. Australia is in a powerful position to unravel the complex interplay between genes and environment because of its strength and experience in large-scale, population-based, case-control studies, in particular, the Australian Breast Cancer Family Study (ABCFS) and the Australian Twin Registry. The participation rates in these studies are among the highest in the world, and the success of ABCFS has led to similar large-scale, case-control studies of malignant melanoma and colorectal cancer. These population-based projects are important to Australia because the prevalence of deleterious alleles in moderate-risk genes is likely to vary widely in different ethnic groups and in geographical distribution. The ABCFS cohort will allow rapid validation of the frequency of newly-discovered moderate-risk genes within the Australian population.

Goals and Priorities

Until now, the aim of most genetic research on breast cancer has been to identify genes involved in initiation of the disease. Understanding causation is still a vital objective but is not the sole benefit that genetics can bring to breast cancer. Genes of many types must be involved in guiding the velocity and direction of the disease, in mustering the body's reaction to the tumour and in determining the response of patients to therapies and preventative treatment. Identification of these genes, a task that would previously have taken generations, has become possible because of the success of the Human Genome Project. However, Australian genetic research, including breast cancer genetic research, will soon lose its competitive edge unless there is a concerted effort to strengthen aspects of

bioinformatics and genomic analysis. If this is not done, one can envisage that in the future, data and biological samples collected in Australia will, of necessity, be sent offshore for analysis.

Three steps are necessary to maintain Australia's international competitiveness in breast cancer genetics:

1 Ensure long-term funding for continuation and expansion of successful large-scale epidemiological projects. There is little point in starting these projects unless the funding organizations come to understand that value of kConFab and ABCFS, for example, will continue to increase for a generation or more

2 Ensure that sufficient research funds are available to genotype the kConFab and ABCFS cohorts

3 Enhance the national genomics centre to serve as a repository and source of expertise in bioinformatic and genomic analysis for use by the entire genetics community.

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Professor Tom Gonda

The Molecular and Cellular Biology of Breast Tumours

Substantial progress has been made in understanding the molecular biology of breast cancer. Nevertheless it is clear that there are still substantial gaps in our knowledge and in our ability to apply the knowledge we have.

Current status of breast cancer tumour biology

It would of course be impossible to review here all knowledge in the area. The US NCI report "Charting the Course: Priorities for Breast Cancer Research" (1998), under the heading "Biology", briefly summarises the status of research at that time. The report pointed out that a number of the genes – oncogenes and tumour suppressors – that are altered in breast cancer have been identified and studied in detail, as have many other contributing molecular factors such as estrogen receptors and growth factors. Oncogenes have been identified mostly due to their overexpression, often with corresponding gene amplification, in tumours; some of the most prevalent are CCND1, CMYC, HER2, FGFRs. Tumour suppressor genes have been identified by LOH and/or by screening known tumour suppressor genes for alteration in breast cancer (e.g. TP53). Other genes associated with progression and metastasis have been identified e.g. those encoding E-Cadherin and Vascular Endothelial Growth Factor. Some of these – and the pathways associated with them – are currently being targeted for therapy with such treatments currently at various stages of development from pre-clinical to adoption into practice (e.g. Herceptin).

In considering selection of priority areas, we should also take into account progress made since 1998. Some of the areas where significant progress has been made are also outlined below.

Progress since the 1998 NCI report

- Mammary gland/breast cancer cell biology was probably less developed at that time, but there have been significant advances more recently in these areas. For example, significant progress has been made in understanding the biology of the normal mammary gland, which was one of the priority areas highlighted in the NCI report. Recent work has advanced our knowledge of normal mammary stem cells and led to the notion that at least some breast cancers, like leukaemia, might be "driven" by a small number of tumour stem cells with properties similar to, but of course not the same as, those of normal mammary stem cells. Such notions have far-reaching implications for targeting treatments, for metastasis and for assessing "minimal residual disease"
- Another significant advance has been the wide application of microarray expression profiling to breast cancer. This has supported and improved the sub-classification of breast cancer, with the recognition that tumours can be subdivided based on sets of genes corresponding to certain normal cell types found within the mammary gland (luminal, basal/myoepithelial etc).

Substantial progress has also been made in understanding the molecular biology of the two key nuclear hormone receptors involved in breast cancer, the estrogen receptor and the progesterone receptor, particularly with regard to their interactions with co-activators and co-repressors.

- Although not restricted to breast cancer, there has also been a significant revival of interest and progress in the area of tumour immunology and tumour immunotherapy
- It is noteworthy that a major focus of research has been and continues to be on HER-2/Neu expression and its consequences. While this clearly reflects the clinical significance of this oncogene, it is overexpressed in ~ 25% of tumours , it may also reflect the fact that molecular biologists and biochemists are relatively familiar with this class of molecule and approaches for its study and manipulation. Note however that HER-2/Neu-overexpressing tumours are usually ER-ve or ERlow, while ~ 70% of all tumours at presentation are ER+ve.

Strengths and Weaknesses

Australia has a fairly small number of scientists engaged in laboratory-based research into the molecular and cell biology of breast cancer, both in terms of numbers and sizes of research groups. There are no institutes or probably even departments that focus exclusively in this area, so breast cancer research groups tend to be rather widely distributed around the country.

Nevertheless, many of the research groups are in institutes or centres with strengths in molecular and cell biology and often with a substantial cancer focus, so these groups are in positions where they can make significant contributions.

STRENGTHS

- A vibrant biomedical research community, with particular strengths in immunology, including tumour immunology; genetics: molecular and population; protein chemistry and structural biology; growth factors and cytokines; stem cell research

  Australia has a strong biomedical research base with several reasonably well-funded and highly productive research institutes, some with international reputations. Many of these have demonstrated strengths in molecular biology, cell biology and experimental cancer research. In addition many of the universities have departments or centres carrying out cutting-edge research in these areas. High-technology platforms such as microarray facilities, proteomics, high-throughput sequencing and genotyping are available in several locations.

  Within this broad base, there are some areas with current or potential relevance to breast cancer that stand out, and that could be further utilised to strengthen breast cancer research nationally. Examples here include proteomics and mammary stem cell research.

- Progress in and potential for establishing breast tumour banks

  Access to well-characterised tumour material is essential for ensuring relevance of lab-based research to human breast cancer as well as being necessary for discovery of tumour associated genes and proteins.

  Currently several centres have small to moderate sized tumour banks and there are plans to establish larger ones. In addition there is the potential for collecting early-stage material – potentially pre-neoplastic – through BreastScreen.

- Familial breast cancer research

  This comes under the heading of genetics but it provides an important resource for tumour biology too.

- High-quality doctoral & post-doctoral training

  The number and success of Australian post-docs in top overseas institutions bears witness to this.

WEAKNESSES

- Small number of research groups working in key areas

- Very limited dedicated breast cancer research funding

  Currently, NBCF is the only organisation providing dedicated funding ($1-2 million p.a.) some of which goes to tumour biology research

- Relatively low impact of much of Australian breast cancer research

- Fragmentation of breast cancer research community

  Until recently, there has been no dedicated meeting for Australian scientists at the more basic end of breast cancer research. Hopefully this year's VBCRC/NBCF meeting will become a regular event

- Access to tissues and tumour samples restricted and complex and needs to be broadened and simplified

- Limited translational research, i.e. development of new treatments, markers etc from basic research

  This is partly due to lack of knowledge of and facilities for this type of work, especially drug development. Needs better collaboration with clinicians, which should be facilitated since many/most attempts at this have failed. There is very limited involvement of the private sector – i.e. biotechnology and pharmaceutical companies. This is partly because big pharma does its research overseas.

Goals and priorities

The NCI report listed a number of priority areas and key scientific questions. Despite the progress since 1998, most of these are still valid as high priorities. The major priority areas are summarised below; this list is based on heavily emphasised or recurrent themes in this section of the NCI report, and particularly those included in the executive summary. Also included are some areas identified by Australian breast cancer researchers, while some areas where substantial progress has been made have been removed. The NCI report also listed several issues pertaining to resources and infrastructure; these are addressed in Section 2 of this plan. Similarly, criteria for identifying areas in which Australian breast cancer research has the potential to make a major impact are discussed in Section 2.

1 Normal biology of the mammary gland

Identifying the stem cells of the mammary gland and understanding the developmental hierarchy of cell types will promote a better understanding of the various types of breast tumour cells and their origins. This will also aid in the identification and characterisation of tumour stem cells (also see above).

2 Identify the earliest lesions and changes in mammary epithelium leading to breast cancer

There is limited knowledge of the earliest lesions and genetic changes e.g. oncogene activation, genetic instability involved in breast cancer, including those that are involved in the transition from pre-cancerous states to overt disease. This has the potential not only to identify new therapeutic targets but also to possibly yield new biomarkers. Expression profiling using human material and relevant animal models is one approach to this problem.

3 Model systems and tissue resources

It is important to develop more relevant models i.e. models that better reflect human breast cancer. For example, virtually all the tumours generated in genetically-manipulated mice (transgenic and "knockout") are ER-ve. Both in vitro and in vivo systems are needed.

The best models will involve the same genetic events and cell types seen in human tumours; of course this relies on the knowledge of the actual events and cell types in human breast cancer.

4 Identify and develop new biomarkers

New biomarkers have applications not only in early detection and classification of tumours, but may, with appropriate validation, be used for guiding treatment choices.

Moreover they may be employed in developing "surrogate" endpoints in clinical studies, and finally as targets for immunotherapy. Technologies for the development of new markers include microarray expression profiling and proteomics.

5 Breast cancer metastasis

While tumour angiogenesis and the pathways involved in motility and invasion are subjects of active invasion more needs to be done. Predictive markers would be particularly valuable. It is also important to continue the recent research investigating the role of stromal influences in the metastatic process. It should be noted though that:

i) Anti-angiogenesis agents are currently under intense development and clinical testing. Indeed one agent, the VEGF antibody Bevacizumab, has recently been approved by the US FDA

ii) Expression profiling data are starting to suggest that the genetic lesions associated with poor prognosis – which often reflects metastasis – are characteristics of primary tumours and are thus acquired relatively early in progression.

6 Developing new treatment approaches at academic institutions

The NCI report noted that there were strong intellectual resources and capacity for innovation. This has been borne out by the fact that many of the recent and most innovative advances in functional genomics and drug development have indeed come from academic centres. The feasibility of targeting a much wider range of molecules, than the classical drug target families favoured by pharmaceutical companies, has become evident. There are, for example, a growing number of reports of targeting intracellular proteins that lack conventional enzymatic activity with small molecules.

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Associate Professor Christine Clarke

Endocrinology – Receptors

Estrogens are essential for the initiation and development of a large proportion of breast cancers. Partial estrogen antagonists such as tamoxifen and raloxifene are an effective treatment for these hormone-dependent tumours, and, in some cases, are preventatives. However, there are complications to long-term therapy such as increased risk of endothelial cancer and acquired resistance to the drug. To increase the effectiveness of antiestrogen therapy, we need better drugs. Tamoxifen was discovered serendipitously but the development of better drugs that display optimal agonist or antagonist activities in various target tissue will depend on basic research into the factors and cellular signalling pathways involved in estrogen-dependent growth and in sensitivity and resistance to antiestrogens.

The challenges ahead

Only breast tumours that express estrogen receptor (ER^+) respond to tamoxifen and other drugs that modulate estrogen action. Why some tumours are receptor-positive (ER^+) and others are receptor-negative (ER^-) is unknown. The genetic make up of the woman is important, since most of the tumours that arise in women with inherited mutations in the BRCA1 gene are ER^-. Conversely, most of the tumours arising in women with functional BRCA1 genes are ER^+. Because the patterns of global gene expression in the ER^- tumours of BRCA1 mutation carriers are strikingly different from those of ER^+ tumours, it seems possible that the two types of tumours arise from different cell populations. However, other explanations are possible. For example, for many years, a single type of ER ($ER\alpha$) was believed to be the sole estrogen-binding protein in cells. However, a gene for a second, shorter receptor, $ER\beta$ was cloned 1996. $ER\alpha$ is expressed in a subset of normal breast epithelial cells that do not proliferate in response to estrogen. In the normal breast, growth is restricted to ER^- cells. If these ER^- cells are the precursors of ER^+ breast cancers, they must at some point begin to express the estrogen receptor. Perhaps BRCA1 protein is simply required for activation of the ER gene. Differences in expression profiles might then be the result of complex crosstalk that is known to exist between the estrogen signalling pathway and other signalling pathways.

The success of tamoxifen is based on a balance between its antagonistic activities in ER^+ cells of the breast and its agonistic activities in bone uterine tissue and the cardiovascular system. Its efficacy in treating breast cancer has been attributed to both its cytostatic and cytotoxic properties. However, the specific targets remain to be identified. Almost all patients with advanced breast cancer who initially respond to tamoxifen eventually develop resistance to the drug. The mechanisms for escape from endocrine sensitivity in advanced disease are complex and diverse. Acquired resistance is not due to an alteration in the ER status of the tumour but may result, for example, by restoration of signalling by epigenetic or genetic changes within the tumour that lead for example, to aberrant expression of coactivators or enhanced phosphorylation cascades.

In addition to estrogen, other steroid hormone pathways are likely to be active in breast cancers and receptors for androgen and progesterone are commonly expressed. The role of these pathways and their interaction with estrogen signalling is unknown. The augmented risk of breast cancer in women taking combined hormone replacement therapy points to a role of progesterone, or androgen, in augmenting risk. This is in line with the evidence for a proliferative role of these hormones in the breast, but although this is a critically important issue from a public health perspective, the data are sparse.

Roadblocks, gaps, impediments

- Model systems for studying normal human breast are almost exclusively lacking in steroid receptors
- The endocrine pathways regulated by the steroid hormones are overlapping and increasingly include rapid, non-genomic events as well as a multiplicity of DNA-mediated effects. Dissection of the relative contributions of the relevant molecules in which the limited available model systems exist is a major challenge.

Goals and Priorities

1 Models of endocrine action in normal human breast cells need to be developed

2 Dissection of the relative sensitivities of normal cells to estrogen, progesterone and androgen, as well as other

endocrine factors such as prolactin, to understand the main drivers to proliferation in human breast. Normal, premalignant and invasive responses are likely to be different

3 Direct targets of the action of these steroids need to be elucidated. Genetic variations in genes in receptor-regulated pathways may form part of individual variation to susceptibility as well as targets for prevention

4 Access to human tissues, particularly normal tissue, needs to be expanded in well-characterised cohorts with accompanying reproductive and hormonal data. Linkage of population-based and laboratory studies is rapidly becoming an urgent priority.

Professor Evan Simpson

23 Endocrine-targeted Therapy

Endocrine-targeted therapy remains one of the most successful treatments for the management of breast cancer. At the present time, most endocrine therapy for breast cancer is directed towards eliminating the growth-promoting activities of estrogen – whether by inhibition of estrogen action or by inhibition of estrogen biosynthesis. However, we are still some way from developing a drug that retains the benefits of estrogen, has no side-effects, and is both an effective treatment for and protective against breast cancer.

Drugs that block the action of estrogen are routinely used at several stages in breast cancer treatment, namely first-line therapy in advanced disease following surgery and chemotherapy or radiotherapy, adjuvant therapy and also neo-adjuvant therapy. The principle drug currently employed in these treatment protocols is tamoxifen. Tamoxifen is also a preventative and several clinical trials that are currently underway or completed show a positive outcome for individuals on the tamoxifen arm compared with the placebo arm. It is worth noting however that tamoxifen is of no benefit to individuals with tumours that do not express estrogen receptors or the subset of ER-positive tumours that are tamoxifen-unresponsive.

Tamoxifen is a ligand that binds with approximately equal avidity to the two estrogen receptors (ERα and ERβ)). The drug inhibits the action of estrogens in some tissues and enhances it in others. In particular, it is an antagonist of estrogen action in breast cancer cells but is an agonist in the uterus as well as in bone. Consequently, it suppresses growth of estrogen-responsive tumours and protects women against bone loss, but enhances their risk of developing endometrial cancer as well as coronary disease. Treatment with tamoxifen is usually limited to a period of 5 years because of breakthrough, where clonal lines of breast cancer cells develop that are either insensitive to the drug or display an agonistic response.

More recently raloxifene, another selective modulator of estrogen action, has been investigated as a chemopreventative. In a clinical trial that had originally been designed to study raloxifene as a preventative agent for osteoporosis, it turned out that women taking the drug had 72% fewer invasive breast cancers diagnosed than those women taking the placebo – a result that was even better than that for tamoxifen. Raloxfene mimics the action of estrogen in bone but, unlike tamoxifen, is antagonistic in uterus and therefore confers no increased risk of endometrial cancer. Whether raloxifene increases the risk of cardiovascular disease is at present unknown. Although tamoxifen has been used for thirty years to treat breast cancer, experience using either tamoxifen or raloxifene as preventative agents is limited and good data on the effects of these drugs when they are used as long-term prophylactics is lacking.

Although both tamoxifen and raloxifene appear to decrease the risk of breast cancer in large populations, much remains to be learned about their effectiveness in different groups of women. A key question is whether tamoxifen and raloxifene work in women who are at highest risk of developing breast cancer, for example, those who have inherited a mutation in one of BRCA1 or BRCA2. Although the Breast Cancer Prevention Trial studied the use of tamoxifen in women at increased risk for breast cancer, assessment of risk was based on previous biopsy findings and family histories. Because participants in the study were not tested for BRCA1 or BRCA2 mutations, we do not know whether these mutation carriers are more or less likely to benefit from tamoxifen than other women. However, we do know women with mutations in BRCA1 or BRCA2 have a reduced risk of developing cancer in the opposite breast when they take tamoxifen to treat an existing cancer. This study provides encouraging evidence that tamoxifen may be useful for preventing cancers in this group of women.

The critical limitations of the first generation estrogen modulator, tamoxifen, have energized an ongoing search for better ways to suppress the estrogen-driven growth of breast cancers. Recently, several promising drugs have been developed that inhibit the activity of a key enzyme – aromatase – that is the chief manufacturer of estrogen in post-menopausal women. Three highly-specific aromatase inhibitors – arimidex, letrozole and exemestene – are capable of reducing serum levels of estrogens many-fold and, in almost every setting studied, have proved to be superior therapeutics to tamoxifen. In the ATAC trial, for example, almost 10,000 post-menopausal women with operable invasive breast cancer who had completed surgery and chemotherapy or radiotherapy were randomised for 5 years either to anastrozole or tamoxifen or anastrozole plus tamoxifen. Anastrozole proved superior to tamoxifen in the primary endpoints which were disease-free survival and

safety/tolerability as well as secondary endpoints, namely incidence of contralateral breast cancer, time to recurrence and survival. Interestingly the combination of anastrozole plus tamoxifen proved to be of no further benefit compared to tamoxifen itself. In four of five further trials where an aromatase inhibitor was compared to tamoxifen as first-line treatment, the inhibitor showed a clinical benefit compared with tamoxifen.

Why should suppressing synthesis of estrogen with aromatase inhibitors be more effective than blocking estrogen action with tamoxifen? A possible explanation is that estrogens promote development of breast cancer in two ways: by directly stimulating division of breast epithelial cells – the traditional view – and by causing damage to DNA. Estrogens are broken down in their target tissues to highly reactive quinones that attack adenine and guanine residues in DNA, leaving the double helix susceptible to breaks. Breast cells, because of their need for estrogen, may contain a high concentration of these estrogen-derived carcinogens and may suffer a high rate of genomic instability – a hallmark of the later stages of breast cancer. By suppressing synthesis of estrogens, aromatase inhibitors may protect cells from DNA damage and may therefore block or retard the progression of breast cancers.

Like tamoxifen and other estrogen modulators, aromatase inhibitors also carry undesirable side effects, notably loss of bone mineral, a marked increase in the incidence of bone fracture and a curious increase in arthritic symptoms. These side effects stem from the fact that aromatase inhibitors block the action of the enzyme in all tissues – not only breast but also bone, brain, vasculature and other sites where aromatase is expressed.

Goals and priorities

1 A major goal must be to understand the molecular basis of agonism and antagonism exhibited by tamoxifen and newer estrogen modulators. The chameleon-like qualities of these drugs can be safely assumed to be the result of their ability to turn banks of genes on and off. But how can such simple molecules orchestrate such dramatically different effects in different cells? The answer is likely to be complex. The choice between agonism and antagonism may be determined by the volume of cross-talk between the estrogen signalling pathway and other hormonal pathways; or it may involve the balance between ERα and ERβ and it almost certainly involves a small army of intermediary molecules such as coactivators and corepressors. A deeper understanding of the structures and interactions of these molecules will create opportunities for rational design of new preventative and/or therapeutic drugs and regimens for drug use

2 In addition to estrogens, steroid hormones such as androgens, and peptide hormones such as insulin-like growth factor-1 and prolactin influence breast cancer risk in postmenopausal women. The synthesis and/or metabolism of these hormones have links to the metabolism of estrogens. But whether or not their effects on breast cancer are independent of estrogen needs to be clarified

3 The idea that the breakdown products of estrogen, rather than the hormone itself, may be the major contributors to cause breast cancer is so far based on strong but circumstantial evidence. Genetic and biochemical studies of the enzymes that are responsible for the formation, activation and deactivation (protection) of estrogens in human breast cells are urgently needed, as are animal models carrying the appropriate sets of genetic markers

4 A large prospective study has shown that risk of breast cancer was decreased by 22% in regular users of aspirin over five years and by as much as 49% in regular users of ibuprofen. These results suggest that inhibitors of the enzyme cyclooxygenase 2 (COX2) might offer effective chemoprevention against breast cancer. Consequently at least two placebo-controlled trials are underway to compare the effectiveness of celecoxib, a specific COX2 inhibitor, with estrogen blockade in reducing the risk of breast cancer. The idea that common non-steroidal anti-inflammatory drugs such as aspirin and ibuprofen could protect against breast cancer might seem implausible. But COX 2 is the enzyme that manufactures prostaglandin E2, a substance that stimulates the synthesis of aromatase uniquely in the breast. A specific COX 2 inhibitor such as celecoxib might therefore have the desirable property of blocking estrogen synthesis in the breast while leaving its formation in bone unaffected.

Dr Rosemary Balleine and
Associate Professor Christine Clarke

25 Pathology of Breast Cancers

The morphology and arrangement of cells in sections of breast cancers tell of the origins and history of the tumour; the proteins produced in the cells can predict, albeit imperfectly so far, the future course of the disease and its response to treatment. Pathology therefore provides the essential link between diagnosis and treatment of breast cancer and research into the molecular biology of the disease.

The importance of pathology: successes and achievements

The definitive diagnosis of all breast disease is based on histologic examination of tissue samples that are increasingly obtained as fine needle aspirates or core needle biopsies. The histologic features of fully invasive breast cancers, documented in the pathology report, include tumour size, tumour type, grade and the presence of axillary lymph node metastases. However, pathology is used increasingly both as a prognostic tool and to match therapy to the biology of the tumour. For example, the histopathologic detection of receptors for estrogen and progesterone in the tumour cells can indicate that endocrine therapy may be a useful therapeutic option. Similarly, an abundance of the HER-2 protein indicates that the tumour may be vulnerable to a genetically-engineered antibody (Herceptin) directed against the HER-2 protein. However, the ability of pathologists to detect subtle differences between similar lesions is limited by the observational nature of conventional pathology – almost all pathology is carried out by visual analysis of fixed sections of tissue in a light microscope. This creates uncertainty in the diagnosis of breast cancers at early stages of the disease, when fewer anatomical indicators of clinical course are available.

Increasingly, pathology is becoming a molecular science. Sophisticated molecular analyses of the patterns of gene expression in tumours have the potential to generate unbiased systems for classification of malignancies and premalignancies into subtypes whose future course and response to treatment can be predicted with accuracy. Van't Veer et al (2002) have already identified 231 genes whose levels of expression are significantly associated with long-term outcome as defined by the presence or absence of metastasis at the 5-year mark. These genes can be collapsed into more manageable sets that can be used to generate histopathology reagents capable of providing an accurate prognosis at the time of first diagnosis of the breast tumour. This type of research, which spans the border between traditional pathology and molecular biology, is still in its infancy and will increase in both accuracy and range as the patterns of gene expression in different subtypes stages of cancer are worked out and as standardized sets of diagnostic/prognostic reagents become available.

Roadblocks, gaps, impediments

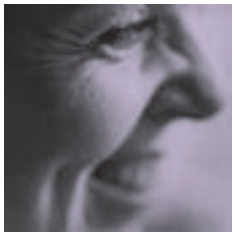
In theory, Australia could become a major force in the molecular pathology of breast cancer. However, this can happen only if roadblocks that stand in the way of progress can be quickly dismantled:

- At present, there are insufficient pathologists in the public hospitals to cover clinical requirements and there are few incentives to attract pathologists into a research career. The National Breast Cancer Foundation, perhaps in combination with other funding agencies, should consider establishing Pathology Research Fellowships in each of the major centres for breast cancer research
- The lack of ready access to large tissue banks of breast cancer specimens with attendant clinical information limits the translation of research results into the clinic. Because of mammographic screening and increasing use of breast-conserving surgery, tumours recovered during surgery are smaller in size, which means that less material is available for research. There is a particular need for large collections of premalignant tissue (such as DCIS) and benign, atypical lesions whose significance and prognosis is poorly understood
- Variability in reporting of pathology results is a major impediment to research on tissue specimens. Standardised reporting formats and data dictionaries should be developed as a matter of urgency
- Ethical review and approval for large-scale research projects should be handled at the national level rather than at the institutional level.

Goals and priorities

Use new knowledge on the biology of breast cancer and data from powerful new technologies, such as microarray, proteomic analysis and pathway analysis to:

1 Identify and validate biologic markers of pre-malignant, early stage, indolent and potentially aggressive disease



2 Develop schemes for improved tumour classification and prediction of tumour behaviour. Better indicators of tumour aggressiveness are badly needed, particularly in small or early lesions. More accurate descriptors of tumour biology must be derived and related to the response of the tumour to therapy and the potential of the tumour to cause death of the patient.

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Professor Ian Olver

Clinical Management

Clinical management includes a broad spectrum of research encompassing prevention and detection through treatment, health services research and psychosocial research to palliative care.

Current Spectrum of Research

The National Breast Cancer Centre (NBCC) has been responsible for researching the ideal delivery of services to patients with breast cancer while serving as a source of information itself. Projects have ranged from researching the role of breast care nurses to examining models of multidisciplinary care. Areas of need such as the increasing need for psychosocial support have been defined and niche areas such as the needs of young women with breast cancer have been reviewed. Special projects such as teleoncology outreach projects have been facilitated. The Australian Cancer Network has been pivotal in producing and disseminating guidelines for breast cancer management.

Clinical practice audits are exemplified by the College of Surgeons computer based audit program for breast surgeons as part of their accreditation activities. The other strong area of research in the clinical management area is the groups conducting clinical trials in breast cancer. The Australian New Zealand Breast Cancer Trials Group (ANZBTG) has co-ordinated large national trials in breast cancer which has been particularly important in the adjuvant studies where participation in large international studies has been vital. Many institutions throughout Australia run smaller studies, particularly in collaboration with the pharmaceutical industry.

Strengths and Weaknesses

STRENGTHS

The major strength in breast cancer management research has been the success of the larger national research groups as exemplified by the ANZBCTG and more recently the Trans-Tasman Radiation Oncology Group (TROG) in co-ordinating trials nationally and providing a focus for international collaboration. Other trial initiatives such as the SNAC trial, studying sentinel node biopsies have been able to gain national support. In addition to this there have been other national initiatives such as kConFab studying high-risk families that has illustrated the strength of the principle of funding large national initiatives over a long timeframe. Groups such as the NBCC have focused on health services research and using guidelines to standardize practice and encouraging communications skills training. Organizations such as NBCC and the National Breast Cancer Foundation also involve consumers in identifying the areas of need for further research. BreastScreen has had a measurable impact on outcomes. The network of cancer registries and data bases have been able to document gains made by changes in treatment practice.

WEAKNESSES

The weaknesses in the system are the fact that multiple different organisations have a stake in management and research in breast cancer and can compete for the same resources and fragment the effort. It is known that there is still great variation in the quality of care and the availability of multidisciplinary care between locations. Even the different state cancer registries are different in the timeliness of the data provision and there are barriers to sharing information in some jurisdictions which acts as a barrier to producing national outcomes data. Whereas the production of guidelines is a strength the amount of effort required and the procedures for obtaining wide input and NHMRC approval mean timely revision of guidelines is a challenge.

Specifically applicable to clinical trials, there may be increasing difficulty recruiting clinical academics as remuneration differentials between such positions and private practices increase. There is also difficulty finding funds for clinical trial infrastructure as opposed to funding each specific trial. Ethical and medicolegal issues are also becoming more complex parts of the trial approval process and there is no widespread acceptance of central ethics committees for multicentre clinical trials. A further problem is the lack of a comprehensive trials register which would enable researchers and patients alike to know what was being done across the country.

Levels and Sources of Funding

The major issue with funding is the lack of national infrastructure funding to run trials groups. This could be an initiative in its own right or as part of a 'National Cancer Institute' initiative. The funding that is available from sources such as NHMRC or cancer councils has been more for projects and short programs. It has not been possible to obtain sustained infrastructure funding for large scale projects (such as genetic projects) which can guarantee funding over greater than five years.

There has also been an enormous differential in degree of difficulty in obtaining research funding for different aspects of the management continuum e.g. basic research and clinical trials vs. health services research, psychosocial and palliative care research.

Much funding for clinical trials has been from the pharmaceutical industry but this then is often restricted to those studies which would lead to registration of a new product.

Impediments to Progress

A major impediment to progress in breast cancer management research is the lack of infrastructure expertise to support clinical research. This is compounded by a multitude of groups often competing for the same resources and not necessarily being aware of the national research landscape because of a lack of a national database of research or register of trials. There is no overarching body to co-ordinate the research effort and indeed no annual all inclusive meeting funding for clinical trials and the need for specific expertise, such as biostatistician for breast cancer researchers but instead a number of national meetings of each of the groups. Particularly lacking at a national level is the integration of basic science with clinical groups. This results in a relative lack of academic leadership in this area and this is further compounded by a lack of incentive for doctors to pursue an academic career. Patient numbers for trials are not large in this country and the problem is compounded by the divide between the public and private sector.

Comparison with Other Countries

The most striking comparison is the restructure which exists in other countries and is exemplified by the National Cancer Institute in the USA and the National Cancer Institute of Canada. The other is the huge differential in funding opportunities which exist in other countries compared to Australia. Perhaps our greatest barrier to contributing high impact research is our relatively small population. This will become an increasing challenge as Eastern Europe and South East Asia become more prominent contributors.

Goals and Priorities

Targets should be set for the next 10 years:

1 By 2013 30% of all women with breast cancer will be in a clinical trial

2 National register of trials

3 Centres of excellence/National Cancer Institute which could co-ordinate research priorities and funding

4 Use databases linked to biorepositories

5 Better collaboration between cancer registries. Agreed data set and pooling of de-identified data between registries and mechanisms to continually provide agreed output measures

6 Encourage training of clinical academics (and funding)

7 Encourage cancer centres of excellence

8 Provide infrastructure for clinical trials and especially biostatistical support

9 Encourage a broader range of clinical research. For example plan to increase the number of funded psychosocial trials

10 Ensure consumer input into breast cancer management research priorities.

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Dr Martin Stockler

Clinical Trials

Clinical trials are research studies that test new and better ways of improving health in people. They are how all new advances are tried, tested and proven. They are the final necessary steps in the long process of turning promising findings from the laboratory into better outcomes for people.

Australia has been an international leader in breast cancer trials for 25 years. Australian researchers pioneered the incorporation of quality of life as an outcome measure in large-scale clinical trials. Australian researchers are leading members of the major international breast cancer trials groups. Australia's international leadership in breast cancer trials is threatened by inadequate funding.

Current Spectrum of Research

Trials are needed and being done along the whole trajectory of breast cancer. Trials of prevention and adjuvant therapy must be international to get sufficient subjects (thousands). Trials in advanced disease require fewer people (hundreds) and can be done within Australia and New Zealand (ANZ) alone. For example:

PREVENTION

2500 women from ANZ participated in the international IBIS-1 trial of breast cancer prevention with tamoxifen. The IBIS-2 trial of breast cancer prevention with anastrazole will be activated during 2004.

SURGERY

900 women from ANZ have been recruited to the SNAC trial or Sentinel Node Biopsy versus Axillary Clearance for operable breast cancer. Early funding from the NBCF was crucial in levering additional funds from NHMRC and others.

ADJUVANT SYSTEMIC THERAPY

ANZ has been a major contributor to international trials of chemotherapy and endocrine therapy to improve cure rates in early breast cancer. Ongoing trials are testing the addition of traztuzumab (herceptin ™) to adjuvant chemotherapy (HERA); trials integrating endocrine therapy and chemotherapy in young women with hormone receptor positive cancer (SOFT, TEXT, and PERCHE). ANZ were the leading recruiters to the last IBCSG trial of adjuvant chemotherapy testing the addition of docetaxel (IBCSG 20, BIG 2-98).

ADJUVANT RADIATION THERAPY

ANZ have recently joined a Canadian international trial testing of adjuvant radiation being auspiced by TROG. Investigators in Perth and Melbourne are initiating a trial of intra-operative adjuvant radiation.

ADVANCED BREAST CANCER

230 of 465 women have been recruited to the ANZBCTG trial of daily oral chemotherapy with capecitabine versus standard intermittent chemotherapy with CMF.

SUPPORTIVE CARE

For example: trials of emotional supportive therapy (Kissane et al), optimism therapy and communication skills (Butow et al) needs assessment (Girgis et al), antidepressant therapy (ZEST).

Strengths and Weaknesses

Expertise and commitment are Australia's greatest strengths in breast cancer trials research. Australian breast cancer trials research is recognized internationally for its:

- World leaders in clinical research
- Centres of excellence: for example the ANZ Breast Cancer Trials Group & The NHMRC Clinical Trials Centre
- Incorporation of quality of life as a key endpoint in cancer trials
- Enthusiastic, committed and highly skilled clinician researchers
- Ability to conduct high quality research on a shoe-string
- Consumer involvement in scientific advisory and trial steering committees
- Limited funding for projects, infrastructure, and divisiveness are Australia's greatest weaknesses
- Funding is piecemeal and must be cobbled together from multiple sources
- There is no long term commitment to fund the infrastructure needed for cancer trials
- Stakeholders compete with one-another for scarce resources.

Levels and Sources of Funding

Breast cancer trials are large, expensive, long-term commitments. Typical trials need funding for 5 to 10 years.

Not doing trials is even more expensive. Successful groups have learnt to seek funds repeatedly from multiple sources. Industry has substantial funds, but sets its own agenda.

The NHMRC is the largest potential source of public funding, but only 1 in 4 of the 1500 annual applications are successful, and NHMRC is reluctant to fund trials from inception. State Cancer Councils and Foundations are valuable funders of cancer research, but funds from these sources must be spent in the awarding state, and the total quanta is rarely more than a small proportion of the total budget. Breast cancer is one of many worthy competitors for funds from NHMRC and State cancer funds. The NBCF has been a crucial source of funds for initiating new breast cancer trials (eg SNAC) and companion-studies assessing quality of life (eg IBIS).

Impediments to Progress

Doing trials is becoming more difficult and expensive because of the:

- Difficulty obtaining funds to initiate and complete trials
- Lack of funding for central infrastructure to maximize the efficiency and productivity
- Lack of funding for infrastructure at participating centres
- Medical indemnity costs and uncertainties
- Inefficiency and duplication for approval of multicentre research.

Comparison with Other Countries

Australia has been a world leader in breast cancer trials participation, publications and methods, despite limited support. Australia will fall behind without adequate investment in cancer trials. Local funding for individual trials is substantially below international comparators, e.g. Canada, Scandinavia, UK, USA. Local funding for infrastructure is almost non-existent, and dramatically below the same international comparators.

Goals and Priorities

1 Improve participation by integrating research in practice: participation in high quality trials guarantees the best available proven treatment or something potentially better. Participation should be available to everyone affected

2 Ensure important questions are answered even if they are not of commercial interest by securing greater financial independence from industry

3 Improve support for research infrastructure: funding research solely on a project by project basis is inefficient and wasteful

4 Bring stakeholders together with funds to support their work to improve productivity, efficiency, and outcomes.

Professor Phyllis Butow and
Emeritus Professor Miles Little

31 Psychosocial and Survivorship Research

Optimal care of the patient with cancer incorporates effective physical and psychological care, through diagnosis and treatment and long-term survivorship. People with cancer suffer significant emotional morbidity. Challenges for patients throughout the time course of cancer include existential concerns, making decisions based on uncertain outcomes, coping with problematic side effects of treatment (both short and long-term), social disruption and financial concerns. With adequate preparation and education about these challenges, caregivers and patients alike can perhaps better pinpoint and effectively manage these issues.

Up to 30% of cancer patients experience clinically significant anxiety disorders and prevalence rates for depression range from 20-35%. These disorders have a major impact on the person's functioning, and that of their family, adversely impact on capacity to cope with disease burden, and may reduce patient adherence to recommended treatments. People with cancer continue to request more information in order to better understand their cancer, its impact on them and their family, and the treatment options available. Patients are only able to participate as they wish in clinical decision-making if they have access to appropriate information. Thus there is an ongoing need to conduct research in, and develop better strategies for, identifying and meeting the psychosocial needs of breast cancer patients.

Treatment of the late effects of breast cancer therapy may involve a large number of clinicians and other specialists, including primary care physicians, oncology specialists, psychologists and counsellors as well as the cancer survivors themselves. Many overseas specialized cancer centres have developed a range of programs and services geared specifically to breast cancer survivors – addressing both the physical and the emotional and psychological effects of the disease and treatment. In addition to providing one-stop medical treatment and psychological support and counselling, these programs:

- Maintain regular contact with patients and provide them with updated information about their therapy and its late effects
- Discuss the need for long-term clinical surveillance and psychological follow-up; and
- Encourage participation in clinical studies when available.

While these programs might provide broad templates for the establishment of similar programs in Australia, they are not readily transportable from one health care system to another. In view of the rising numbers of long-term survivors, it is essential that the Australian breast cancer community develops its own system of downstream support for survivors and increases its knowledge about late treatment effects in the Australian context through the use of systematic research, better use of cooperative groups and cancer registries, and through the establishment of survivor clinics and registries.

Strengths and Weaknesses

Psychosocial breast cancer research is an area of strength in Australia. Psychosocial predictors both of developing breast cancer and of outcome in patients with early and late stage breast cancer have been explored. Documentation of the incidence and prevalence of clinically significant levels of anxiety, depression, general distress and reduced quality of life (including sexual functioning and lymphoedema) in breast cancer patients and their families has been undertaken. Measures of unmet needs in breast cancer patients and their carers along the disease trajectory (including survival) have been developed, and difficulties, issues and the level of unmet needs in these groups have been documented. Individual and group interventions have been evaluated for breast cancer patients, patient/partner couples and siblings of patients to reduce psychological and social morbidity, and improve quality of life. Communication difficulties experienced by patients and doctors have been identified and patient and health-professional-based interventions to improve doctor-patient communication are being developed and evaluated. Several sets of psychosocial guidelines have been developed, including, in a world first, comprehensive evidence-based guidelines for the psychosocial care of patients with breast cancer. In particular our work on the documentation of unmet needs, doctor-patient communication and issues in survivorship has attained international recognition.

This level of success has been achieved for a number of reasons. The research climate has shifted in Australia over the past 15 years towards providing greater support for psychosocial research. This has resulted in part from the

improvements in breast cancer treatment, leading to a greater focus on quality of life rather than mortality alone. The strengthening influence of consumer groups in Australia, who place a priority on psychosocial concerns, has influenced funding bodies. The National Breast Cancer Centre and the National Breast Cancer Foundation have provided strong leadership in placing psychosocial concerns on the national agenda. The establishment of a Psycho-Oncology group within the Clinical Oncological Society of Australia gave this discipline credibility within the clinical groups. Collaboration between Psycho-Oncology research groups has increased, leading to larger studies with stronger designs. However, collaborative links would benefit from strengthening, to ensure optimal planning of research and uptake of research opportunities. Most projects remain small and local and therefore fail to have an impact on the international scene.

Levels and Sources of Funding

It is difficult to obtain funding for psychosocial research. A review of funding in 2003 showed that of 111 grants awarded by the Cancer Councils and the National Breast Cancer Foundation, eight were psychosocial. This poor result may be because submitted grants are of poor quality, or because psychosocial research is regarded as having low priority by reviewers and granting bodies. Many of the Cancer Councils have behavioural research units, which have quarantined funds, but this represents a small percentage in total of Psycho-Oncology research output. There are no monies put aside for investigating the problems of survival. Qualitative research is still poorly funded by comparison with quantitative research by NHMRC. Much of the research that has been done has been funded from a variety of private trusts and small charitable bodies.

Impediments to Progress

Poor funding is certainly an impediment to progress. National meetings, committees and associations repeatedly stress the importance of psychosocial issues, but resolutions do not seem to be enacted. What research has been done has minimal impact on the cancer community, and is repeatedly relegated to relative unimportance. Thus implementation of research findings is lacking. The absence of a co-operative group of Psycho-Oncology researchers reduces the chances of creating and funding large-scale psychosocial research projects. The lack of systematic collection of psychosocial data on a national scale disallows monitoring of progress over time.

Comparison with Other Countries

Given the poor level of funding, Australia has done extraordinarily well in comparison with other countries in terms of output. The latest NCRI report from 2002 indicates that 6% of research dollars were spent on cancer control, survival and outcomes research, a mixed bag including patient care and pain management, surveillance, behaviour and education, and supportive and palliative care. Given the absence of breast cancer specific data in Australia and overseas, and of a specific breakdown of psychosocial research, direct comparisons cannot be made.

Goals and Priorities

While there is now ample evidence of high levels of unmet needs in breast cancer patients and their carers, and that psychosocial and communication interventions can reduce these unmet needs, the priority for the next 5/10 years is to ensure that these interventions are implemented. A greater focus on survivorship research is required as the number of women living with and beyond cancer increase.

1. A firm commitment to psychosocial research is required from national peak bodies that fund and support cancer research
2. Research needs to focus on barriers to implementation, cost-effective ways to deliver interventions and strategies to encourage uptake
3. Health services research concerning the interaction between system factors and psychosocial outcomes is needed. For example, optimal organization of services to promote excellent psychosocial care and reduce stress and burn-out in health professionals working in cancer care
4. Emerging data suggests that strategies to reduce morbidity in carers is urgently needed
5. With the development of evidence-based medicine, ongoing development and evaluation of strategies to support decision-making in breast cancer patients, such as question prompt lists, decision aids and internet information systems, is required
6. Underpinning all of these goals and priorities is the need for psychosocial performance indicators to be put into place, to allow assessment of psychosocial outcomes associated with strategy implementation

7 Collaborative links with other research streams is needed, to ensure that psychosocial and clinical research is integrated, and opportunities for large-scale studies are not lost. A good example of how this can work is the Psychosocial Working Group within kConFab. This has resulted in several large-scale psychosocial projects of international significance, which would have been impossible without the resource of a large registry of families and data sharing. Similarly, quality of life and decisional support studies integrated with large clinical trials offer unique opportunities to conduct high quality psychosocial research

8 Similarly, we need to develop mechanisms for facilitating research collaboration between psychosocial research units and clinics that treat cancer

9 Finally, we need to create and maintain a national database of psychosocial and survival-related projects, and a national register of research expertise.

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Ms Sue Carrick

Palliative care

Palliative care[i] is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Palliative care is not confined to any one disease or life threatening illness. It is pertinent to breast cancer however because an increasing number of women now live for much longer with the disease.

The provision of palliative care services has grown rapidly since the inception of specific funding for palliative care service delivery in Australia in 1998. However, there is some concern amongst health care providers that palliative care is not as fully integrated into the cancer care continuum, as it should be. Despite the progress made over recent decades in terms of the early identification of breast cancer and the identification of new treatment options, a significant number of women experience relapse and progression of their breast cancer while others die. Thus, palliative care clinicians and nurses correctly believe that palliative care should be part of routine treatment discussions, especially when the disease has progressed beyond stage 1.

With an increasing number of women living much longer with breast cancer unique issues emerge. These include new medical, social, and political challenges to determine the type of research needed that reflects the important role palliative care plays in a cancer patient's life from the moment of diagnosis and throughout the cancer continuum. This includes for example, investigating the needs and appropriate models of end of life care for diverse populations, new drugs and interventions for symptom management, ways of improving and researching quality of remaining life issues among cancer patients and the special needs of their carers.

Palliative care is commonly promoted in Australia as a specialist service centred on a multi-disciplinary care team with access to, and authority for, intervention at all sites where a patient might be receiving care. While this role involves consultation with professional carers in each site, palliative care providers maintain their own contact with the patient and family to ensure coordination and continuity of care, especially in the case of the dying patient. Sites of care may include hospitals, hospices, family homes and aged care facilities. Penetration of specialist palliative care into acute hospitals for example has also highlighted the distinction between specialist and generalist models of care. The emphasis, distribution and delivery of palliative care services vary from place to place often in response to resource constraints, geographical differences and population characteristics. There is little research evidence available to support the development of the most appropriate models of palliative care delivery for different sites of care and patient

groups. Responses to the increasing need for palliative care services have in the past been developed largely based on the experience of busy clinicians with little time or support to reflect on appropriate solutions or to investigate alternative measures. In Australia and internationally, palliative care is a relatively young discipline and health service. Hence, its research community is also very young. It is argued that traditionally, most palliative care research projects have been isolated, short term and poorly followed-up. Funding has been seen as haphazard and opportunistic; sometimes supporting pilot projects with poorly defined outcomes, which have not led to, improved service or strengthened clinical activity. Despite this Australia provides notable international leadership in the discipline.[ii]

Strengths and weaknesses

If Australia is to maintain its international status and contribute to the development of evidence based palliative care, quality research is urgently required which utilizes its strengths and implements strategies to address the barriers.

Australia can currently demonstrate some major strengths in palliative care. These include: world class service delivery programs; the presence of a number of skilled, well trained researchers in palliative care, medicine, nursing and allied health; national and international collaboration activities; collaboration rather than competition and openness to new ideas. Of particular importance is the recognition by the NHMRC of the need to support an emerging palliative care research culture with the establishment of a Palliative Care Research Program. The program aims to improve the quality of palliative care by undertaking research capacity building initiatives, including postgraduate scholarships and fellowships awards and funding research into palliative care. Twelve research grants were funded in 2004.

In addition to the strengths inherent in palliative care, there are several challenging barriers that inhibit research in Australia. These include: clinical responsibilities; methodological and ethical difficulties to conducting empirical research; a lack of laboratory research; and dispersion of talent.

Priorities

Areas requiring further research include symptom relief and management, rehabilitation; prognostication; effective ways of communicating information about prognosis; health outcomes; the role of the General Practitioner and specialist nurse; needs of special groups; bereavement services; family meetings; spiritual care and ethical issues. Similarly there is a need to determine whether or not palliative care makes a difference to those at the end of their life and how to overcome some of the difficulties associated with outcome measures and undertaking randomized control trials in palliative care.

Despite the young nature of the palliative care research community, it has an impressive record of doing much with little. If this is to continue the talent needs to be fostered to meet the needs of the next generation.

i WHO Definition of Palliative Care http://www.who.int/cancer/palliative/definition/en/

ii Australia's Future in Palliative Care Research: A Collaborative Approach, the findings from a Scoping Study of Palliative Care Research to the Commonwealth Department of Health and Aged Care in 2000 is available from http://www.pallcare.org.au/pca_research.html

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Ms Lyn Swinburne and Ms Gerda Evans

Consumer Involvement

In recent years, the voices of women affected by the disease have become a source of enlightened commentary on research into breast cancer. So that these voices can be heard more clearly, consumer involvement in the development and implementation of research policies should be formalized and extended.

Consumer representatives bring first hand knowledge of the breast cancer experience to research. By providing a perspective that is complementary to scientific expertise, these women help researchers and funding organizations identify and promote research that will impact on the community and that will reflect the human concerns and needs of patients, clinicians, survivors and their families. Consumer representatives should therefore, actively participate in all aspects of research of concern to them, from strategic planning and prioritizing of research to peer reviewing of grants, to dissemination of results and to the translation of research results into clinical practice.

Consumer involvement in decisions concerning research – particularly the direct involvement of consumer representatives in the grant reviewing process – has sometimes been viewed with apprehension by scientists and clinicians. There is however, evidence to show that these fears are misplaced. For example:

- In the extensive Congressionally Directed Research Program on Breast Cancer, administered by the US Department of Defence, community representatives participate in both peer review and programmatic review and sit on all panels along with scientists and clinicians. In the case of peer review of grants, two or three representatives, selected on the basis of their consumer advocacy and experience of breast cancer, sit on each panel. They represent the views of their community and have the same voting rights and responsibilities as other panel members: they are assigned grants to review, prepare written critiques addressing the relevancy of the research to their community's issues, are called upon to discuss these views after the scientific review of each proposal. For advice on technical aspects of research, consumer reviewers can turn to assigned mentors and panels of experts. Scores provided by community reviewers are weighted equally with scores provided by scientist reviewers. During the years that community involvement has been a part of the scientific reviewing process, no major drawbacks have been identified. Instead, the reviewing panels usually find great value in the community perspective.
- The California Breast Cancer Research Program (CBCRP) for example, not only encourages but also requires community participation in all phases of research. Community representatives and scientists work in partnership to identify research questions, develop plans carry out the research, interpret the results and disseminate the information to the community. Judged from the productivity and quality of the research sponsored by CBCRP (http://www.cbcrp.org/research), community involvement can work well both in the engine rooms of science and at the contentious level of grant reviewing.

The peak national body for those affected by breast cancer – Breast Cancer Network Australia – has united thousands of Australian women and families personally affected by breast cancer and formed an effective, approachable and influential large group that can be involved with both input and evidence for breast cancer research initiatives. Through its quarterly magazine, website, educational and training initiatives, BCNA can be receptive to the issues and needs of its members, advocate on behalf of their constituents, inform them of emerging issues, and promote available trials and prospective studies. Breast Cancer Network Australia's 'A Seat At The Table' initiative, which is considered international best practice in consumer involvement, provides informed, trained and supported women who have experienced breast cancer to represent the members on a range of committees, in research organisations and in the media. Similarly, other consumer organizations, including the ANZ BCTG Consumer Advisory Panel, (IMPACT – Improving Participation & Advocacy for Clinical Trials) and Breast Cancer Action Groups of NSW and Victoria, also provide consumer perspectives in the research environment.

Some examples, which have translated to research input, are the 'SNAC' trial, lymphoedema research and identification of issues of various groups eg advanced breast cancer, young women's issues and family cancer issues. The power of the BCNA members has been shown in several areas (identification of consumer priorities in national research; accessibility to pharmaceuticals eg Herceptin; the establishment of Risk-Management clinics). The members of Breast Cancer Network Australia value the importance of high quality, collaborative and targeted research, and would

also have a role in encouraging and inspiring researchers to find the answers women so desperately seek for our future generations, and to improve the quality of treatment and care being provided to Australians with breast cancer.

In 1999, BCNA received a grant from the Federal Government to document its model to select and support consumer representatives. The results of this project have been collated to provide a resource guide and package for use by community organisations working with consumer representatives.

For all sorts of political reasons, breast cancer research in Australia depends on the active support of BCNA and similar organisations. This support will be enlivened and strengthened if the consumer is actively involved in the planning and fulfilment of breast cancer research.

Goals and priorities

1 The "Seat at the Table" Program should be expanded so that community representatives are:

   i) included at all stages of the Strategic Plan – from conception to implementation

   ii) offered opportunities to involved with research groups in a significant way

   iii) appointed to grant reviewing panels

2 The results of research projects should be made available to the community in the form of summaries, written in accessible, plain English with as little jargon as possible

3 Support should be made available to establish and maintain a national consumer reference group to which researchers could turn for advice

4 Free registration to conferences, seminars and workshops should be made available to nominated grants consumer representatives. Wherever possible, time should be granted to community representatives to speak at scientific meetings and symposia on breast cancer

5 The annual symposium on breast cancer research, organized by the National Breast Cancer Foundation, should be continued and expanded.

38 Strengths and Weaknesses of Breast Cancer Research in Australia Summarized from the Breast Cancer Continuum

Area of breast cancer continuum	Strengths	Weaknesses	Goals and priorities
Across the continuum	A sophisticated research workforce Population based cancer registries in each state with the ability to provide up-to-date incidence data Successful large national collaborative research groups (Eg. ANZBCTG, TROG) Cooperative & supportive population	Lack of national research and funding facility Multiple number of organizations with a stake in the management of breast cancer which are fragmenting the effort Fragmented and limited dedicated breast cancer research funding Lack of research infrastructure funding Under-funding of consortia, large-scale science and longitudinal research Cumbersome and inefficient ethical review process Lack of timely national breast cancer data, particularly related to stage at diagnosis and outcomes Large differential in degree of difficulty in obtaining research funding for different aspects of the management continuum e.g. basic research and clinical trials versus health services research, psychosocial and palliative care research	Increase collaboration between breast cancer research funding agencies Provide opportunities for large scale, long term national research projects Increase opportunities to enhance Australia's research capability with support for research infrastructure and career development
Epidemiology (Page 11)	Internationally recognised epidemiologists Ethnically diverse population Population-based studies for genetic, environmental, lifestyle & psychological factors (Eg. ABCFS/MCCS	Difficulty in obtaining medical documentation Limited funding for large-scale, long-term projects Perception that bases are already covered	Establish causal relationships between environmental and genetic factors and the incidence of breast cancer Search for factors, both environmental and genetic, that informs strategies for earlier detection of breast cancer and that influence prognosis and health-related quality of life Create easier and seamless access to cancer registries, death records, medical records and archival pathological samples

Area of breast cancer continuum	Strengths	Weaknesses	Goals and priorities
Screening (Page 13)	The BreastScreen registry databases which could provide a comprehensive dataset for research	No agreed program of research for BreastScreen No current relevant randomised control trials or single national BreastScreen dataset to demonstrate the impact of population based screening in Australia Lack of research infrastructure of BreastScreen	National five year strategy including funding and audit strategies to be agreed by all stakeholders in breast screening in Australia Agreement by all state programs to publish annual data. These data reports to be linked to Cancer Registry and national death data to ensure full evaluation of outcomes Regular – at least biennial – national scientific meetings on screening results in Australian programs Seek collaboratinos with international groups
Genetics (Page 16)	Internationally significant collection of well-characterised breast cancer families from across Australia (Eg. cKonFab) Unique collection of population-based breast cancer case-control-families (Eg. ABCFS) Support from the majority of Australian publicly-funded familial breast cancer clinics Access to facilities essential for breast cancer genetic research, including high-throughput molecular analytical instruments, transgenics and proteomics	Limited access to bioinformatics as a research tool Limited database management resources available to ensure the long-term viability of the breast cancer family and population study collections being amassed at present	Ensure long-term funding for continuation and expansion of successful large-scale epidemiological projects Ensure that sufficient research funds are available to genotype the kConFab and ABCFS cohorts Enhance the national genomics centre to serve as a repository and source of expertise in bioinformatic and genomic analysis for use by the entire genetics community
Tumour biology & molecular & cell biology (Page 18)	High-quality basic biomedical science environments provided by many institutions in most States Progress in establishing institutional tissue banks Familial breast cancer research	Small number of scientists engaged in laboratory-based research Fragmentation of breast cancer research community Access to tissues & tumour samples restricted and complex	Normal biology of the mammary gland. Identify the earliest lesions and changes in mammary epithelium leading to breast cancer. Develop model systems and tissue resources. Identify and develop new biomarkers. Increase understanding of breast cancer metastasis. Develop new treatment approaches at academic institutions

Area of breast cancer continuum	Strengths	Weaknesses	Goals and priorities
Endocrinology (Page 21)	Long tradition of work of extremely high quality in ovarian hormones, their receptors and their modes of action Internationally recognized work on inhibitors of enzymes involved in hormone synthesis Strong interfaces between basic and clinical research	Better integration of clinical trials and fundamental research Lack of pharmaceutical companies with large-scale research facilities in Australia Variability in pathology reporting	Develop models of endocrine action in normal human breast cells Dissection of the relative sensitivities of normal cells to estrogen, progesterone and androgen, as well as other endocrine factors such as prolactin, to understand the main drivers to proliferation in the human breast Elucidate direct targets of the action of these steroids Access to human tissues, particularly normal tissue, needs to be expanded in well-characterised cohorts with accompanying reproductive and hormonal data. Linkage between population-based and laboratory studies is becoming an urgent priority Understand the molecular basis of agonism and antagonism exhibited by tamoxifen and newer estrogen modulators Clarify whether or not the effects of steroid and peptide hormones on breast cancer are independent of estrogen Genetic and biochemical studies of the enzymes responsible for the formation, activation and deactivation (protection) of estrogens in human breast cells are urgently needed, as are animal models carrying the appropriate sets of genetic markers Further investigation of inhibitors of the enzyme cyclooxygenase 2 (COX2) and its potential to offer effective chemoprevention by blocking estrogen synthesis in the breast while leaving its formation in bone unaffected

Area of breast cancer continuum	Strengths	Weaknesses	Goals and priorities
Pathology (Page 25)	Expertise in cell biology	Lack of molecular pathologists Lack of access to tissue, including premalignant (DCIS) and benign atypical lesions Variability in reporting Variation in access to genetic testing	Identify and validate biologic markers of pre-malignant, early stage, indolent and potentially aggressive disease Develop schemes for improved tumour classification and prediction of tumour behaviour
Clinical Management (Page 27)	Developing, disseminating and implementing guidelines in early and advanced breast cancer and psychosocial support Growing health services research Organizations such as NBCF and NBCC have provided a focus for breast cancer research and management and have involved consumers to ascertain priorities Growth in programs embracing psychosocial support, palliative care, communication skills etc in addition to traditional focus on anticancer treatment	The amount of time and effort to produce(and revise) management guidelines that satisfy all groups and are NHMRC approved Variation in quality of care between locations and the availability of multidisciplinary care Lack of patterns of care research Lack of biostatistical expertise Lack of research involving surgical and radiological interventions	By 2013 30% of all women with breast cancer will be in a clinical trial National register of trials Centres of excellence/National Cancer Institute which could co-ordinate research priorities and funding Use databases linked to biorepositories Better collaboration between cancer registries with agreed data set and pooling of de-identified data Encourage training of clinical academics (and funding) Encourage cancer centres of excellence Provide infrastructure for clinical trials and especially biostatistical support Encourage a broader range of clinical research Ensure consumer input into breast cancer management research priorities

Area of breast cancer continuum	Strengths	Weaknesses	Goals and priorities
Clinical trials (Page 29)	International recognition for World-leading investigators Centres of excellence Quality of life as a key endpoint in trials Enthusiastic, committed and highly skilled clinical researchers Ability to conduct high-quality research on a shoe-string Consumer involvement in scientific advisory and trial steering committees	Lack of a national register of all clinical trials Perception that only a small percent of eligible patients are offered the opportunity to participate in clinical trials Difficulty in obtaining funds to initiate and complete trials Lack of infrastructure to support clinical trials	Improve participation by integrating research in practice Ensure important questions are answered even if they are not of commercial interest by securing greater financial independence from industry Improve support for research infrastructure Bring stakeholders together with funds to support their work to improve productivity, efficiency, and outcomes
Psychosocial and survivorship research (Page 31)	International recognition for work on: Assessment of unmet needs Analysis of, and interventions to improve doctor-patient communication Understanding the experience of cancer survival Palliative care	Still generally small, local studies Limited power and impact Poor cohesion amongst psychosocial groups Low levels of funding Lack of national data collection of psychosocial benchmarks Lack of survivorship research	Focus on barriers to implementation, cost-effective ways to deliver interventions and strategies to encourage uptake Health services research concerning the interaction between system factors and psychosocial outcomes is needed Emerging data suggests that strategies to reduce morbidity in carers is urgently needed Ongoing development and evaluation of strategies to support decision-making in breast cancer patients Underpinning all of these goals and priorities is the need for psychosocial performance indicators to allow assessment of psychosocial outcomes associated with strategy implementation Collaborative links with other research streams is needed, to ensure psychosocial and clinical research is integrated, and opportunities for large-scale studies are not lost

Area of breast cancer continuum	Strengths	Weaknesses	Goals and priorities
Palliative care (Page 34)	World class service delivery programs A number of skilled, well trained researchers in palliative care medicine, nursing and allied health National and international collaboration activities Collaboration rather than competition and openness to new ideas. NHMRC Palliative Care Research Program.	Clinical responsibilities Methodological and ethical difficulties to conducting empirical research A lack of laboratory research Dispersion of talent	Undertake further research into symptom relief and management, rehabilitation; prognostication; effective ways of communicating information about prognosis; health outcomes; the role of the general practitioner and specialist nurse; needs of special groups and carers; bereavement services; family meetings; spiritual care and ethical issues Determine whether or not palliative care makes a difference to those at the end of their life Investigate ways to overcome some of the difficulties associated with outcome measures and with undertaking randomised control trials in palliative care
Consumer involvement (Page 36)	Vibrant, organised, and well informed national consumer movement Background of collaborative partnerships between consumers and researchers Strong community support for the cause	Difficulty in accessing clinical trials Few 'lay' summaries of and poor communication about research findings Duplication resulting in 'participant fatigue' Little or no quality research into complementary therapies	Expand the "Seat at the Table" Program Make the results of research projects available to the community in the form of plain English summaries Provide support to establish and maintain a national consumer reference group to which researchers could turn for advice Ensure easy access to conferences, seminars and workshops to nominated grants consumer representatives, including time to speak at scientific meetings and symposia Continue to expand the annual symposium on breast cancer research, organized by the NBCF

Professor Joe Sambrook

44 How Effective is Breast Cancer Research in Australia?

Breast Cancer Research

Cancer research broadly consists of two types of endeavours: research that is firmly focused on specific types of tumour, and generic research that is relevant to many or all cancers. Each of these endeavours can be divided into portmanteau programmatic areas – fundamental, pre-clinical and patient-focused research – and each of these can in turn be divided into specific disciplines and sub-disciplines. Generic fundamental research, for example, comprises a deep well-spring of activities from mechanistic studies of individual biochemical reactions to integrated analyses of intracellular signalling circuits and onwards into the wider world of genes, genomics and evolution. At the other end of the spectrum, patient-focused research that is relevant to all cancers encompasses palliation, drug delivery systems and cancer education and communication.

How should investment be distributed between the various branches and divisions of cancer research so as to lighten the burden of the disease on the community? A problem here is that there are a number of ways to measure the "burden of disease" including incidence, mortality, morbidity, disability, costs of diagnosis and treatment and life-years lost. Furthermore cancers vary both in the type and intensity of health burden they impose on the community and in the severity of the challenges they present to scientific and medical researchers. Consequently, different levels of research investment may be required to achieve equivalent progress with tumours of different types.

The Lack of Data about Breast Cancer Research in Australia

Unfortunately, no reliable figures are available in Australia for spending on particular types of tumour or on the various programmatic areas, disciplines and sub disciplines that comprise cancer research. There are no trustworthy and comparative data on the patterns and trends of spending by the major research funders. Without these data, it is impossible to accurately analyze cancer research activity, develop rational research policies, monitor progress, set milestones or measure the costs of progress. It is therefore a strong recommendation of this Plan that all agencies that fund cancer research in Australia collaborate to set up and maintain a cancer research database that accurately describes the programs, projects, fellowships and scholarships directly funded by these institutions.

The Australian database of cancer research should be modelled after the database established in the UK by the National Cancer Research Institute (NCRI), which is a partnership of the fifteen organizations that fund the vast majority of cancer research in the UK. Information about NCRI and a description of the database is available on the web.[iii]

In brief:

- The NCRI database includes details of the researcher(s) carrying out the work and an abstract
- Every entry entered into the database is classified using three internationally recognized coding systems: the Common Scientific Outline (CSO), Disease Site Codes and Medical SubHeadings (MESH). The CSO was developed by an international consortium that includes the US National Cancer Institute, NCRI, the US Department of Defence, the American Cancer Society, the Medical Research Council (UK), the Susan G Komen Breast Cancer Foundation, CapCURE and other cancer research organizations
- Individual research projects are classified by Disease Codes and then into one of seven broad areas of cancer research defined by the CSO as:
  - Biology
  - Etiology
  - Prevention
  - Early Detection, Diagnosis and Prognosis
  - Treatment
  - Cancer Control Survival and Outcomes Research
  - Scientific Model Systems

  Each of these broad areas is then subdivided, giving a final list of 38 individual CSO codes.

Use of these three internationally regulated systems (CSO, Disease Code sites and MESH):

- Provides an internationally regulated framework that ensures compatibility and consistency
- Allows accurate and meaningful comparisons between national and international cancer research portfolios
- Provides a mechanism for downstream linking of funded research to published outcomes.

An Australian database of research classified by CSO, Disease Code sites and MESH should be made available on the web, where it would be a resource for researchers to plan their future research and to identify collaborators and potential sources of data and reagents. In addition, the database would be a readily accessible fund of information about research for the general community.

A Survey of Breast Cancer Research in Australia

Because of a lack of reliable data on the activities of granting agencies and grant holders, we have little idea of the distribution of research funding across the areas, disciplines and sub disciplines of cancer research, of the levels of spending, or of the impact of research on the causes, prevention, diagnosis and treatment of breast cancer. However it is possible to gauge the scale and reach of Australian breast cancer research by measuring its output – the canon of papers published in scientific and medical journals. It is fairly obvious that this inventory is neither complete nor free of bias: "successful" research is far more likely to be published than are reports of negative results; and some areas – particularly clinical trials – may be systematically under-reported. While dehydrated descriptions of individual quanta of information are not equivalent to reductions in incidence of breast cancer or improvements in survival rates, research papers are milestones of our progress towards these goals.

Australian Publications on Research into Breast Cancer

A total of 520 papers were retrieved when PubMed, the database of worldwide scientific and medical publications maintained by the US National Library of Medicine, was searched for papers on breast cancer published from Australian addresses between 1998 and 2003. From the information provided in the abstracts, each of these papers could be classified using the CSO coding system.

This method of searching and retrieval is not perfect. For example, papers published from a non-Australian address with an Australian included in the list of authors would not necessarily be retrieved. However, the number of such papers where the Australian contribution is fundamental is not likely to be large. More significantly, papers dealing with the basic biology of normal cells (CSO Codes 1.1 – 1.5) or the generic abnormalities found in cancer cells (CSO Code 1.6), would have been under-retrieved. Clearly, the knowledge gained from generic research into cancer may flow to several other types of cancer, including breast. In the UK, where accurate estimates of the national spend on cancer research are available, slightly more is spent on fundamental research that is relevant to all cancers than on research focused on a specific tumour type. However, the amount of information flowing into breast cancer research from basic biological research or generic cancer research studies is unknown.

The PubMed database was searched for entries in each year from 1998-2003 (inclusive) containing the words "breast" or "mammary" and "cancer" in either the title, abstract or MESH terms and "Australia" in the address. Reviews (92), case reports (34) and published comments on other papers (4) were then removed and the abstracts of the remaining 529 papers were classified using the 38 CSO codes, each being given a single CSO code. Nine papers did not contain abstracts and were discarded from the analysis. Table 1 shows the distribution of papers each year across the 38 codes. (See Appendix 1)

The distribution of papers of Australian papers across the 38 CSO codes shows that:

- Approximately 100 Australian papers/year are published each year on breast cancer, which amounts to approximately 1.5% of the international research effort[iv] to understand and contain the disease
- The overall scope of Australian breast cancer research is large, with publications in each of the seven major CSO codes. The breadth of research is encouraging because it provides a broad base of skills and specialities on which to build a strategic plan for breast cancer research
- There is no single area that dominates Australian breast cancer research and the overall distribution of papers across most of the CSO codes has changed little between 1998 and 2003. However, the number of papers classified as CSO code 2.2 (Endogenous factors in the origin and cause of cancer) increased markedly in 2002 and 2003, perhaps reflecting the growing impact of large-scale studies such as kConFab and the Australian Family Breast Cancer Study on breast cancer research in this country.

The Quality of Australian Breast Cancer Research

Analysing the quality of scientific and medical research is a notoriously difficult problem. In the absence of quantitative objective markers, surrogate indicators are used that are less a measure of the quality of research than of the appeal of a particular paper to the scientific and medical community. The two most widely-used markers are Impact Factors and Citation Indexes.

Impact Factors rank scientific and medical journals according to the frequency with which articles in a particular journal are cited by other researchers. The higher the ratio of citations to papers published, the greater the impact factor of the journal. Journals that appear weekly and reach huge readerships *(e.g. Nature or Science)* typically have impact factors of 25 – 30 while specialist journals with small readerships may have impact factors <1. In between lies the vast middle class composed of archival journals of impeccable quality *(e.g. J. Biol Chem.)* and generalist journals that serve very large areas of cancer research *(e.g. J. Natl. Cancer Institute)*. So, to publish in journal with an impact factor of five is to achieve respectability; an impact factor >10 is to be cherished.

FIGURE 1. IMPACT FACTORS OF THE JOURNALS IN WHICH AUSTRALIAN BREAST CANCER PAPERS WERE PUBLISHED BETWEEN JANUARY 1998-DECEMBER 2003

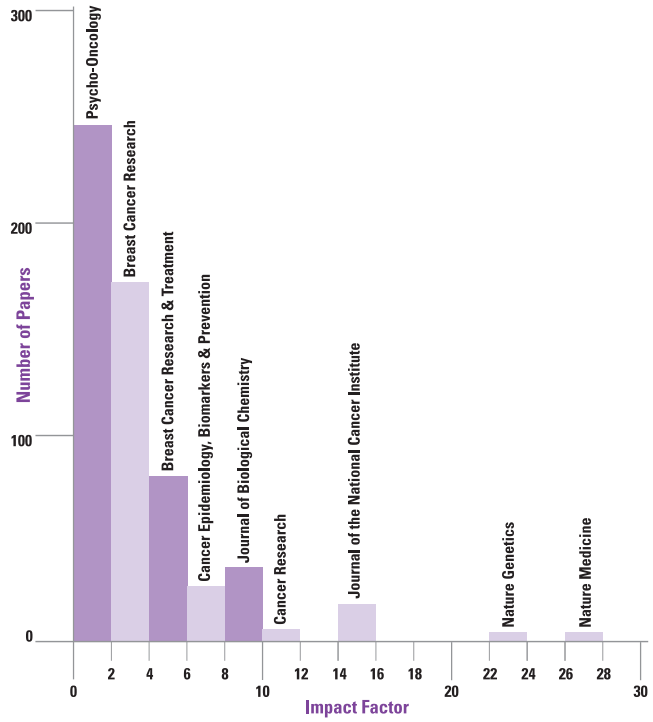


TABLE 2 PRESENTS THE DATA OF FIGURE 1 IN TABULAR FORM.

	Impact factors of journals				
	<2	2-5	5-10	10-20	>20
Number of papers	241 (46%)	172 (33%)	84 (16%)	19 (4%)	4 (0.7%)

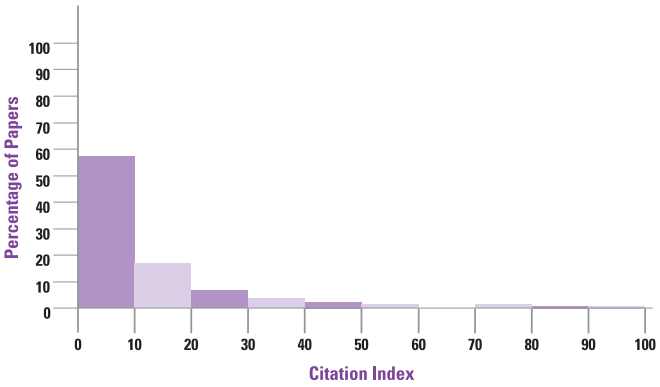
The data in Figure 1 and Table 2 show that a significant fraction of Australian breast cancer papers (>20%) are published in journals with impact factors >5. However, 46% of papers are published in journals with extremely low impact factors (<2). Although there may be some undiscovered jewels amongst them, many of these papers have been cited less than ten times and have passed into the archives virtually unnoticed by the international community.

Citation Indexes are the numbers of times a specific paper is been cited within a certain period. Citation indexes can be used to calculate, for example, the citation rates of papers of Australian papers classified in different CSO categories. Figures 2 shows the number of times Australian breast cancer papers published in the period 1998 – 2002 had been cited by March 2004.

Legend to Figure 1

The bar-graph shows impact factors of the journals (x-axis) in which Australian breast cancer papers were published between January 1998 and December 2003 (x-axis). Examples of the impact factors of several journals that published Australian breast cancer articles in this period are superimposed on the bar graph. The set of impact factors used in the analysis were taken from the 2002 edition of the ISI Journal Citation Reports, which at the time of this analysis (March 2004) was the latest set available.

FIGURE 2. AUSTRALIAN BREAST CANCER PAPERS, PUBLISHED BETWEEN JANUARY 1998 AND DECEMBER 2002.



Legend to Figure 2

Four hundred and twenty five Australian breast cancer papers, published between January 1998 and December 2002, retrieved from PubMed and classified as described in the legend to Figure 1, were individually submitted to the ISI Web of Science. The citation indexes for 410 papers were recovered. No citation indexes were available for the remaining 15 papers. These papers were excluded from the analysis. The bar chart (shows the percentage of papers with 0-10 citations, 10-20 citations, etc.

There is no accepted number of citations above which a paper can automatically be deemed influential. However, many scientists regard a citation index of 50 or more, achieved within two years of publication as evidence that a paper has significant impact internationally. Approximately 3% of Australian breast cancer papers achieve this level of visibility (Figure 2). However, none of these papers can match the citation frequencies of the most prominent international publications on breast cancer. For example, during the last five years, twenty-five papers have been marked as "of outstanding interest" in reviews of breast cancer biology published annually in Current Opinion in Oncology. These papers, none of which were from Australia, achieved an average citation index of 290 in the years 1998-2002.

How does breast cancer research in Australia compare with other branches of research?

Table 3 compares the citation indexes of Australian papers on breast cancer with papers on related areas and sub-areas of science funded by NHMRC.

TABLE 3: CITATION INDEXES OF (1) AUSTRALIAN PAPERS ON BREAST CANCER AND (2) PAPERS RESULTING FROM NHMRC-FUNDED RESEARCH

1. Australian Breast Cancer Papers (1998-2003)		**2. NHMRC Supported Research (1996-2000)**	
Area of Research	Average no of citations per page	Area of Research	Average no of citations per page
All (CSO Codes 1-7)	10.6	Basic Science + Clinical Medicine	7.1
CSO Code 1 Biology	17.5	Biochemistry & Cell Biology	8.6
CSO Code 2 Etiology	13.3	Genetics	9.0
CSO Codes 3-7	6.8	Medical & Health Sciences	6.7
Prevention		Medical Sciences	
Early detection		Immunology	
Treatment		Pharmacology	
Cancer Control		Medical Physiology	
		Clinical Science	
		Public Health	
		General Medicine	

Legend to Table 3

The left-hand columns of the Table show the citation indexes of 410 Australian papers on breast cancer, published between January 1998 and December 2002, arranged according to CSO codes (see Table 1). The right hand columns of the Table show the citation indexes of papers published between 1996 and 2000 with the aid of grants from NHMRC (data taken from Butler [2003]). These papers are classified into areas and sub-areas defined by NHMRC.

Because of differences in the classification systems and in the periods of collection, accurate comparison of the two sets of data is not possible. Nevertheless the data indicate that the rates of citation of Australian breast cancer papers are similar to those in wider areas of biomedical science supported by NHMRC. Papers in some areas of breast cancer

research are more heavily cited than the corresponding areas of research funded by NHMRC. For example, papers on the Biology (CSO Code 1) and Etiology (CSO Code 2) of breast cancer are cited more frequently on average than papers on Biochemistry and Cell Biology and Genetics. By contrast, breast cancer papers at the medical end of the research spectrum (CSO Codes 3-7) are cited with approximately the same frequency as the set of NHMRC papers categorized as Medical and Health Sciences. Overall, however, breast cancer researchers in Australia perform slightly better than their colleagues working in related areas of medical and scientific research (Table 3).

Conclusions

- The standard of breast cancer research in Australia is at least equal to that of the bulk of NHMRC-funded research
- A small number of very good papers are published in first tier journals and achieve high rates of citation. Not surprisingly, these papers are in areas of breast cancer research in which Australia is strong – for example, epidemiology, genetics and steroid receptor function
- A significant fraction of Australian breast cancer papers are of sufficient standard to be published in highly reputable, middle-rank journals. Not all of these papers are earth-shaking but many of them have an impact internationally
- Papers published from Australia on breast cancer cover most of the major CSO codes, reflecting the wide range of skills available in the research community. The total output of papers seems reasonable enough (1.5% of world output) given the small size of the breast cancer community in Australia and the comparatively miniscule size of research grants in this country
- Approximately 79% of papers that are cited infrequently (<10 citations) are published in Australian journals with low impact factors. Often, these papers deal with clinical issues of national concern or with translation of overseas research into an Australian context. These papers may be valuable, but because their readership is small, they cannot achieve spectacular citation indexes
- Papers dealing with highly specialized areas of cancer research tend to be published in journals dedicated to that speciality. Because the readership of these journals is small, these papers are undervalued when measured by indicators such as citation indexes and impact factors. Systematic bias in the assessment system may therefore mask strengths of Australian research in certain highly specialized areas. However, examination of the distribution of papers by CSO codes indicates that the number of publications affected by this type of bias is small.

A mixed picture emerges from this analysis. On the bright side, Australia pulls its weight in the numbers of papers published world-wide. And the average number of citations per breast cancer paper is superior, overall, to that achieved by the bulk of NHMRC-funded research. And there are areas of breast cancer research that are of extremely high quality (see below Strengths of Australian Breast Cancer Research). However, too many breast cancer papers disappear without impact into the scientific and medical literature; only a few them are influential and none are revolutionary. A fair overall assessment of Australian breast cancer research might be passing grade but not cutting edge.

So, is this the best we can do? Certainly not. The Australian community has high expectations of its researchers. If the breast cancer research community is to meet these expectations and justify continued investment of funding, we need to develop long-term strategies to increase the speed of discovery, identify and build on our areas of strength, raise the level and increase the velocity of performance, and produce incisive data of direct relevance to the disease and its management. Specific proposals to achieve these goals are presented in Section 8.1 of this report.

iii Descriptive information about research databases and CSO coding is available at http://www.nih.gov/news/pr/jun2003/nci-26.htm. An example of a database organized according to CSO codes is available at http://researchportfolio.cancer.gov/

iv A total of 6739 research papers on breast cancer were published in 2002.

Appendix 1

Table 1. Distribution of papers retrieved each year across the 38 CSO codes

	1998	1999	2000	2001	2002	2003	TOTAL 98-03
BIOLOGY							
1.1 Normal functioning of cells						1	
1.2 Cancer initiation: alterations in chromosomes	2					1	
1.3 Cancer initiation: oncogenes and tumour suppressor genes						1	
1.4 Cancer progression and metastasis	2		1	3	1	4	
1.5 Resources and infrastructure	1						
1.6 Cancer-related biology	22	28	18	21	16	13	
	27	**28**	**19**	**24**	**17**	**20**	**135**
ETIOLOGY							
2.1 Exogenous factors in the origin and cause of cancer					1	2	
2.2 Endogenous factors in the origin and cause of cancer	6	6	9	9	25	18	
2.3 Interactions of genes/polymorphisms with risk factors					6	4	
2.4 Resources and infrastructure related to etiology						1	
	6	**6**	**9**	**9**	**32**	**25**	**87**
PREVENTION							
3.1 Personal behaviours that affect risk						1	
3.2 Nutritional science in cancer prevention					1		
3.3 Chemoprevention					2	1	
3.4 Vaccines	5		4	4	1	1	
3.5 Complementary and alternative approaches to prevention							
3.6 Resources and infrastructure related to prevention							
	5		**4**	**4**	**4**	**3**	**20**
EARLY DETECTION, DIAGNOSIS & PROGNOSIS							
4.1 Technology development and/or marker discovery			5	3	2	2	
4.2 Fundamental parameters of marker development/evaluation				7	8	2	
4.3 Technology and/or marker testing in a clinical setting	6	8	6	4	7	4	
4.4 Resources and infrastructure related to detection, diagnosis						2	
	6	**8**	**11**	**14**	**17**	**10**	**66**

	1998	1999	2000	2001	2002	2003	TOTAL 98-03
TREATMENT							
5.1 Localized therapies – discovery and development	1		1	2	1	1	
5.2 Localized therapies – clinical applications	1	5	8	5	5	6	
5.3 Systemic therapies – discovery and development			2	1	1	2	
5.4 Systemic therapies – clinical applications	2	7	4	3	2	1	
5.5 Combination of localized and systemic therapies		2	1	3			
5.6 Complementary and alternative approaches to treatment							
5.7 Resources and infrastructure related to treatment	3	1	1			2	
	7	**15**	**17**	**14**	**9**	**12**	**74**
CANCER CONTROL, SURVIVORSHIP & OUTCOMES							
6.1 Patient care and survivorship issues	5	6	12	6	11	11	
6.2 Surveillance	5	11	9	8	4	6	
6.3 Behaviours related to cancer control	3	3		5	1	2	
6.4 Cost analyses of health care delivery		6				3	
6.5 Education and communication	3	2	4	1	2	1	
6.6 End-of-life care			2				
6.7 Ethics and confidentiality in cancer research					1	1	
6.8 Complementary and alternative approaches for supportive care							
6.9 Resources and infrastructure related to aspects of cancer control						1	
	16	**28**	**27**	**20**	**19**	**25**	**135**
SCIENTIFIC MODEL SYSTEMS							
7.1 Development and characterization of model systems							
7.2 Application of model systems			1				
7.3 Resources and infrastructure related to aspects of model systems					2		
			1		**2**		**3**
	67	**85**	**88**	**85**	**100**	**95**	**520**
UNCODED	1		1	2	2	3	**9**
REVIEWS	21	16	11	19	15	10	**92**
CASE REPORTS	4	7	6	6	6	5	**34**
COMMENT		1			3		**4**

Section 2

51

Breast Cancer Research in Australia: A Plan for Action

52 The Case for an Action Plan

This document is the third report to have been published within the last twenty-four months on cancer research in Australia. All three documents draw similar conclusions. The National Cancer Control Initiative's *Report of a Survey of Cancer Research in Australia*[3] states:

> Cancer research is a worldwide endeavour to which Australia is potentially a major contributor. This country has laboratory and clinical scientists and epidemiologists who are the equals of any in the world. However there are severe structural faults that vitiate cancer research endeavours in this country. Chief amongst these is the lack of a clear and coherent cancer research policy. The lack of high level strategic planning and co-ordination means that there is simply no mechanism to ensure that scarce research dollars are spent on areas where the need is greatest and where the chances of reducing the incidence or severity of the disease are highest. There has been an almost complete absence of strategic planning and co-ordination between funding agencies – both private and public, and between consumers, health service providers, the pharmaceutical industry and researchers across all areas of the continuum…Little thought or energy appears to be given, for example, to the creation and maintenance of a diverse research portfolio, or to the need to support high priority areas of cancer research; nor to the maintenance of the appropriate infrastructure, or to the relevance of the research to the incidence, severity and cost of specific disorders.

Similarly, the principal criticism raised in the National Breast Cancer Foundation report *Breast Cancer Research In Australia: Meeting the Challenges*[1] was not the quality of research but the lack of a strategic plan coupled to funding policy:

> Participants consistently identified the lack of a national breast cancer funding strategy as being an important issue that needs to be addressed. Many participants indicated it would be preferable to have a national cancer research strategy as being a priority, but…at a minimum, such a plan should be developed. Researchers, clinicians and consumer advocates were concerned about the lack of ongoing processes to…undertake strategic reviews of breast cancer research to inform the priority setting process, to create an inventory of current breast cancer research in Australia and to monitor the impacts of recently-completed research activities. Many participants also expressed concern about the lack of co-ordination among organizations raising money for breast cancer research; most of these people were of the opinion that a national breast cancer research strategy should also address co-ordination of funding.

Australia's lack of organization, funding and policy for cancer research now stands in stark contrast to the revitalised position of the USA, Canada and the UK, all of which have developed coherent cancer research policies in recent years that are tailored to their particular strengths and needs.

In the UK in 2001, the National Cancer Research Institute (NCRI) was formed as a partnership between Governmental and private sectors to accelerate the advancement of cancer research in the UK. The NCRI has since published a detailed overview of British cancer research activities that involves 15 of the major UK funding organizations. An overall strategy for cancer research has emerged from this initiative, which includes strategies to identify gaps and opportunities in current research, to facilitate collaboration between funding bodies and to monitor progress. In addition, in collaboration with the National Cancer Institute (U.S.), NCRI has developed a comprehensive database of international cancer research.

The National Cancer Institute's plan is essentially a comprehensive (and occasionally imaginative) catalogue of everything that money might buy in breast cancer research[v]. Each of the major sites of cancer is covered in detail, with timelines, milestones and outcome measures. Although such an all-embracing program is far beyond the financial capacity of Australia, introducing a system of periodic external monitoring of the progress of research, which is a feature of the NIH in the US, would bring substantial benefits and efficiencies to Australian research (see Action A1 below).

The Canadian Breast Cancer Research Alliance (CBCRA) (see panel page 54) was created in 1993 as a result of a groundswell of support from Canadian women, activists, survivors, and women in Parliament who came together to focus attention on ways to prevent and ultimately cure breast cancer. The current members of the Alliance include Avon Flame Foundation, the Canadian Breast Cancer Foundation, the Canadian Breast Cancer Network, Canadian Cancer Society, Health Canada, the Canadian Institutes of Health Research and the National Cancer Institute of Canada. With major financial commitments from these members, CBCRA has become the primary funder of a coordinated program of breast cancer research in Canada.

During CBCRA's second five-year term (1998-2003), the Canadian federal government provided $15 million in addition to the $10 million pledged by the Canadian Institutes of Health Research. The National Cancer Institute of Canada pledged a further $10 million with funds raised by Canadian Cancer Society volunteers. Two new funding partners, the Canadian Breast Cancer Foundation and the Avon Flame Foundation, each contributed $5 million over five years to CBCRA. With this increased and renewed support, the CBCRA has a total budget of $45 million over five years to fund breast cancer research across Canada.

Australian funding for breast cancer research is administered by several agencies, particularly the NHMRC, the NBCF and the State Cancer Councils. NHMRC has its own system for assessing grant applications and has no formal links with other agencies. By contrast, the NBCF and the Cancer Councils have in recent years shared a common process for reviewing and ranking grant applications. But this is as far as co-ordination of funding goes; after the reviewing process is complete, each agency makes its funding decisions independently. The result, as can easily be imagined, is a collection of funded grants that add up to no more than the sum of their individual parts. In the absence of a long-term plan for breast cancer research, strategy is set annually simply by default and amounts to no more than the grants that happen to be successful in a given year.

The NBCF report[1], further pointed out that the NHMRC and Cancer Councils' granting processes favour short-term projects and impede the development of new and innovative research. Large-scale national research programs suffer particularly badly in this process. Australian granting agencies are conservative bodies, reluctant to commit to long-term funding, chiefly because substantial forward commitments would leave few funds available to support new projects. Although short-term, small-scale projects have in the past been fruitful, the increased complexity, global reach and accelerating speed of present-day breast cancer research dictates a need for new and complementary approaches to funding in Australia.

In the last ten years, only one new large-scale national program in breast cancer research (see Table 4) has been funded in Australia, in large part because the funding agencies have not created effective granting mechanisms to accommodate internationally competitive long-term projects. In Australia, such projects are generally funded in a piecemeal fashion from an overlapping patchwork of grants. The funding organizations make little effort to coordinate or even inform each other about their funding decisions or the duration and extent of their financial support. Both the principal investigators of the large scale-projects and the funding organizations are condemned to a revolving mill of grant applications. Administration of the project turns into a financial juggling act and the smaller funding agencies increasingly feel they are victims of cost-shifting rather than partners in a national enterprise.

In summary, the system of distributing funding for breast cancer research in Australia needs to mature further into a nationally coordinated plan. Each of the three plans outlined above (UK, USA, Canadian) has elements that can be applied to the Australian research environment with major long-term benefits. In particular:

- Forging ties and setting common goals among multiple funding agencies, both private and public
- Establishing systems to identify and support large-scale multi-year projects of national and international significance
- Establishing better systems of communication between research groups through the use of CSO codes and shared databases; and
- Cataloguing the course and velocity of breast cancer research across the entire spectrum, including prevention, early detection, treatment, fundamental laboratory investigation and quality of life.

The aims of the actions recommended in the following pages are to take better advantage of the strengths of our present system and to minimise its current weaknesses. As the direction of research is hugely influenced by research policy, our first priority has been to address the challenging issue of a national strategy for research funding. In addition to prioritising the scientific and medical challenges of breast cancer, it is vital that we set our national system of funding breast cancer research to ensure that Australia is effective in its goal of reducing the incidence and impact of breast cancer on our community.

v In fiscal year 1993, NCI invested US$548.7million in breast cancer research. However, in that year, the total amount of funding for breast cancer research from all sources (Komen Foundation, US Department of Defence, American Cancer Society, California Breast Cancer Research Program, Howard Hughes Foundation, Avon Foundation etc) was close to US$1 billion.

An Alliance in Action

The experience of the Canadian Breast Cancer Research Alliance (CBCRA) demonstrates that the government, non-profit charity, and private sectors can join together effectively in an alliance.

"In CBCRA's experience we had no problem with organizations being subsumed and losing identity. We followed several organizational principles that helped avoid such a problem:

- *Each partner or full member has two seats on the Board of Directors, regardless of the amount pledged:*

  A minimum contribution was established to become a partner or member, and once a partner, the organization has two seats. Each seat has one vote. Thus, the bigger contributor, such as government, may be contributing $3 M/yr, while a smaller non-profit is contributing $1 M/yr, but both have two seats on the Board, and therefore two votes.

- *CBCRA and its Board actively try to ensure that the needs of all partners or members are addressed:*

  We recognize that each sector will have different needs: the private sector has very different needs from the government sector. For example, when we drafted our Communications Policy, we ensured those with strongly different needs were directly involved in formulating the policy, and we worked hard to find compromise solutions.

  Similarly, everyone recognizes that each partner or member has different strengths and weaknesses, which often relate to the sector's profile, and the Board representatives tend to defer in their discussions to those with appropriate knowledge and expertise. For example, the partner or member from the private sector may be knowledgeable about communications strategies, but have no understanding at all of peer review or grant competitions, so we would ask that Board representative to lead the discussion on communications.

  When the strong will of the group is to make the partnership work, the members are willing to bend a bit. For example, for 10 years we called the member organizations partners. When signing the memorandum of understanding for the third five-year term, we wanted to change our name to Canadian Breast Cancer Research Partnership. However, our government partner received unexpected advice from its legal department that it could no longer enter into "partnerships." So we all quickly agreed to change the word Partnership in our name to Alliance, and we redrafted the memorandum of understanding to specify that we are composed of organizations that become Members, and that although our government member is not a signatory to the memorandum of understanding, it will have two representatives on the Board in recognition of its support for the Alliance.

- *CBCRA has its own Board of Directors.*

  Although one member serves as the "administrative home" for CBCRA, providing accounting functions, etc., that member still receives only two seats on the Board. Originally, when CBCRA was smaller, that same member's Board oversaw it, but when we invited new members to join, it became clear that a fundraising organization could be compromised by belonging to an organization that reported to another organization. So when we expanded our membership, we established our own Board of Directors"

Marilyn Schneider, Ph.D. Executive Director,
Canadian Breast Cancer Research Alliance

Table 4

Examples of Existing Large-Scale Research Projects

Title of Project	Date	Summary	Sources of Funding
ANZBCTG www.anzbctg.org	1975 – present	The ANZ Breast Cancer Trials Group conducts a program of national trials for the treatment of all stages of breast cancer. This consortium, the vanguard of clinical breast cancer research in Australia, has been involved with both international as well as nationally-initiated programs since its formation in 1975. Inevitably, Australia's relatively small population and geographical isolation have meant that ANZBCTG has mostly been a participant in US- or European-led trials; nevertheless, as a group it has had a significant say in both development of protocols and interpretation of the results of clinical trials. By recruiting proportionally more of those eligible than other countries, the ANZBCTG has been responsible for ensuring that Australian women have had the earliest opportunity to receive new agents potentially useful in reducing morbidity and mortality from breast cancer.	
Breast Cancer Family Registry www.cfr.epi.uci.edu/.	1995 – present	A population-based, case-control-family study of the genetic epidemiology of breast cancer. Understanding familial aggregation is a key to understanding the causes of breast cancer and to facilitating the development of effective prevention and therapy. To address urgent research questions, the National Cancer Institute (USA) supports a collaboration of six academic research institutions and their medical affiliates in the USA, Canada and Australia. The sites have developed core family history and epidemiology questionnaires, data dictionaries and common protocols for biospecimen collection, processing and pathology review. An information centre collates, manages and distributes data. Nearly 12,000 families have been enrolled in the Registry. The data and biospecimen resources are available for collaborative, interdisciplinary and translational studies for the genetic epidemiology of breast cancer.	National Cancer Institute (USA) NHMRC VicHealth Cancer Council NSW Victorian Breast Cancer Research Consortium Total funding + $10M over 10 years
The SNAC Trial (Sentinel Node vs Axillary Clearance Trial)	2002 – present	Conducted by the Royal College of Surgeons. The trial is comparing two operations for detecting cancer cells in the lymph nodes of women with early breast cancer. 1 Axillary clearance (AO) – removing most of the lymph nodes under the armpit. 2 Sentinel Node Biopsy (SNB) – removing only the first few nodes most closely related to the tumour. It is the first large trial of surgical treatment of breast cancer in Australasia. It is expected to provide important information on the effects of axillary surgery and the quality of life of women having breast cancer surgery. When data from this trial are combined with data from other similar international trials, a metaanalysis will have adequate power to show whether axillary surgery influences recurrence of breast cancer and survival.	National Breast Cancer Foundation $330K for 3 years Medical Benefits Fund Commonwealth Department of Health and Ageing NHMRC project grant 2003- 2007 – $1.4M for 5 years

Title of Project	Date	Summary	Sources of Funding
kConFab www.kconfab.org	1995 – present	The Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) is a multidisciplinary, collaborative framework for the investigation of familial breast cancer in Australia. The primary aim of kConFab is to foster and facilitate research into the causes and impact of familial breast cancer through construction of a research resource containing genetic, epidemiological and clinical data and appropriate biospecimens. kConFab's objectives required the development of infrastructure, novel in Australia, for large-scale recruitment and data collection from families with multiple cases of breast and breast/ovarian cancer, identified through the network of Family Cancer Clinics around Australia. Comprehensive genetic, biological and epidemiological data are currently held on 822 families (11,422 consented individuals). Germline DNAs are stored for 7389 individuals including 1159 carriers of BRCA1 or BRCA2 mutations. Fresh frozen tumours and normal specimens are available for 253 consented individuals. This resource is available to researchers anywhere in the world, who may apply to kConFab for biospecimens and data for use in ethically-approved, peer-reviewed projects. Multiple research projects based locally and overseas now depend in whole or in part on kConFab. These projects include long-term prospective studies of clinical outcome and psychosocial predictors of developing breast cancer, evaluation of unclassified variants in BRCA1 and BRCA2, linkage-based and candidate gene searches for novel breast cancer susceptibility loci, and searches for environmental and genetic modifiers of cancer risk in carriers of mutations in BRCA1 and BRCA2.	NBCF (since 1997) NHMRC (since 2000) Various Australian State Cancer Councils (since 2001) Several private non-profit organizations Total funding = $5.5M over 8 years
Victorian Breast Cancer Research Consortium Inc. www.vbcrc.org.au	1997 – present	VBCRC operates as an "Institute without Walls" with research groups located in host research institutes where they can benefit from infrastructure support and intellectual collaboration. VBCRC is unique in Australia and probably in the world. It is an assembly of six research groups in Melbourne that conduct basic research into different areas of breast cancer. Together they cover the major branches of breast cancer biology, namely, molecular pathology, mesenchymal-epithelial interactions, transcription factors, molecular genetics, epidemiology and hormonal aspects of cancer. From the outset, a major goal of the Consortium was to forge strong interactions and collaborations between the laboratories, in order to optimize cross-fertilization of ideas and skills. The group-leaders were recruited by an international search, and three out of the five were recruited from the USA and UK. After a favourable review of the Consortium in 2002, the Victorian Government is being approached about funding another round, which is essential to allow the projects which are underway to reach fruition, and to translate research findings into improved therapies.	Victorian State Government $30M over 10 years.

Title of Project	Date	Summary	Sources of Funding
The Melbourne Collaborative Cohort Study (MCCS)	Early 1990s – present	The goals of MCCS are to investigate prospectively the role of diet and other lifestyle factors in causing common chronic diseases – especially cancers of the prostate, breast and bowel – and to investigate possible interactions between these exposures and common genetic variants. MCCS is designed to address important questions concerning health maintenance and disease reduction in middle-aged Australians. Between 1990 and 1994, 41,500 people (24,500 women and 17,000 men) aged 40-69 were recruited. About 30% of the cohort are southern European migrants to Australia who were deliberately over-sampled to extend the range of lifestyle exposures and to increase genetic variation. Extensive information was collected at baseline in face-to-face interviews that included questionnaires (diet, physical activity, etc.) and physical measurements, including lean and fat mass by bioelectric impedance, and blood pressure. Blood samples were drawn and aliquots stored for analysis of DNA and other molecules of interest (e.g. sex hormones and growth factors, carotenoids and fatty acids involved in disease pathways). The cohort was followed up by mailed questionnaire and by telephone to update lifestyle exposures and self-reports of non-cancer, non-fatal health events at 3-4 years after baseline. The MCCS is matched regularly to cancer registries and death indices to capture cancer incidence and deaths. The 40 to 69 year-olds who were recruited in 1990-94 are now aged 50 to 85 years. This age group spans that stage of life in which ageing begins to take its toll in terms of onset of chronic disease, increased disability (and concomitant decreased quality of life), and premature mortality. We know that southern European migrants, who comprise 30% of the cohort, enjoy a longer life expectancy, and reduced rates of cancer and heart disease, than do their Australian-born counterparts. As part of the NHMRC Program Grant "ECHIDNAS" 2002-2006, all living participants are being followed up to update time-dependent exposure variables, repeat physical measurements and repeat blood sampling. The MCCS is now positioned to deliver useful information in terms of the predictive power of lifestyle and genetic variation for the risk of common cancers such as breast, bowel and prostate. The significance of the MCCS is in its unique design, adopted to overcome problems of measurement error, retrospectivity, and lack of population and temporal relevance. Our cancer studies are innovative in that we are retrieving archival tissue, performing a review of histopathology and carrying out immunohistochemical assays. In this way we will be able to subgroup cases for analysis according to known or established criteria, eg. ER-positive and ER-negative breast cancer. This approach is novel in epidemiological studies of this size and will yield much better information on pathways to cancer.	Recruitment of cohort VicHealth $1.4M Cancer Council of Victoria $3.6M Data management and follow-up $3M over 10 years Total funding = $8M over 14 years NHMRC Program Grant – $5M

Actions

A An Alliance of Breast Cancer Funders

ACTION A1

Establish an alliance of breast cancer funders to implement strategic funding of breast cancer research in Australia. The alliance should co-ordinate and streamline, review, prioritise, and broker the funding of breast cancer grants. A major goal of the alliance should be to fund more high-quality breast cancer research than individual sponsoring agencies can support on their own – in particular large-scale, multi-year projects.

With the creation of an alliance, individual funding organizations might fear a loss of their public identity and of their ability to support projects of particular interest to them. However the Canadian experience with CBCRA shows that, with care, identity can be protected and even enhanced through the formation of a national alliance, particularly when the funding results in a major advance. The key has been to ensure that members retain their claim to a fair share of public credit. In addition, funding organizations in Britain that were previously fierce rivals now work harmoniously together for the common good under the banner of Cancer UK.

Common sense would dictate that an Australian alliance, like in the UK could act as both as a broker of funding and as a strengthened charity for the collection of donations targeted towards Australian breast cancer research. At a stroke, the formation of an alliance would act to reduce competition for public and private dollars, as well as reducing public confusion about the roles of these many competing organizations. In the long run, it would be sensible for individual funding organizations to join forces with the alliance. However, linking these organizations together at an early stage might be a bridge too far. Member agencies funding breast cancer research should be encouraged to retain their present policies of funding smaller-scale research projects that are of special interest to them, particularly as there are many areas of breast cancer research that could continue to be funded by individual organizations as traditional project grants.

We suggest that the alliance would create a platform, hitherto unavailable in Australia, for new, long-term, national, large-scale research projects in breast cancer that are beyond the reach of the present funding system.

However, to succeed in this role, the alliance would need to have the capacity and influence to attract funding from Federal & State governments, private foundations and the lay public. The alliance would therefore need to identify large-scale projects that would catch the public's imagination and be attractive to existing funding organizations.

B Large Scale, Long Term National Projects

ACTION B1

The Australian alliance of breast cancer research organizations should create a fund to support several large-scale long-term projects of national and international importance.

As pointed out in the NBCF report *(Breast Cancer Research In Australia: Meeting the Challenges*[1]*)*, a major deterrent to mounting large-scale research projects of national and international significance has simply been the lack of a plan around which funders, researchers across the entire breast cancer continuum and the interested public can coalesce.

Yet Australia has huge potential for major research enterprises:

- Australia has a strong base of fundamental research with many institutions and groups functioning at an internationally-competitive level
- Its population is diverse and generally keen to become involved in medical research
- Its population is aggregated into a few cities that are served by large hospitals, an arrangement that facilitates recruitment into large projects
- Compared with other countries, there is relatively little population migration between cities, which facilitates long-term follow-up
- Much of the health care system is publicly-funded which, at least in theory, facilitates access to medical records
- Data in State-based cancer registries and national death registries is accessible, given that appropriate ethical permission is obtained; and
- Collection and use of biological specimens is easier in Australia than in other countries, an important fact that needs to be respected and protected. We believe that this is best achieved by high quality research, which is national coordinated and which welcomes widespread public scrutiny.[vi]

This is not to say that Australia is ideal for large-scale projects. Obtaining permission from multiple human research ethics committees in institutions across the country, for example, to access archival pathological specimens and fresh surgical specimens can be a daunting deterrent. As discussed earlier the practice of slicing the grant pie into small packets is a major impediment to the development of large-scale, long-term research. In addition, retrieving paper medical records from individual hospitals instead of a common electronic database can be a huge logistical task. These barriers can be progressively ameliorated with time, and perhaps solved, as long as researchers and the wider community can see value in doing so (See Action C10 Ethical Issues, page 69).

At present, several large-scale research projects relevant to aspects of breast cancer are underway in Australia. While each of these projects has its own clearly-visible strengths (See Table 4. Examples of Existing Large-Scale Projects), none displays all the qualities desirable in a national, large-scale project. Three of the existing projects (kConFab, ANZBCTG, SNAC) are tightly-focussed on specialized areas of breast cancer research; one (VBCRC) is state-based rather than national; and the two epidemiological studies (Melbourne Cohort and BCFR) were not set up to collect fresh tumours and so have only limited opportunities to correlate epidemiological findings to the molecular properties of breast tumours.

Few new large-scale national research projects on breast cancer have been established in Australia during the last ten years. Almost all of the existing projects were designed in the period between 1989 and 1995 and all but one (VBCRC) are funded from a patchwork of sources. In consequence, none is well-placed to take advantage of the rapid and massive advances in the molecular analysis of cancers that have occurred since 1997. These include: the use of dense oligonucleotide arrays for parallel analysis of gene expression, and for cataloguing pathogenic loss, gain, translocation and mutation of genomic sequences; the capacity to develop *catalogues raisonnées* of the proteins present in normal and tumour cells; the ability to apply these techniques to very small numbers of cells recovered from fresh histological preparations; and finally, the development of powerful bioinformatics tools to mine and extract data and to classify tumours according to their molecular characteristics.

We therefore believe that the time is overdue for creation of new large-scale projects that would take advantage of these and other advances in breast cancer research. New large-scale projects should:

- be focused on topics where Australia already has a critical mass of expertise and is competitive internationally
- foster collaboration between researchers of many different disciplines
- provide materials and data for a large number of downstream and spin-off projects across the entire continuum.

Almost every section of the breast cancer research continuum could propose a large-scale project that would have a strong chance of improving prevention, detection and/or treatment of breast cancer. In practice, however, projects upstream of the breast cancer continuum may be too risky, while those towards the right hand may not have sufficient downstream bonuses. The projects with the greatest payload probably map at or just after the beginning of the research continuum and have the potential to fertilise large areas of downstream research.

As soon as possible, the alliance should call for expressions of interest and should provide financial support for a short list of three or four candidate projects to develop full-scale, realistically-costed proposals. Funding for large-scale projects should be awarded by a transparent, competitive process, The projects should be internationally competitive and potentially able to attract overseas funding.

In the following pages, we list several potential areas that could benefit from a large-scale research Australia. This list is intended to be exemplary rather than exhaustive or guiding. To give some idea of the scope that large-scale projects should have, one of the projects is described in some detail.

vi Since April 2003, collection of biospecimens in the USA has been heavily encumbered by new regulations promulgated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA). These regulations impose substantial restraints on the use and disclosure of medical information, even for legitimate research purposes. The HIPAA regulations are reinforced by governmental audits and by civil and criminal penalties. Similar restrictions are affecting tissue collection in Europe. For example, in Sweden, a tissue donor must have information about each study in which his/her tissue is to be used and must give consent for that particular use. Australia, at present, takes a more balanced view. Patients can consent to the use of residual tissue in broad categories for future research projects. Their right to make informed and voluntary decisions about the use of their tissue is protected by safeguards, which include review of the projects by the relevant Human Research Ethics Committees, absolute right of withdrawal, disclosure of details about commercial arrangements and provision of information about subsequent contact.

60 Examples of Possible Large-scale Projects

In the following pages, we list several potential areas that could benefit from a large-scale research program in Australia. This list is intended to be exemplary rather than exhaustive or guiding. To give some idea of the scope that large-scale projects should have, one of the projects – the 1,000 Women Project – is described in some detail on pages 62-64. We expect that the other large-scale projects listed in this table would be of similar length and cost.

Title	Scope	Goal
1,000 women project	Recruit a cohort of 1,000 women at first diagnosis, and then catalogue the genomic changes and expression profiles of the tumours in great detail. The idea is to create a highly enriched dataset containing a characterization of the biology of the tumours, epidemiological information, family history and pathological information, and then to follow the women as they progress through the various phases of the breast cancer continuum	Correlate the molecular properties of the tumours with epidemiological exposures, response to treatment and other downstream clinical parameters
Biology and genetics of early breast cancer	Analyze the significance, grading and prognosis of ductal carcinoma in situ and assess the biological, prognostic or diagnostic significance of benign and atypical lesions in the breast that are now detected by mammography and subject to diagnostic biopsy	Identify the earliest molecular/genetic lesions and the sequence of events that correlate with progression
Mammary stem cells as progenitors of breast cancer	Develop methods to identify lineage markers mammary stem cells, define their physiological niche, measuring the kinetics of stem cell production and division, catalogue the patterns of gene expression in stem cells of various lineages, identify stem cells with malignant potential. and developing methods to deplete and repopulate mammary stem cell compartments	Identify and selectively eradicate mammary stem cells with malignant potential
High throughput functional screens for oncogenes involved in breast cancer	Apply high throughput cell transfection technologies to screen for oncogenic changes (gain- or loss-of-function) in mammary cells	Identify oncogenes that are the molecular drivers of growth of breast cancer cells. Genes of this type are likely markers for diagnosis and classification of disease as well as targets for therapeutic intervention
Biology of the normal breast	Delineate the structure, function and response to ovarian hormones of the normal breast throughout life	Shed light on understanding the normal breast and variations from normal that occur in the population and to contribute to early detection and prevention strategies

Title	Scope	Goal
Women at high genetic risk	Develop and sustain schemes for long-term follow-up of high risk families to determine more comprehensively the natural history of BRCA1/2 loss-of-function and hypomorphic mutations Measure the effectiveness of: clinical interventions such as surveillance, chemoprophylaxis and prophylactic surgery, and psychosocial interventions aimed at improving long-term outcomes	Search for modifying influences, both environmental and genetic, with the aim of improving risk assessment for women with inherited susceptibility to breast cancer
Clinical research	Use new technologies such as microarrays to select the optimum treatment option for specific subgroups of patients to replace the more empirical approach. This is in addition to continuing the search for an investigation of new agents that will specifically target breast cancer Test dissemination and implementation strategies for guidelines with the endpoint of their incorporation into routine practice. This assumes that the process of generating and updating guidelines becomes more efficient so that guidelines reflect the best current evidence	Incorporate new technologies into routine clinical practice Improve the standard and currency of clinical guidelines
National audit	Continue and further develop an audit of surgeons' performance against national guidelines. This audit has the ability to provide a rich source of data for health delivery research. Over the past 12 months, the project has adopted a far more collaborative and inclusive approach, with the formation of an advisory committee which includes representatives of BCNA and the NBCC. The program requires long-term funding and has the strong backing of both BCNA and NBCC. now in electronic form	Improve the care of women with breast cancer on a national basis
Management of the recovery process	Develop a national cohort to investigate aspects related to communication between clinicians and patients, management of fatigue and treatment-related side effects, recovery of upper-body function, prevention of lymphoedema, and research related to other aspects of health-related quality of life, especially residents of rural/remote and those with less access to the kind of medical care offered in metropolitan cities	Improve the quality of life of women recovering from breast cancer

Example 1: The 1,000 Women Project

Tissue banks and high throughput technologies and breast cancer outcomes and downstream clinical projects

Breast cancer, like other human malignancies, is ultimately the result of damage to DNA. Even tumours detected at the very earliest stage of the disease show profound disturbances in gene structure. These abnormalities cause large-scale changes in the patterns of gene expression that reflect the history and, in some cases, the origins of the tumours. But the patterns of DNA damage and alterations in gene expression may also have the power to predict the future course of the disease and the response of the tumour to treatment. A major goal of the 1,000 women project is to generate a rich matrix of molecular, epidemiological, psychosocial, pathological and clinical data that would be accessible to researchers working across the entire continuum of breast cancer. As the cohort of women progresses along the continuum, they would have the opportunities to take part in many additional research projects designed to clarify the complex relationships affecting the outcomes of breast cancer.

We outline a scheme to:

- Assemble a dedicated tissue bank of 1,000 breast tumours and appropriate normal tissues (see Action C1)
- Collect comprehensive prospective and retrospective clinical, genetic, psychosocial and epidemiological data
- Analyze the patterns of gene expression in breast tumours by hybridization to dense oligonucleotide microarrays
- Analyze the patterns of serum proteins in breast cancer patients by proteomic methods
- Map genetic and epigenetic changes in breast tumours by high throughput hybridization of tumour DNA to SNP arrays and by hybridization of sequence simplified tumour DNA to dense oligonucleotide arrays and methylation microarrays; and
- Collect all data centrally and make it promptly available for ethically-approved, peer-reviewed and funded research projects.

The logic behind this project is straightforward: If we define in precise detail the molecular characteristics of a large set of breast tumours we should be able to understand breast cancer and improve every aspect of the disease. Comprehensive retrospective and prospective clinical data linked to molecular analysis of a large set of breast tumours using high-throughput technologies for genomic, proteomic and pharmacogenetic analysis should lead to identification of better diagnostic and prognostic markers and should allow prediction of individual response to both standard therapeutic treatment and new drug therapies for patients.

Breast cancers have dramatic changes in their chromosomes, including deletions, epigenetic chemical modifications, amplifications and complex rearrangements. These changes, the pockmarks of each tumour's history, are the outward and visible signs of a generalized genomic instability that powers the evolution and progression of the cancer. Completion of the human genome sequence provides an opportunity to construct high-resolution maps of the sites of DNA damage, rearrangement, amplification and modification in tumours. In the past, studies on this scale have been impossible because of the vast size of the human genome and the lack of affordable, automated analytical techniques. However, molecular analyses of entire tumour genomes are now approaching "industrial" speed and scale with the development of high-throughput methods and the computing tools required to analyze and parse massive

amounts of data. By applying these methods to a large cohort of breast tumours we can construct comparative maps of DNA damage, search for recurrent aberrancies in gene expression, and can show how these changes distort signaling networks, disrupt metabolic pathways and drive cells into malignancy. Many researchers would argue that if we cannot solve breast cancer by this type of deep multidimensional molecular analysis of tumours, then the disease will remain beyond our understanding.

EXPRESSION MICROARRAY TECHNOLOGY

This provides the means to examine the activity of several thousand genes in a tissue at a single time and to classify tumours according to their patterns of gene expression. This has the potential to highlight new diagnostic/prognostic markers and therapeutic targets, particularly when comparisons to appropriate normal tissues are included.

ARRAYS OF SINGLE NUCLEOTIDE POLYMORPHISMS

SNPs are changes in DNA that have arisen once during human evolution. Many of the 10 million or so known SNPs have been mapped to precise locations in the human DNA sequence. High-density arrays of SNPs can be used to construct detailed genotypes of both normal tissues and tumours and hence to identify predisposing genes and alleles involved in both initiation and progression of tumours.

METHYLATION

Epigenetic modification of DNA by methylation is a common event in breast tumours and is a major mechanism for suppression of transcription of genes. Until recently, the extent and intensity of methylation was measured one gene at a time. However, high-throughput technologies are now available to assess genome-wide patterns of methylation in tumours. Again, this type analysis has the potential to reveal both useful markers and genes, such as tumour suppressors, that are causally involved in breast cancer.

CHANGES IN COPY NUMBER

Many high-throughput methods have been developed to identify genomic regions that undergo changes in copy number during tumour development. These methods include hybridization of total genomic DNA to BAC arrays or hybridization of simplified genomic DNA (i.e. DNA from which repetitive sequences have been removed) to high density oligonucleotide arrays. Increased copy number often reflects the presence of an amplified oncogene that contributes to tumour formation or progression while loss may indicate the genomic location of a tumour suppressor gene.

CHARACTERIZATION AND QUANTIFICATION OF MAMMARY PROTEINS PRESENT IN THE SERUM OF WOMEN WITH BREAST CANCER BY COMPREHENSIVE, HIGH-THROUGHPUT PROTEOMIC METHODS.

Although this area of research is still emerging, it has the potential to identify markers for early detection and non-invasive mass screening. In the past, logistic difficulties have imposed restrictions on the types of samples that can be analyzed by high-throughput technologies. For example, until a year or so ago, virtually all studies used larger tumours, from which spare tissue, excess to that required for a diagnosis, may be more easily obtained. However, the sensitivity of molecular analyses has now increased to the point where it is feasible to carry out most molecular analyses on breast tumours at the time of diagnosis.

Downstream Projects

The following examples, both taken from the psychosocial area illustrate how downstream projects would be linked to the 1,000 women project. Although useful information could be obtained from these projects in isolation, the availability of detailed molecular data and ultimately outcome data will define subsets of breast cancer, which may influence women's mental states and psychosocial responses and may vary with age of diagnosis and type of treatment.

PSYCHOSOCIAL PREDICTORS OF OUTCOME.

There is mounting evidence that responses to stressful life events, and common psychological states such as depression, can disturb many areas of the immune system and that impaired immune system function

predisposes to malignant growth.[11,12] It is unclear whether the adverse effects of psychosocial factors might impact directly on endocrine, immune and nervous systems or indirectly by affecting behaviours such as diet, exercise and disturbed sleep which themselves have links to endocrine and immune functioning.

Research in this area has in general been marred by small sample sizes and a failure to take into account potential confounders. The strongest study to date was conducted by Watson and colleagues who assessed 575 women with early breast cancer at diagnosis and followed them for five years.[13] Severe depression was a strong predictor of death (hazard ratio=3.59); however the number of severely depressed women in the sample was very small (n=10). This important finding deserves replication in a larger sample, and the 1,000 women study would be an ideal setting. The opportunity to relate psychosocial data to epidemiological and biological data should not be missed. This study will be the strongest study conducted in this area internationally to date.

THE DIFFERING NEEDS OF YOUNGER VERSUS OLDER WOMEN WITH BREAST CANCER.

The National Breast Cancer Centre has recently produced clinical practice guidelines for the care of young women. There is some evidence that prognosis and possibly biology of tumours in young and very young women is different to both older pre-menopausal and post-menopausal women. Over the past five years it has become clear that young women with breast cancer have unique needs pertaining to social, psychological and existential issues. The 1,000 women study will include 150 women under 45 years, so will be able to compare and contrast their needs with those of older women and the degree to which current services meet their needs. This will be a detailed longitudinal observational study into:

- Biology and prognosis
- Local disease recurrence and control issues
- Endocrine consequences of treatment
- Special issues relating to long-term side effects treatment (such as premature ovarian failure), fertility, pregnancy-related cancers, sexuality and relationship issues, as well as the financial and family consequences of diagnosis and treatment. Measures of these could be self-reported using developing internet technology which ensures long-term capture of data and follow-up (as being set up VirtualMedicalCentre.com).

In theory, Australia, with its high degree of technical expertise and with a cooperative patient population that is supportive of research, is well positioned to become a leader in large-scale research extending across the entire continuum. But success will require working on a larger scale and for a longer time-period than has been acceptable in the past to funding bodies in this country; it will require high levels of collaboration between scientists and clinicians at least equivalent to those achieved by kConFab; and, of course, it cannot happen without the ongoing support and participation of large numbers of affected women.

Actions

C Enablement

As discussed elsewhere breast cancer research in Australia is severely constrained by the absence of a strategic policy, by a shortage of money for large-scale projects, by a lack of appropriate specimens (breast tumours, matched normal samples, bloods, cell lines) and by bottlenecks that thwart and delay access to necessary infrastructure (medical records, cancer registries etc). The actions outlined below are aimed at solving (or at least improving) the present unsatisfactory situation.

A National Bank of Annotated Breast Tumours

ACTION C1

As a matter of priority, the alliance of breast cancer research funders should support the creation and ongoing maintenance of a national bank of comprehensively annotated breast tumours and relevant normal tissues.

With the development of reagents and therapies tailored to specific biological abnormalities, the detection, diagnosis and treatment of breast cancer will change dramatically during the next decade, Full and rapid implementation of advances in knowledge will require translational research based on ready access to large quantities of well-characterized human tissues. The UK, Iceland and Japan are creating their own national biospecimen resources while the USA is planning to establish a very large bank of cancer tissues. In Australia, hospitals and research institutes around the country for many years have banked tissues in disparate ways that suit their own use. The tissues have been gathered and stored according to different protocols, with varied levels of clinical annotation and informed consent. Current collections of breast tumours are of varying quality, are generally unlinked to medical records, lack epidemiological and lifestyle information, and are generally dependent for survival on funding from project-type research grants. For historical reasons, access to many banks of breast tumours is restricted to researchers working in specific institutions or defined geographical areas.

The recent formation of the Australasian Biospecimens Network (ABN, http://www.abrn.net) offers the prospect of a more coordinated approach with national standards, protocols and a reduction in bureaucracy. In addition, the current round of NHMRC enabling grants has provided the seed funds to set up the first "National" tissue bank of breast cancers. However it is already apparent that the money on offer is insufficient to develop and maintain a resource that is linked to clinical and health information and is large enough to service large-scale retrospective and prospective projects.

We believe that the best way forward would be for the national alliance of breast cancer funders to contribute financial support to the "National" bank of breast cancers and normal mammary tissues recently awarded as an enabling grant by NHMRC (Chief Investigator Associate Professor Christine Clarke). The goal of the bank should then be to contain several thousand breast tumours and matching blood samples that are collected and processed according to standardized protocols. An integral part of the bank is the simultaneous collection of retrospective epidemiological, family history and clinical data and prospective clinical data. The marriage of these data sets is a challenging task for the tissue bank but is an essential step to create the national resource necessary for Australia's future competitiveness in breast cancer research. A subset of the tumours, genomic DNAs (from bloods) and data could be used for Action B1 described above and the results would be made freely accessible to researchers. The remainder of the tumours, matching bloods and normal tissues would be available to the breast cancer research community for ethically-approved, peer-reviewed and funded research projects.

The infrastructure required to bank human breast samples linked to clinical health information includes:

* Identification and consenting of eligible patients
- Gathering and processing fresh tumour and normal tissue from clinical services
- Accessing archival material (pathology archives)
- Carrying out pathology review of all cases
- Manufacturing tissue microarrays
- Accessing clinical and personal health-related information
- Establishing and maintaining a database linked to a laboratory information management system and including web-based access to potential users
- Setting up a system of quality control of samples

- Setting up a system to allow access to and distribution of anonymized data and specimens for ethically-approved, peer-reviewed and funded research projects. It would be a condition of access to material that results obtained through use of the data or biospecimens would be lodged with the Tissue Bank and promptly made available to researchers.

The decentralized nature of Australian medicine makes collection of retrospective and prospective clinical data more difficult and expensive than it need be. But there is also some prospect that collection of clinical data may become easier in the future. In November 2003 the Commonwealth Department of Health and Ageing presented its National Service Improvement Frameworks (NSIF), which has cancer as its first priority disease. Within this framework is the recognized need to collect detailed cancer information on patients and discussion is underway as to how the agreed data dictionary of the National Cancer Control Initiative (NCCI) might be implemented.

Access to a fully annotated set of breast tumours would provide huge advantages to Australian breast cancer researchers. Collection of biospecimens and associated clinical data has become extremely difficult in the US because of restrictive regulations that were introduced in 2003 (see footnote on page 59). The availability of materials and data in Australia would do much to foster collaborations between Australian and US researchers and would facilitate access of Australian researchers to US funding.

Database of Breast Cancer Research and Funding

ACTION C2

The alliance of breast cancer research funders should establish an on-line database of all grants awarded by agencies that fund Australian breast cancer research. To maximise its effectiveness, the database should comply with the Common Scientific Outline, MESH terms and disease sites, in line with accepted international practice. In addition to brief summaries of the goals, timelines and milestones of funded projects, the database should contain the annual reports and lists of publications of all research projects across the entire continuum of Australian breast cancer research.

As discussed elsewhere in this report Australia has no accessible database of ongoing cancer research. In fact, many of the funders of cancer research do not provide detailed information on their activities. Many advantages would arise from the establishment of a single Australia-wide, consolidated database of cancer research, based on the Common Scientific Outline, which is now a widely-accepted classification system introduced by the Cancer UK and US National Cancer Institute, used by virtually all public and private agencies that fund cancer research in Europe and North America. The use of this classification system by all cancer funding agencies in Australia would, for the first time, provide an accurate overview of cancer research and hence would facilitate comparison of international research strategies, would guide the research investment of funding organizations and would show how and where organizations are spending their money.

Monitoring Progress of Australian Breast Cancer Research

ACTION C3

The alliance of breast cancer research funders should produce a biennial report on the totality of breast cancer research in Australia.

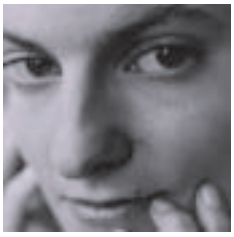
As well as measuring progress against milestones etc, the report should provide a blueprint for the next two years. It should offer solutions to problems, outline new or emerging research opportunities and suggest strategies for further improving the efficiency and effectiveness of Australian breast cancer research.

Changes to the Granting System

ACTION C4

The alliance of breast cancer research funders should encourage the establishment of grants to provide rapid, one-time funding to test and develop truly novel ideas with the potential to change the course of breast cancer research.

Each critical discovery or major advance in breast cancer is the end result of a chain of events that begins with a new idea. Regrettably, Australia – unlike other countries – has no mechanism to fund breast cancer research in its vulnerable earliest stage: converting a promising but risky idea to the point where it can compete for funding as a conventional



project grant. These grants should be for a fixed amount (say ~$75,000) for a period of 18 months and should jump-start new areas of investigation based on good science that push the boundaries of research. There should be no deadline for applications.

ACTION C5

The alliance of funders of breast cancer research should establish a limited number of Collaboration Grants of $10,000 for Australian breast cancer researchers to cover the travel and living expenses required for short-term (up to three months) research projects with collaborators. Preference should be given to applicants with well-defined, cutting-edge projects who will collaborate with researchers working in outstanding laboratories or medical institutions overseas and in Australia.

Any researchers worth their salt collaborate with colleagues. At a minimum, these collaborations facilitate the translation of new techniques into the research environment. Optimally, however, they exploit complementary materials or skills and hence enable research projects of significance that neither partner could carry out alone.

ACTION C6

Change the existing intake/reviewing cycles from one to two per year spaced a few months apart.

The three major organizations that currently fund breast cancer research in Australia (NBCF, NHMRC and the State Cancer Councils) accept project grant applications only once in each calendar year. Grant applications are written in February in time to meet deadlines for submission that are bunched together in March/April, and the results of the assessment process are made available many months later, in late Spring. The combination of single-entry, bunched application dates and a lengthy review process may be administratively convenient but it does nothing to speed the course of research. For example, if someone, just after the annual deadline for grants submission, has a great new idea with the potential greatly to improve understanding, detection or treatment of breast cancer, twenty-one months will pass before there is any possibility of obtaining funding for the necessary research. Alternatively, if a grant application fails to achieve funding by a narrow margin, there may be insufficient time for the researchers to answer the reviewers' criticisms by experiment before the next annual deadline for submission rolls around.

The slow turn and great length of the submission/reviewing cycle places Australian researchers at a disadvantage compared with their international colleagues and competitors. For example, the American Cancer Society and Cancer Research UK have two intakes/reviewing cycles of grant applications each year, while NIH and CBCRA have three. As far as we know, Australia is the only advanced country where the various sources of research funding are so tightly synchronized and so sluggish to respond.

We recognize that a bi-annual system of grant intake and reviewing will bring increased costs for the funding organizations and more work for the reviewers. But the present intake/reviewing system, with its rounds of review, rebuttal and re-review acts as a brake on the progress of cancer research in Australia. It would be far more efficient to adopt the faster (and some would argue, fairer) study section system that has been used successfully for years in the USA. The experience of people who have worked in both systems is that the speed and standard of review achieved by study sections in the USA far exceeds that attained in Australia. Researchers in this country will always be disadvantaged unless the system is brought to current international standards. This single step would both enhance Australia's international competitiveness in cancer research and speed the delivery of benefits to Australian women.

ACTION C7

The alliance of breast cancer funders should encourage researchers to focus more on the critical gaps which effect breast cancer research by establishing at least four fellowships.

For example:

Fellowships for pathologists to collaborate with researchers whose projects involve studying malignant and premalignant breast disease at the morphologic and molecular levels.

Pathology review of tumours is the essential link that joins research to breast cancer as a disease. Traditionally, the role of the pathologist in the diagnosis and prognostic evaluation of tumours has been through the use of light microscopy in assessing the morphologic features of tumours. In recent years, immunohistochemistry and molecular-based methods of analysis of populations of cells recovered by laser-capture microscopy have greatly

enhanced the ability to define precisely the lines of tumour differentiation and also provide additional prognostic and therapy-related information. Everything from surface receptors to intercellular matrix components to intracellular hormones receptors can now be determined with relative ease and used to pinpoint the cell type, the degree of immunophenotypic differentiation, and even the functional state of the cell. As a consequence, pathological staging of tumours has become more precise and prognostic and therapeutic information for breast cancer has become more valuable. Early successful examples include the clinical utility of determining estrogen and progesterone receptor status and the levels of Her2/neu expression.

All this pathological information is essential not only to the clinician but also to the researcher. In some cases, the sufficient information for the researcher can be retrieved from the pathologist's original diagnostic report. However, when more modern or comprehensive tests are required, or when samples come from diverse sources, it is often necessary to obtain blocks of the original fixed sample and carry out a pathological review.

Pathology workforce issues remain a significant roadblock to increased participation of pathologists in research, even in teaching hospitals. There is a chronic shortage of academic pathologists who have the time to review archival samples for research purposes. Support and incentives for diagnostic pathologists and pathology trainees to participate in research are required to redress the issue. The availability of fellowships for pathologists to concentrate on research-related work for a defined period is crucial if the specialty is to succeed in integrating molecular genetic technologies into the routine pathological assessment of tumours.

Communication

ACTION C7

The alliance of breast cancer funders should help support a more coherent community of breast cancer researchers by promoting a biennial national meeting and by facilitating other means to enhance communication and exchange ideas.

Although the breast cancer research community in Australia is small – perhaps two or three hundred people – communication is still a problem. Rather than being a national collaborative effort, research is embedded in a series of scientific oases scattered across the country, separated by thousands of barren kilometres. This year, for the first time, there has been a move to establish a dedicated meeting (Melbourne, November 2004) that all researchers across the entire breast cancer continuum could attend. While this is a good start, the meeting needs to become a regular event if the breast cancer research community is to develop the requisite amount of synergy.

There is no database in Australia listing resources for breast cancer research – for example, cell lines, mouse strains, protocols, clones and antibodies, links to other databases and sites, notices of upcoming meetings, contact details of researchers together with their fields of expertise, activity and links to other databases.

Moving Research Results into Practice

ACTION C8

Facilitate translation of research into practical outcomes through the development of new models to improve implementation of and access to clinical trials and to accelerate the production of evidence based clinical guidelines.

In the last thirty years, we have made tremendous strides in our understanding of the molecular events that trigger cancer and shape the course of the disease; and there have been slower advances in prevention, detection and treatment of breast cancer. But the gap continues to widen between our intellectual grasp of the disease and our ability to ensure that all patients reap the benefits of these new tests, drugs and procedures. Much more effort is required to bring the two ends of the research continuum together and to improve the pace at which research findings make their way to the clinic.

Breast cancer is a heterogeneous disease and our knowledge of the complexity of this heterogeneity will increase further as the sophistication of molecular analysis increases. In Australia, we have no effective strategies for production and adoption of evidence-based guidelines for cancer or for the efficient translation of research results into clinical practice. We need to explore ways to modify clinical practice against a constantly changing backdrop of research findings.

Currently, progress in breast cancer treatment is inextricably linked to the ability to conduct clinical trials. Current standards of care are the direct result of past clinical trials and future advances are dependent upon the outcome of

such studies. But as molecular methods to stratify breast cancers into their constituent families, genera and species become more sophisticated, the large-scale trials of the past will lose power. Instead of testing drugs, singly or in combination, against all breast cancers, we will need to find ways to test drugs that have been designed with specific subclasses of tumour in mind. It will be increasingly essential also to develop the infrastructure to translate molecular pathology findings into practice. Current implementation research in molecular pathology requires new approaches, such as definition of rigorous and applicable correlates between expression signatures, obtainable in a research setting, and DNA copy number measurable in archival tissue-based specimens. This implementation research is not and will not be part of ongoing discovery research, but requires a separate activity, with attendant infrastructure.

The alliance of funders should offer grants to support the infrastructure costs required to develop improved models to test new agents or technologies. The aim of these models should be to decrease the time required to perform a clinical trial, to efficiently identify patients with breast cancers whose molecular characteristics are appropriate for the agents under test, to increase the participation rate of patients by making clinical trials more accessible and by increasing the number of drugs, modalities or technologies under test. These goals might be best achieved by consortia that include specialized cancer hospitals, community-based practices, consumer/survivor groups and the pharmaceutical industry. The infrastructure to carry out implementation research in molecular pathology might be best achieved by consortia centred around significant molecular pathology technology such as laser capture microdissection, supported by highly trained technical staff, and including tertiary pathology departments and private pathology services.

Evidence-based guidelines also need attention. At present, it can take five years for a set of evidence-based guidelines to be planned, commissioned, written and approved by the appropriate agency (usually NHMRC). All too often by the time guidelines appear, they are out-of-date. The alliance of funders should offer grants to explore ways (i) to cut to 12 months the time required to produce a set of evidence-based guidelines – from planning to adoption, and (ii) to update guidelines section by section instead of en bloc.

Ethical Issues

ACTION C10

Access to data patients' biological specimens and associated medical information should be made simpler for researchers.

1. **MEDICAL RECORDS AND BIOLOGICAL SPECIMENS**
   Alongside the growing need for human tissue and blood samples in breast cancer research is a parallel requirement for access to medical information relevant to each sample. Such information is used for a number of research purposes – for example, to advance fundamental, laboratory-based science, to monitor changes in patterns of health care, and to trace the patterns of inheritance of disease. While research of this kind can sometimes be carried out without access to identifiable patient records, other research relies on personal identifiers – for example, verification of diagnoses or collection of data on response to treatment.

   Most countries permit only limited access to patients' medical records for research purposes. In Australia, access must conform both to the NHMRC guidelines (1999) on "Ethical conduct for research in humans" and the relevant and State Privacy Acts. Ideally, informed consent is given by the patient for researchers to access both their biospecimens and their relevant health information, but there are provisions to permit access without consent if the research is not likely to cause harm and consent would be difficult or impossible to obtain retrospectively. However, researchers around the world face now increasing obstacles when they seek access to personally identifiable medical records. These obstacles, which can be bureaucratic or legislative, have the potential to cause serious damage to cancer research. The recent Wanless report on epidemiological research in the UK describes "the possible danger to public health research which arises from the difficulty of obtaining access to data because of the need to strike a balance between individual confidentiality and ..... research requirements".[14] The German National Ethics Council in its recent report "Biobanks for Research" points out that since 1995 there has been a "sacralization" of human tissues that has resulted in unwieldy, complex legalistic and obtuse ethical consent forms.[15]

In Australia we have so far avoided enacting ill-considered legislation such as the US HIPAA regulations (Health Insurance Portability and Accountability Act) and potentially the UK Human Tissue Act, but instead have reached a reasonable and balanced position through a consultative process led by the Australian Law Reform Commission (ALRC) and the Australian Health Ethics Committee (AHEC). The resulting document submitted to Parliament, entitled "Essentially Yours", makes recommendations which will assist not only with access to human biospecimens, but also to medical information in general.

Several tissue banks in Australia already store biospecimens and linked health information with broad consent for use in an area of medical research such as "cancer research". There is accumulating evidence that patients who consent to use their tissue are keen to see that the maximum benefit will be obtained by its use. Consent should be broad and open (Proposal 12-2 in the ALRC "Essentially Yours" would provide guidelines for obtaining consent for unspecified research), delegating responsibility to HRECs to regulate appropriate usage. To consider a system of requiring re-consenting of patients for each use of their tissue or medical information would not only be impractical but could also be considered an invasion of privacy since the individual would have to be recontacted.

In practice, consent is generally given for tissue and medical information to be used in a broad area of research, eg breast cancer, even where a specific project is in mind. Additional information regarding the nature of the specific project is often provided, with the caveat that the future studies will not be limited to this specific endeavour. In a recent American survey, the majority of donors gave their consent for generalized research.[15] Importantly, 91.9% of respondents would not impose greater safeguards to prevent their samples being used for research into a different disease. The NSW Human Tissue and Anatomy Legislation Amendment Bill, 2003 suggests that patients may give broad or restricted consent at their own discretion. Internationally, the German National Ethics Council also recommends that "donors should be able to give generalized consent to the use of their samples and data for the purposes of medical – including genetic – research." There should be no limit to the length of storage or use of the data or biological specimens.

Even when broad consent is available, there is a well-recognised need in Australia, to streamline the ethical review of multicentre applications. Some National research projects presently must make applications to several dozen Human Research Ethics Committees (HREC), all on different application forms and all with differing requirements. The resulting multiplication of effort imposes large costs on the researchers and increases the workload of the members of the individual HRECs. Several initiatives have begun to establish mechanisms for recognising the approval given by one duly-constituted HREC by others – for example, the reciprocal recognition in Perth by the HREC's of all teaching hospitals, and a similar multicentre system in Melbourne.

Whilst AHEC are currently seeking solutions to this issue at a national level, we believe that national strategies to harmonise ethical review processes to minimise re-review can be initiated through a register of HRECs that are willing to recognise one another's approvals. Public awareness of such a register, together with increasing education of the specific role of an HREC as led by AHEC and the ALRC, will ultimately achieve facilitated multicentre approval.

2. CANCER REGISTRIES

By law, all cancers must be reported to registries held by the Australian States and Territories. Although these archives could be a rich source of data for breast cancer research, any national research project wishing to access data held by the cancer registries quickly realizes that the system is far from perfect

- There is no consistency in the data sets held by the cancer registries of the various States and Territories. For example, it may be possible to find out from one registry whether a reported cancer is a primary or secondary tumour, but the same information may not be available from the registry of another State. Stage at diagnosis is a particularly important piece of information that is only rarely available
- Some registries are able to supply the name of the treating hospital so that laboratory and treatment reports can be followed up by the research team. Other registries are prevented by State legislation from providing this information to researchers, who are deemed to be a 3rd party, even though the patient may have given consent to access the information.

Again, harmonizing legislation is required

- Making individual applications to the ethics committees in charge of access to data held by registries in each State and Territory is cumbersome. Each ethics committee has a different application form, which makes the researchers' task unnecessarily burdensome. An agreed national form with a common set of questions would be more efficient
- Even though the registries recover costs from researchers, long delays are often experienced in obtaining the requested data. This problem could be ameliorated if researchers were allowed electronic access, with agreed restrictions, to the database where the datasets are stored. Such schemes are used by some States, but not all
- The Australian Institute of Health and Welfare (AIHW) holds a registry of all reports of cancer in Australia. Because the information in the AIHW registry is provided by the States and Territories, a researcher must obtain ethical approval from all State and Territory cancer registries to access the data held by the AIHW. Each State and Territory has a different application form, and the form required by AIHW is different from any of those used by the States and Territories. AIHW holds the data downloaded to them by the State and Territory registries and, as mentioned above, the data sets are not congruent. Because AIHW holds no data about treating hospitals, researchers are obliged to approach each State registry for clinical information. One State registry (SA) is not allowed to download names and addresses to AIHW. Researchers requiring this information are obliged to deal directly with the SA Registry in addition to AIHW.

In summary, retrieving information held in Australian cancer registries is a frustrating business – chiefly because of unnecessary inconsistencies between the legislation of the States and territories. These inconsistencies undermine the effectiveness of the registries and vitiate the very purposes for which the registries were established. National legislation is needed to harmonize the data sets held by different registries and standardize procedures for access to the data sets.

7.2 Summary of the Proposed Research and Funding Actions

A. An alliance of breast cancer funders

A1	Establish an alliance of breast cancer funders	Fund more high-quality breast cancer research than can be supported through individual sponsoring agencies on their own, in particular large-scale, multi-year projects

B. Large scale long term national projects

B1	Create a national breast cancer research fund	Support large-scale long-term projects of national and international importance

C. Enablement

C.1	National bank of annotated breast tumours	Maintain a national bank of comprehensively annotated breast tumours and relevant normal tissues
C2	Database of breast cancer research and funding	Maintain an on-line database of all grants awarded by agencies that fund Australian breast cancer research
C.3	Biennial report to the alliance of funders	Report on the totality of breast cancer research in Australia including measures of progress against agreed milestones and provide a blueprint for the next two years
CHANGES TO THE GRANTING SYSTEM		
C4	"Novel Ideas" Grants	Provide rapid one-time funding to test and develop truly novel ideas with the potential to change the course of breast cancer research
C5	Collaboration grants	To facilitate Australian researchers to collaborate with international researchers with short term support for travel and living costs
C6	Change the existing intake/reviewing cycles from one to two per year	Increase the responsiveness of the granting process and enhance Australia's international competiveness in cancer research and speed the delivery of benefits to Australian women
C7	Establish four research fellowships in breast cancer research	Alleviate the shortage of researchers in key areas. Support excellence in career development and large-scale national projects
COMMUNICATION		
C8	Facilitate communication and exchange among breast cancer researchers	Increase the exchange of information about all aspects of breast cancer research including resources and potential partnerships across the spectrum of breast cancer researchers
MOVING RESEARCH INTO PRACTICE		
C9	Develop new models for clinical trials and evidence based guidelines	Make clinical trials more accessible and decrease the time required to translate the results of breast cancer research into clinical guidelines
ETHICAL ISSUES		
C10	Establish mechanisms to facilitate ethical reviews and timely access to patient medical information and associated bio-specimens and standardised cancer registry data for research purposes	Reduce multiplication of effort, costs of research and increase the timely completion of research

73 Next Steps

How this report was produced

The Expert Advisory Committee was formed in the Spring of 2003, met in October of that year and again in April of the following year. Other communication was by e-mail and conference calls. The first draft of the report, written in April 2004, was sent out for review and face-to-face comment at meetings in four cities. In addition, the recommendations of the report were presented by committee members at several seminars and scientific meetings over the course of the Australian winter.

The attendees at the face-to-face meetings were asked to score each of the Action Points in the report. Because the attendees were small in number (~40) and may not be representative, we cannot attach much significance to the results. Nevertheless, the respondents were almost unanimous in their very high enthusiasm for the two major recommendations, Action A1 and B1. Opinion about all of the other Actions was also strongly positive. However, the respondents were markedly less optimistic about the chances that the Action Points could be implemented.

We are very grateful to the many people whose suggestions during the consultative process have been incorporated into the final report, which was completed in September 2004.

Going forward

With the positive response to the actions cited in the document the National Breast Cancer Foundation will continue to lead the process for implementation. A working group will be established to form the Alliance of Breast Cancer Research Funders and to develop the detailed plan for implementation.

74 References

1. National Breast Cancer Foundation. Breast cancer research in Australia: meeting the challenges. National Breast Cancer Foundation. Sydney 2003.
2. Marlin A, Redman S, Clarke C, Clark R, Boyle F, Breast cancer research in Australia: current research and future priorities. NHMRC National Breast Cancer Centre. Kings Cross 1996.
3. Cancer Research Review Working Group. Cancer Research in Australia – A Survey of Cancer Researchers. Edited by C Anderiesz. National Cancer Control Initiative, Melbourne, 1-53.
4. Beatson, G.T. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. *Lancet* 1996; 2:104.
5. IARC. 2004. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. Lyon: IARC Press.
6. AIHW. 2003. Cancer in Australia, 2000 (Cancer Series Number 23). Canberra: Australian Institute of Health and Welfare. WHO. 2003. The World Health Report, 2003: Shaping the Future. Geneva: World Health Organization.
7. AIHW. 2000. Australia's Health, 2000: The seventh biennial health report of the Australian Institute of Health and Welfare. Canberra: Australian Institute of Health and Welfare.
8. AIHW. 2002. Australia's Health, 2000: The seventh biennial health report of the Australian Institute of Health and Welfare. Canberra: Australian Institute of Health and Welfare.
9. WHO. 2003. The World Health Report, 2003: Shaping the Future. Geneva: World Health Organisation.
10. Seglen, P. (1997) Why the impact factor of journals should not be used for evaluating research. *Brit. Med J.* 314: 497-503; Garfield, E. (2001) *Cortex*37:575-577.
11. Morley JE, Benton D, Solomon GF. The role of stress and opioids as regulators of the immune system. In: McCubbin JA, Kaufman PG, Nemeroff CB (eds). Stress, neuropeptides and systemic disease. Academic Press, San Diego, 1991, 233-260.
12. Rabin BS, Cohen S, Ganguli R, Lysle DT Cunnick JE. Bidirectional interaction between the central nervous system and the immune system. Crit Rev Immunnol 1989; 9: 279-312.
13. Watson M. Haviland JS. Greer S. Davidson J. Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. *Lancet.* 1999; 354(9187):1331-6.
14. German National Ethics Committee (Nationaler Ethikrat). *Biobanks for research 2004.* Available in English at kontakt@ethikrat.org
15. Wendler D, Emanual E. The debate over research on stored biological samples: what do source think? *Archives of Internal Medicine* 2002 162: 1457-1462.

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Table 1. Shows the distribution of papers retrieved each year across the 38 CSO codes.

Table 2. Presents the data of Figure 1 in tabular form.

Table 3.Citation Indexes of (1) Australian Papers on Breast Cancer and (2) Papers Resulting from NHMRC-funded Research.

Table 4. Examples of existing large-scale research projects.

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Figure 1. Impact factors of the journals in which Australian breast cancer papers were published between January 1998-December 2003.

Figure 2. Australian breast cancer papers published between January 1998-December 2002.

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