Commentary

Breast cancer research: where we are and where we should go

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Introduction

Every new year, a common ritual is to reflect on the past year and resolve to improve, in increments, one's life for the next. With the new millennium upon us, the introspection and the projections take on a grander scale. Certainly, the span of a thousand years dwarfs the lifetime of any individual. Therefore, the thoughts and the hopes are for a community, and not the individual. Furthermore, the millennial resolutions we make are about achieving dreams beyond the boundaries of current reality. In breast cancer research, given the progress in the field, it is an appropriate time for us to take stock of our past accomplishments, and to make projections on where we would like to be. Then, with these plans in hand, we may plan the first steps on a journey that will encompass the next 30 generations.

History in brief

We have come a very long way in breast cancer treatment and care. Our history will tell us, however, that these advances have only come in the past 30–40 years of a 1000-year retrospective. The first advance in breast cancer treatment was the work of William Halsted, whose radical mastectomy provided relief from locally advanced disease. It is safe to say that very little organized research was done in breast cancer aetiology or treatment from the turn of the century to the 1960s. In the 1970s, when clinical trial methodologies were formalized and implemented, the major clinical advances took place: the equivalence of the breast sparing surgeries to radical procedures; and the demonstration that adjuvant chemotherapy can significantly alter survival outcome. These treatment advances also challenged the scientific principle that breast cancer metastasizes primarily through the lymph nodes, which dominated the field for over 60 years. In its place, the primacy of hematogenous spread was acknowledged. The sole molecular triumph from this period was the development of the estrogen receptor as a diagnostic and prognostic factor, as well as the target for chemically based interventions (diethylstilbestrol and tamoxifen).

From the 1960s to the early 1980s a parallel path of discovery based on molecular biology and cloning provided the first molecular fundamentals in breast cancer. Although these findings were important in building an understanding of the cell biology of experimental systems, they were of little clinical consequence. The impact advances in breast cancer research were still from the clinical sector, and represented significant but incremental improvements in surgery and adjuvant chemotherapy. Definitive breast cancer surgery was progressively reduced in scope, and the introduction of new potent agents such as doxorubicin and taxol, supportive agents such as granulocyte colony-stimulating factor, and effective antiemetics allowed the full application of dose intensity in the adjuvant setting.

In the 1980s and through the 1990s, the advent of polymerase chain reaction, advances in molecular cloning, and transgenic manipulations of the mouse allowed a linkage between molecular biology and clinical breast cancer care. For the first time, scientists were able to analyze microscopic amounts of archival tissues, thus permitting the association of molecular mutations with clinical outcome. This was a major advance because breast lesions were small and getting smaller with better early detection. It was also during this period that several fundamentally important molecular discoveries were made with impact on clinical breast cancer. First, the discovery that human epidermal growth factor receptor-2 (HER-2) was amplified and overexpressed in 20–30% of primary breast cancers and can induce mammary carcinomas in transgenic mice led to its subsequent use as a predictive

HER-2 = human epidermal growth factor receptor-2.

marker of chemotherapeutic selection, and as a target for an effective antibody-based therapy (Herceptin®; Genentech Inc, San Francisco, California, USA). Second, the identification of *BRCA1* and shortly thereafter of *BRCA2* as the major cancer susceptibility genes in human breast cancers was of practical and conceptual importance. Practically, a test was derived that can determine predilection to breast and ovarian cancers. Conceptually, that both susceptibility genes appear to be primarily involved in DNA repair suggested that breast cancers emerge from faulty DNA repair rather than from direct imbalances between growth and death.

In the 1990s, the promise of impact from early detection and prevention appeared to be finally validated. Irrefutable evidence of the effectiveness of mammographic screening in postmenopausal women made mammography a standard public health intervention. The Tamoxifen Prevention Trial, showing a substantial reduction in breast cancer incidence in those taking tamoxifen, provided proof of the principle that chemical interventions can significantly alter the onset of this disease [1].

It is our current belief that the reduction in breast cancer mortality seen in the USA in the 1990s is due to many of these clinical and basic discoveries and their effective implementation – mainly the effects of mammography and adjuvant therapy. Because the period required for a scientific discovery in cancer research to show an impact in population statistics is in the range 20–30 years, we are just now reaping the benefits of work that was begun over a quarter of a century ago. This, therefore, gives us great hope that the next quarter of a century will bring tangible relief to the suffering of women and men with this disease. With this optimism, the question is, given all the leads that we have, where should we go?

Where do we go: scientifically?

Rising to this challenge, the US National Cancer Institute (NCI) in 1997 constituted Progress Review Groups (PRG) to review the national portfolio of research for particular disease sites. The ultimate goal was to take heed of where we are, and to project, for the NCI, where we need to be. The group studying breast cancer chaired by Drs Hal Moses (Vanderbilt University, Nashville, Tennessee, USA) and Nancy Davidson (Johns Hopkins University, Baltimore, Maryland, USA) was composed of experts spanning a broad range of disciplines and funding organizations who met eight times from May 1997 to June 1998. Their final report, which can be accessed at the NCI web site at http://wwwosp.nci.nih.gov/planning/prg/, provides concise recommendations for improving discovery in all sectors: clinical, epidemiologic, and basic. Structurally, they pointed to the need for programs that foster deep cross-disciplinary interactions, such as the Specialized Programs of Research Excellence; for stronger ties between academia, government, and industry; for programs that foster innovation; and for more national repositories of common reagents such as tumor tissues, clones, mouse models, and even data. Specifically, the Breast Cancer PRGs identified 13 critical factors and objectives that needed attention and that span the continuum of breast cancer research:

- our limited understanding of biology and developmental genetics of the normal mammary gland is a barrier to progress;
- better model systems for human premalignant breast disease and breast cancer are needed – animal models, human mammary cell and organ culture;
- our current knowledge of the genetics and biology of precancerous lesions and their progression to invasive, metastatic cancers is incomplete (ie gene mutations and gene expression in breast epithelial cells through all stages of breast cancer development and progression);
- key biomarkers and surrogate end points for epidemiologic studies and prevention and therapy trials need to be identified;
- pivotal research needs, appropriate tools and technologies, and funding is seriously deficient for developing and disseminating new technologies;
- academic health centers need resources for drug screening, genomics, and chemistry infrastructure to support discovery and development of new therapeutics in prevention and treatment – partnerships between academia, industry and government will be critical for new drug development efforts;
- faster mechanisms for designing and conducting innovative clinical and translational trials in prevention and therapy are needed;
- breast cancer research should address patient and survivor needs;
- the study of behavioral mechanisms in decision-making that is relevant to breast cancer prevention, detection, and treatment need more emphasis – the goal is to support behaviors that are consonant with better medical outcomes;
- there is a need to attract new investigators to breast cancer research and to provide multidisciplinary training;
- the multidisciplinary nature of breast cancer research requires better communications among investigators;
- funding mechanisms should be developed that support innovation and to accommodate longitudinal studies; and
- current approaches to informed consent and confidentiality are a major barrier to breast cancer research.

More broadly put, these critical areas for breast cancer research can be organized into three major clinical operational goals that we should carry into the next millennium. The first is to prevent breast cancer from ever occurring; the second is to cure or control metastatic disease; and

the third is to develop ways to enhance the lives of those who have survived breast cancer. Our first line of defense is good early detection and prevention, but once a cancer evades this defensive perimeter the cause of mortality remains metastatic disease. Thus, the achievement of the first two goals will make a tangible impact on the reduction in breast cancer incidence and mortality. Success in the third goal will improve the quality of life of breast cancer survivors, who represent an ever-increasing number of women. Unfortunately, it is clear that, despite our advances, we remain ignorant of many fundamentals.

In prevention, the knowledge deficits that impede our prevention goals are not subtle. That carcinoma *in situ* of the breast has similar molecular mutations as those seen in more advanced cancers suggests that carcinoma *in situ* is already an established cancer, and that the true precursor lesion still needs to be identified. We cannot image precursor lesions, and thus we have no true measure of end organ risk assessment. We know very little about how normal epithelial cells convert to committed cancer cells, and therefore very little about how to intervene. It is not even clear that we have reasonable animal models for breast cancer induction.

In the realm of treatment, we are not certain that the screens we use to identify good anticancer agents are truly effective. Although we are beginning to identify molecular targets for therapeutics that are specific or appropriate for breast cancer, we do not have good mechanisms to speed the clinical interrogation of these targeted therapeutics, or to monitor their success. We are also not taking advantage of advances in other disciplines such as chemistry and computer sciences that can speed our rate of discovery. For those who appear cured of their breast cancer, we are just beginning to understand the medical sequelae of cytotoxic drug exposure, the psychological impact of having cancer, and possible post-therapy interventions that may minimize recurrence, and maximize quality of life.

In response to the Breast Cancer PRG report and these realities of our current knowledge, the NCI developed an implementation plan that led to a series of initiatives. Interestingly, many of the Breast Cancer PRG recommendations were similar to those raised by other disease site PRGs and by review groups examining other aspects of the institute, such as the developmental therapeutics program, the cooperative groups, and the cancer prevention program. This permitted the NCI to create a number cross-cutting initiatives that would address multiple, but overlapping needs, and that will support disease-based communities who use the same experimental tools and who face the same logistical problems. In fact, it was clear to the NCI staff creating these programs and to our extramural advisors that limiting these initiatives to only one disease site would create intellectual silos and would not be optimal.

Thus, the Specialized Programs of Research Excellence have been expanded and better coordinated as an experimental consortium. The cooperative group structure has been changed to permit more open interaction with individuals outside the cooperative group ranks. Pilot studies are planned within the cooperative group structure that will test new systems in clinical trials management, such as the establishment of Clinical Trials Support Units that serve as a single station to allow access to NCI-supported clinical trials. The drug discovery program has been dramatically altered, as manifest in the Rapid Access to Intervention Development (RAID) program (http://dtp.nci.nih.gov/docs/raid982.html). RAID was developed to overcome the logistical hurdles of moving therapeutic agents from academic institutions to the first clinical studies. New models of review are being explored that will speed the funding of innovative clinical trials, and to improve the funding for clinical investigations. Moreover, innovative approaches for screening new compounds are being supported by such programs as the Non-Mammalian Organisms for Anti-Cancer Drug Discovery program (http://www.nih.gov/grants/guide/pa-files/PAR-99-019.html).

In addressing the problem of animal models, the NCI created the Mouse Models for Human Cancers Consortium, which includes 19 of the nation's best groups for the purpose of supporting data sharing, the development of new models, and other issues raised by the PRG. In bringing new technologies to the field, the Director's Challenge grant will fund institutions to use novel technologies in devising molecular classifications for human cancers including breast. A recent competitive supplement supported over 20 cancer centers to develop their indigenous microarray programs. Phased Innovation Awards were made available whereby investigators could receive 'seed' resources to explore new leads without much preliminary data, that can be followed by larger phase II funds if the exploration was successful.

The Early Detection Research Network is funding a number of sites to identify early markers of cancer, including breast, and to support their development for clinical use (http://www.nih.gov/grants/guide/rfa-files/RFA-CA-98-028.html). The NCI has recently funded the Diagnostic Imaging Network which is a multi-institutional network for cooperative studies in diagnostic imaging, including innovative breast imaging technologies (http://www.acrin.org). Acknowledging the importance of genetics in epidemiologic investigations of breast cancer, the NCI has established a Cancer Genetics Network that is a multicenter consortium for the study of genetic susceptibility (http://www.nih.gov/news/pr/july98/nci-28.htm). Plans are being developed for funded coordination of large cohort studies, especially in the realm of biomarker analysis, and support for cancer communications research is undergoing rapid expansion. A detailed summary of these NCI ini-

tiatives in breast cancer research can be viewed at the NCI website: http://www.nci.nih.gov/bci.html.

Where do we go: socially?

It would be incorrect to highlight the scientific advances without acknowledging impact of the social climate on science. What was permissive to the development of oncology and clinical investigations in oncology in the latter half of the 1900s was the willingness of individuals to talk about their cancer, and the reversal of the nihilistic view of cancer treatment that pervaded clinical practice. What has uniquely characterized the 1990s, however, has been the beginnings of an unprecedented cooperation between clinical, population, and basic scientists in attacking breast cancer. Although some of this is due to the power of the technologies that permit basic questions in human diseases to be asked, and to new funding mechanisms such as the Specialized Programs of Research Excellence, a lion share of the credit must be given to the force of the breast cancer advocacy movement. Not only were they able to increase funding for breast cancer research, but they also participated substantially in forcing disparate scientific communities and funding agencies to work together. This new spirit of collaboration, along with the scientific tools that are now available, has fueled an unparalleled rate of scientific discovery in breast cancer research.

We will need to extend this sense of collaboration and linkage from the academic realm to a wider context. For example interactions between advocacy groups, industry, academia, and government will be needed to tackle difficult clinical and research resource questions. Data sharing, common data elements, and the posting of primary data will be progressively more important in lessening redundancy and in accelerating the principles of evidence-based medicine. Clinical investigations cannot proceed without proper support from public or private health insurance organizations, and therefore a funding pact between insurance industry, government, and research organizations for clinical research will soon be necessary. There is no question that effective communications and organization among funding health agencies will accelerate the implementation of effective prevention, screening, and treatment approaches. This, by itself, will significantly reduce the time from discovery to clinical impact. Finally, legal resolutions to the current problems that involve informed consent and confidentiality will be needed to advance clinical and epidemiologic investigations. This will require consensus among professional, legal, ethics, and government bodies.

Conclusion

The foundations for a robust and innovative national portfolio of discovery and implementation have now been established. Now it is in the hands of capable investigators to take advantage of these platforms and resources to make an impact. Given how far we have gone in the latter 40 of the past 1000 years, it is clearly within our grasp to achieve the millennial goals noted herein: to prevent breast cancer from ever starting, to cure metastatic disease, and to make the lives of those who have survived breast cancer better.

Reference

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