

DILEMMAS IN BREAST DISEASE

Breast Cancer from a Public Health Perspective

Richard R. Love, MD,* Susan M. Love, MD,[†] and Adriano V. Laudico, MD[‡]

**Department of Medicine, University of Wisconsin, and University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin, [†]Department of Surgery, University of California School of Medicine, Los Angeles, California, and [‡]Department of Surgery, Philippine General Hospital, Manila, Philippines*

■ **Abstract:** By 2010, the majority of approximately 1.5 million annual new cases of breast cancer will be diagnosed in women in countries with limited resources. Public health approaches to medical problems emphasize the importance of practical, limited toxicity and very inexpensive interventions. While clinical trials in Western countries are testing the concept of breast cancer prevention, they are not defining useful public health approaches. Early detection of breast cancer using mammography, while effective, is a high-technology, expensive approach. Adjuvant systemic and radiation therapies are increasingly expensive; careful consideration of efficacy and cost-efficacy data appear warranted. Public health perspectives thus suggest that many current “standard” approaches to breast cancer in Western countries cannot help the majority of women in the world. ■

Key Words: public health

Some of the current controversies in breast cancer and the makeup of the national, high-profile research portfolio for this malignancy suggest that taking public health perspectives into account might usefully influence our efforts in developed as well as developing countries to better prevent and more successfully treat this disease. This communication is offered to highlight such perspectives, and *not* as a comprehensive synthesis of the state of the art in interventions for breast cancer.

Globally the total number of new cases of breast cancer diagnosed annually currently exceeds 1 million, and this figure is expected to reach 1.5 million by the end of the decade because of major increases in the number of cases in countries with limited resources (1). Before 2010, total annual number of cases in countries with limited resources will exceed the number in developed countries. Even in higher-incidence countries like the United States, the absolute fractions of women diagnosed, and particularly those who die of this disease, are small (2). While the word “epidemic” is often used to describe the frequency of this cancer in the United States, the attack rate for breast cancer is much lower than those which have characterized infectious disease epidemics.

The key aspect of the frequency issue is that, at any given specific time, the likelihood that a healthy American

woman could be diagnosed with breast cancer is very, very low, and the likelihood that she will develop the disease in the next 5 years is also low. These circumstances mean that large numbers of women without any signs or symptoms of breast cancer have to be screened to have any chance of finding cancers likely to be clinically important or lethal. Large numbers will also have to be effectively “treated” to have any chance of preventing breast cancers or deaths. These circumstances also mean that given finite resources, treatment of women with breast cancer will compete with treatment for other health problems in the population. The ethical principle of distributive justice challenges us to recognize that rationing of health services for some of our global citizens is occurring and to work harder to have these decisions made on a rational basis. These perspectives lead to considering public health models of successful health interventions.

Public health models focus on populations and suggest that beyond having rigorously demonstrated efficacy, widely applicable and useful interventions need to be (a) practical, which means easily and sustainably reproducible or feasible under many circumstances; (b) associated with limited or no side effects or toxicities; and (c) very inexpensive. Depending on disease frequency, interventions that appear to have these characteristics may be of limited value in some populations and of greater value in others. How do some of our current activities in breast cancer prevention, early detection, curative treatment, and therapy of advanced disease look as public health interventions?

Address correspondence and reprint requests to: Richard R. Love, MD, 256 WARF, 610 Walnut St., Madison, WI 53726-2397, USA, or e-mail: rrllove@facstaff.wisc.edu.

PREVENTION: TRIALS TESTING THE CONCEPT

In some Western countries, mortality from breast cancer has recently declined to levels of 20 years ago (3). While widespread use of screening mammography combined with effective adjuvant therapies in pre- and postmenopausal women appear to explain this salutary trend, mortality rates remain high, and these useful interventions are not easily applied in many countries for a variety of reasons. In prevention, two high-profile American multi-million dollar clinical trials have investigated tamoxifen, and currently tamoxifen and raloxifene. The first American tamoxifen trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1, showed a reduced incidence of breast cancer in tamoxifen-treated women; reduced mortality from breast cancer was not shown and is unlikely (4,5). Canadian investigators are unconvinced that this intervention is worthwhile, so much so that they have organized a breast cancer prevention trial with a placebo arm.

Tamoxifen treatment for healthy women appears practical, but the side effects are a major problem and short-term toxicities can be very serious. Uterine cancer, pulmonary embolism and stroke, and other long-term consequences in healthy women have not been completely defined and will not be defined from the NSABP P-1 trial because the studied patients are no longer being followed (4). Detailed studies have been done and have defined the limited, more specific healthy populations in whom the benefits of tamoxifen exceeded the risks (6), but these data and analyses fall short of what is needed because the risks profile is incomplete. Finally, the cost: At present under patent in the United States, tamoxifen purchased by the individual without disease currently costs about \$100 per month. While various insurance and benefit programs can transfer this cost, for many American women this is not affordable. In countries with limited resources and much less expensive generic tamoxifen, the relative costs are still prohibitive.

The second major American trial of tamoxifen versus raloxifene is in postmenopausal women, who were found less likely than premenopausal women to have a favorable risk benefit in the first trial, and focuses on the hypotheses that raloxifene will be associated with lower risks of uterine cancer and greater benefit in reducing the incidence of breast cancer. At this time the plans for long-term follow-up of toxicities in this trial are uncertain, and in any event, data will be difficult to evaluate given the absence of data for a comparable untreated group, similarly followed.

While the American trials have received the greatest attention, three European trials put the NSABP P-1 trial into better context. A Royal Marsden trial of tamoxifen did not demonstrate a benefit from tamoxifen (7), as occurred also in an Italian trial (8). More recently the multicenter International Breast Cancer Intervention Study (IBIS) has reported benefits from tamoxifen, although less than those found in NSABP P-1 (4). While these two trials are undoubtedly providing interesting data about the natural history and biology of breast cancer, it is clear that they are unlikely to define “public health interventions”—interventions that can be widely applied with the expectation that they will measurably impact on breast cancer incidence and mortality in the American population—for the reasons noted. Indeed, one study has found that less than 5% of high-risk women opted to take tamoxifen (9). It is fair to caution, however, that these trials are already commonly considered to be defining new standards of care for large populations of women at risk of breast cancer, when in fact they are only testing whether the concept of preventing breast cancer is a viable one, and contributing to current understanding of the biology of this disease.

From a public health perspective, where should the emphasis in prevention research be? First, more specific identification of individual women at risk is needed. Current risk models are, as noted, certainly unconvincing to patients (9). Vogel et al. (10) have suggested that finding of cellular atypia influences patients’ perceptions of risk. Such ability can only follow from a better definition of the developmental model for this disease, including specific, well-characterized biological “steps” and time frames. Second, we need to be testing public health interventions—practical, nontoxic, and potentially inexpensive approaches.

EARLY DETECTION: MAMMOGRAPHY QUESTIONS

The numerical challenges of screening for early detection have been better understood than perhaps those of prevention. It is commonly appreciated that at any time, the frequency of breast cancer in even a high-risk asymptomatic population is likely to be very low. What has been less appreciated are the more subtle uncertainties about (a) the scientific methods and processes of assessing for benefit from the most used screening test—mammography (11); (b) the natural history of screening-detected “cancers,” the majority of which are benign; and (c) the potential harmful consequences of the sequence of mammography and biopsies, particularly in premenopausal women (12,13). To a great extent in the United States, we have

been less focused from the beginning on the public health requirements of mammography than would now seem appropriate for early detection intervention. It is fair to conclude, despite the perhaps misstated skepticism, that screening mammography is associated with decreases in mortality from breast cancer, but it is also reasonable to be concerned that the costs of these benefits remain very unclear.

Two developments suggest that other “early detection” approaches may be feasible. First, in theory, proteomics may allow identification of breast cancers in their true preclinical premetastatic infancy by assessment of serologic tumor products (14). Second, the ductal origins of breast cancers may allow detection of cytologic (a breast “pap” test) or ductal fluid products that characterize early lesions (15).

ADJUVANT THERAPIES: BELIEFS, UNCERTAINTIES, AND DATA

In treating individuals with a confirmed diagnosis of cancer, it would seem that focus on the best available therapies is appropriate and that the cardinal questions concern efficacy. Increasingly, however, our attention has been trained almost exclusively on the demonstration of significant efficacy, with little consideration of the magnitude of the potential benefit and “public health” suitability for widespread application. For both adjuvant radiation therapy and adjuvant chemotherapy there are current circumstances where, across the spectrum from efficacy, through practicality, side effects, and costs, broad reconsideration of standard approaches is warranted.

With respect to care of most patients undergoing mastectomy who have evidence of metastases in one to three axillary lymph nodes, for more than two decades the standard of care in the United States has been *not* to use radiation therapy. With reports of two highly publicized trials in 1997 suggesting a significant survival benefit of 8% from radiation therapy in such patients (16,17), and of a meta-analysis of 40 unconfounded trials suggesting that this treatment provided breast cancer survival benefit, but marginal overall survival benefit (because of increased long-term cardiovascular toxicity) (18), many authorities felt that a new randomized trial specifically in this one to three lymph node–positive group, using modern planning techniques, should be conducted, and this has been done. However, some radiation oncology specialists support the idea of a trial, while others say that providing radiation therapy treatment to this group of patients has become the new standard of care (19). This has likely contributed to

poor accrual in the new study, because radiation therapists respond to the common question about what they would recommend if the patient did not wish to be in the study by saying that they would recommend treatment. Of interest is that two analyses of adjuvant radiation therapy have found this to be cost effective (20,21). Thus, for the patients who potentially have the most to gain and lose from adjuvant radiation therapy, unless accrual to the most rigorous North American trial markedly increases, the prospects for determining the precise benefits and risks are not bright. It would certainly appear that given the impracticality, potential toxicities, and significant expense of adjuvant radiation therapy, greater certainty about its efficacy and potential drawbacks is needed before asserting that for this one to three lymph node group, this should be the standard of care.

With respect to adjuvant systemic therapies—chemotherapy and hormonal therapy—American medical oncologists have been more convinced of the benefits of chemotherapy for premenopausal women and have not considered in comprehensive ways the relative impracticality, multiple toxicities, and total costs of adjuvant chemotherapy and the accompanying antiemetic and growth factor regimens. While older analyses suggested a reasonable cost efficacy of adjuvant chemotherapy, these antedated the routine use of better, but more expensive antiemetics, growth factors, and taxanes (22). More recently it has become clear that, in fact, combined hormonal therapy—ovarian ablation or suppression and tamoxifen—is equivalent to or in some cases superior to commonly used adjuvant chemotherapy regimens in terms of efficacy (23–27), and the cost efficacies and toxicities of combined hormonal therapy in some populations may be remarkably high and low, respectively (28). The status of hormonal therapy and chemotherapy in hormone receptor-positive populations remains uncertain (29). Further analyses of one combined hormonal therapy trial have suggested that the timing during the menstrual cycle of surgical oophorectomy treatment may be associated with major differences in efficacy (30), which if confirmed would remarkably further improve the cost efficacy of this treatment.

A recent editorial highlighted the differences in international (29) and American perspectives (31). A major American intergroup trial proposes to investigate two succeeding dose-dense (two interval) chemotherapy regimens (doxorubicin/cyclophosphamide \times 4 followed by paclitaxel \times 4). The wholesale costs of the cancer chemotherapeutic, antiemetic, and growth factor pharmaceuticals alone for each patient treated in this study appear to be approximately

\$40,000. From a public health perspective then, for the adjuvant treatment of the majority of premenopausal women who have hormone receptor-positive tumors, further data about comparable side effects and the cost efficacy of combined hormonal therapy alone and with chemotherapy are needed to define optimal strategies for populations (32).

METASTATIC BREAST CANCER: EVIDENCE OF TREATMENT IMPACT

Currently in the United States, practically all women with metastatic breast cancer receive some form of anti-cancer treatment, yet there are in fact no randomized study results from which to estimate the magnitude of the benefits, if any, of anticancer treatment compared to good palliative treatment alone. The presumed benefits of current therapies on survival can at best be deduced (33); the favorable impact of cytotoxic therapies on quality of life has been difficult to prove (34). There is a relative paucity of published data on symptom relief methods and techniques compared to those for anticancer treatments (35). Comprehensive Western assessments of the quality of life impact of therapy for metastatic disease have limited relevance in most of the world. Part of the explanation for this situation is a perception that using “no anticancer treatment” controls would be unethical. The World Health Organization (WHO) has been trying to promote the role of palliative care in metastatic cancer (36,37). Data suggest large differences in attention to palliative care in different countries: For the period 1994–1998, the average daily consumption of defined daily doses of morphine per million inhabitants was 6993 in Denmark, 2310 in the United States, 14 in the Philippines, and 9 in China (38). These data suggest that, globally, considerably more attention to practical symptom relief methods is needed.

A GLOBAL PROSPECTIVE

Globalization, which so much characterizes our times, was initially associated with economic-related activities, subsequently with environmental concerns, and very recently with the dark reality of terrorism. Yet the “globalization” of many human activities, including health care, has been going on for many decades, accelerating in step with advances in information technology. Rightly or wrongly, and whether intended or not, many health care professionals in developing countries look to what Americans are doing, or are perceived to be doing, as “state of the art” and current best practice that should be copied.

The activities reviewed here and our recent history with bone marrow transplantation suggest that current “standard of care” U.S.-defined interventions are ill-suited to global use.

The right to health presented in the Universal Declaration of Human Rights has been explained more broadly in the International Covenant on Economic, Social, and Cultural Rights (39). Unfortunately, widespread absence of public health approaches to breast cancer has made realization of such rights for women impossible. Impractical, toxic, and extraordinarily costly interventions for breast cancer cannot help the vast majority of women in the world at risk for or who develop this disease.

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