

The Global Challenge of Reducing Breast Cancer Mortality

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Disclosures of potential conflicts of interest may be found at the end of this article.

Breast cancer, the second commonest cancer worldwide in 2008 (1.4 million new cases: 11% of all global cancers and 360,000 deaths), is the commonest potentially fatal cancer of women [1]. Breast cancer incidence has been increasing worldwide for decades, and there is currently a greater than 4-fold variation in age-standardized incidence rates between countries with the lowest (East and Southern Africa) and countries with the highest (Western Europe, North America and Australia/New Zealand). It is potentially one of the most curable of cancers; however, 5-year relative survival rates currently cover a 7-fold range based on analysis of data from cancer registries worldwide: 13% in Gambia, 31%-54% in India, 40% and 55% in the Philippines, 46% in Uganda, 57%-66% in Thailand, 57%-81% in South Korea, 58% in Zimbabwe, 58%-90% in China, 70% in Cuba and Costa Rica, 77% in Turkey, 60%-80% in Europe and 92% in the USA [2-4]. Note that 5-year survival rates are artificially high in some countries with established mammographic screening because of overdiagnosis [5].

Breast cancer mortality trends are not affected by overdiagnosis and are available for many high-income countries. After being on a plateau for decades, breast cancer mortality began falling in a number of those countries in about 1990, but in some countries such as Sweden as early as 1975 [6]. These declines in breast cancer mortality have mainly occurred where either or both of two effective interventions, shown to significantly reduce breast cancer mortality in randomized controlled trials (RCT), had been introduced into routine management of breast cancer: adjuvant therapy and mammographic screening. The first two of these sets of RCTs both began about half a century ago. One showed that a short course of adjuvant cyclophosphamide after clinical diagnosis and surgical removal of a breast cancer produced a statistically significant mortality reduction [7]. The other showed that screening for breast cancer with clinical breast examination (CBE) combined with mammographic screening could reduce breast cancer mortality (almost statistically significant) [8].

CURATIVE ADJUVANT THERAPY FOR BREAST CANCER

Adjuvant biological, endocrine, and chemotherapy for breast cancer is now well-established therapy for reducing breast cancer mortality. The Early Breast Cancer

Trialists Collaborative Group (EBCTCG) has been producing systematic reviews of all published RCTs of adjuvant therapy every five years since 1988 [9]. Early breast cancer is defined by the EBCTCG as where "disease is detected only in the breast or, in the case of women with node-positive disease, the breast and loco-regional lymph nodes and all detected disease can be removed surgically" [9, 10]. The 2005 review [10] reached the following conclusion: "Allocation to about 6 months of anthracycline-based poly-chemotherapy reduces the annual breast cancer death rate by about 38% for women aged under 50 at diagnosis and by about 20% for those aged 50-69 years; and that for ER-positive disease only, at any age, allocation to about 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31%. These effects were each seen irrespective of other treatment or tumour characteristics".

Evaluations of declining breast cancer mortality rates in a number of European countries, Australia, and the United States have concluded that most of the reductions in breast cancer mortality that have occurred in the last quarter century are attributable to improved adjuvant treatment with hormonal and chemotherapy after initial surgery [5, 11-17]. Therefore, the first priority for reducing breast cancer mortality in any country must be to ensure that most women can be diagnosed with surgically removable breast cancer and that effective adjuvant treatment is available.

EARLY DETECTION OF BREAST CANCER

The World Health Organization guidelines on early detection of cancer clearly distinguish two programmatic approaches: screening that focuses on detecting cancer in asymptomatic women and clinical downstaging (or early diagnosis) that focuses on detecting cancer early in symptomatic women [18, 19]. Clinical downstaging does not imply any screening test and aims simply to ensure that women who have early symptoms go promptly to a health care professional and receive a competent evaluation and diagnosis. Clinical downstaging is a cheap and easy-to-implement alternative to screening, relevant to all countries and can result in women being diagnosed with earlier and curable disease (stages I and II), rather than later with mainly incurable breast cancer (stages III and IV). It is particularly suited to middle and

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lower-income countries (LMI), where most of the world's women reside. Clinical downstaging programs intend to make better use of the available health care resources and include: educating first-line health care staff in symptoms of early breast cancer and CBE; public education about early symptoms of breast cancer and the benefits of early detection, and training in breast self-examination; and improved referral procedures and patient flow to ensure that women who present with early symptoms get rapid diagnosis and competent treatment. Clinical downstaging can be integrated into existing health care programs [19]. CBE is now being tested for efficacy in the context of screening in a RCT being conducted in India, and early results show that the stage distribution of breast cancer at diagnosis is significantly better in the screened than in the control group [20]. This RCT holds promise that primary health care-based CBE screening for breast cancer will be an effective control strategy for this cancer.

Population-based mammographic screening was shown to be efficacious in reducing breast cancer mortality in a series of 11 RCTs, which began randomizing women in 1963 and ended in 1997 [21, 22]. However, it is not suitable for any except high-income countries with high-quality, universally available health care systems. Australia's experience contains salutary lessons for any country contemplating this approach to breast cancer control. There has been a 28% reduction in breast cancer mortality since the Australian free biennial mammographic screening program, which invites women aged 50-69 years for screening, began in 1991. Participation of this age group has been about 55% since 1996 [23]. However, the balance of evidence in Australia and a number of other high-income countries demonstrates that most of the reductions in breast cancer mortality that have occurred since the national mammographic screening programs began

are not attributable to mammographic screening, but to improved adjuvant therapy [11-17, 24].

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Today the dilemma in high-income countries is whether the balance between the, at most, modest benefits of mammographic screening are now outweighed by the harms of overdiagnosis [25]. Overdiagnosed breast cancers are cancers that would never have become apparent to women if they had not undergone screening [26]. The unnecessary treatment received by a woman who is overdiagnosed is all harm--resulting in significant morbidity and even mortality [27-29]. The Nordic Cochrane Centre, which has been publishing systematic reviews of mammographic screening since 2001, now recommends against this strategy for reducing breast cancer mortality [30]. This debate has important implications for all countries using or introducing mammographic screening for breast cancer and emphasises the importance of concentrating on programs that educate women and health care professionals so that breast cancer is diagnosed early and women are competently treated.

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