The reasons for the decrease in breast cancer mortality in many populations — adjuvant therapy or screening mammography?

By Dr. RC Burton

The modern era of breast cancer treatment began in the 1970s with the USA National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized controlled trial (RCT) of anti-cancer chemotherapy given in cases of early breast cancer (EBC) as adjuvant therapy after surgical removal from the chest wall and adjacent axilla of all detectable breast cancer [1]. The watershed study of adjuvant chemotherapy was the 1976 Italian RCT that reported a statistically significant reduction in breast cancer mortality using a combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMP) adjuvant chemotherapy compared with observation in women with EBC [2]. After these results adjuvant therapy began to be introduced to the routine management of EBC [1].

Diagnosis of EBC has been a priority in breast cancer management for more than half a century [1]. However, it is critical to note that as breast cancer treatment improves for both EBC and late/advanced breast cancer the impact of early diagnosis on breast cancer mortality decreases, and that this particularly applies to the screening of asymptomatic women [3]. The first RCT to evaluate the effect of screening mammography in breast cancer (the Health Insurance Plan (HIP) in New York State) began in 1963 in the US when a combination of screening mammography and clinical breast examination (CBE) was compared to usual care [4]. By 1990, a total of 10 RCTs of screening mammography with or without CBE versus observation or CBE alone in women between 40-74 years had finished recruiting and in 1990 it was being reported that screening mammography had significantly reduced breast cancer mortality. For example, an Australian meta-analysis revealed that screening mammography was associated with a relative mortality reduction (RMR) of 19% (95% Confidence Interval-CI 0.06-0.30) [5]. This and other reports led to the initiation of population and opportunistic screening programs in many countries throughout the world from the late 1980s onwards [6]. An 11th RCT in women 40-49 years of age in the United Kingdom (UK) was completed in the 1990s [7]. Meta-analyses by the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) of five Swedish RCTs comparing screening mammography with observation in women aged 50-69 years showed a statistically significant reduction in breast cancer mortality ($p< 0.05$), with an RMR of 25% (95% CI 15 - 33) [6, 8]. There were no other age groups of women for which screening mammography +/- CBE resulted in a statistically significant reduction in breast cancer mortality when meta-analyses were performed [6,8].

The Early Breast Cancer Triallist Collaborative Group (EBCTCG) based in Oxford in the UK has been conducting systematic reviews for over 30 years of the effects on breast cancer mortality of adjuvant biological, endocrine and cytotoxic chemotherapy in women with EBC; the fifth EBCTCG review was published in 2005 [1, 9]. It reported that breast cancer-specific mortality in women with EBC would be approximately halved by the use of six months of anthracycline-based chemotherapy followed by 5 years of adjuvant tamoxifen over the next 15 years. It was also reported that for premenopausal, middle-aged women with estrogen receptor positive (ER+) breast cancer, the administration of this adjuvant chemotherapy for more than one year plus adjuvant tamoxifen to all women for more than two years would significantly reduce their cumulative breast cancer mortality [9]. Therefore, the impact of competent adjuvant therapy on breast cancer mortality should be apparent within two years in a population of women receiving the appropriate competent adjuvant therapy. Adjuvant therapy for breast cancer was progressively initiated in high/middle income countries starting from the 1990s [1].

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To reduce breast cancer mortality by screening mammography, breast cancer must be detected at an early stage, i.e. when a cure by available treatment is still possible [12]. Therefore, the monitoring of the effect of screening mammography in populations being screened should include routine regular measurement of the stage at diagnosis in order to determine if screening is reducing the incidence of late/advanced, mainly incurable , breast cancer in favor of EBC, i.e downstaging. EBC is defined by the American Joint Cancer Commission (AJCC) as stages 1 and 2 breast cancer confined to the breast +/- mobile apical axillary lymph nodes with metastases [10]. Late/advanced mainly incurable breast cancer is AJCC stage 3, i.e. cancer locally invasive beyond the breast and/or with metastatic breast cancer in fixed axillary lymph nodes and any lymph node metastases in regional non-axillary lymph nodes. Stage 4 breast cancer is defined as hematogenous metastases to organs and tissues distant to the breast [10]. In 2016, the IARC recommended measuring the rates of advanced stage lesions as mandatory for monitoring screening mammography [Ref 8, page 295,]: "*the rates of advanced-stage disease are still a very direct measure of the impact of early detection by screening*" .

To estimate the potential beneficial effect of screening, not only should the simple proportion of cases with advanced stage disease be reported but also the reduction in the absolute numbers of advanced stage disease. This enables EBC to be diagnosed 4-6 years before a woman would have presented to health care professionals with late/advanced stage breast cancer [11].

The Tumor Nodes Metastasis [TNM} is the staging system which is widely used throughout the world [10].

The Surveillance, Epidemiology, and End Results (SEER) system covering localized/regional/distant [metastatic] lesions is also used, but mainly in the USA [10]. Only the AJCC stage 4 and the SEER distant disease definitions are identical: metastases via the bloodstream to distant organs and tissues [10, 12]. This fortunately allows comparison of the impact of screening mammography on breast cancer mortality, where the incidence of the metastatic stage of breast cancer must decline over time if screening can be said to have a direct impact on mortality: downstaging [12].

Unfortunately, to date such monitoring of stages at diagnosis has only rarely been carried out. The World Health Organization [WHO] International agency for Research on Cancer (IARC) 2016 systematic review of breast cancer screening [8] reported that screening mammography was available to some or all populations of women in 72 countries, where more than half all the world's women live. However, trend data over decades of advanced stages as described above have not been reported for any country [Ref 8, Table 5.9]. Thus, the effectiveness of screening mammography in those countries cannot be evaluated from the report.

However, analyses of long-term advanced breast cancer incidence trends from population Cancer Registries over decades are now available for populations screened by mammography in the States of Victoria and New South Wales (NSW) in Australia [13, 14], and also in the USA [12], Norway [15] and the Netherlands [16]. In all these populations, advanced breast cancer incidence either remained stable [12, 15, 16] or increased [13, 14] after screening mammography began, i.e. downstaging to EBC was not detected.

In 2012, before population trends in the incidence of stages of breast cancer were available, we evaluated screening mammography in Australia by studying the trends of relative reductions in breast cancer mortality (RMR) over the period 1992 to 2007 in three age ranges of women who participated in BreastScreen, the Australian national screening mammography program. The groups of women studied were: those of 50-69 years of age and invited by BreastScreen to biennial screening; women aged 40-49 years; and those of 70 years and older who had access to free biennial screens from BreastScreen, but were not specifically invited to participate [3].

We found that the women who had been screened least, i.e. those aged 40-49 years (approximately 20% BreastScreen participation) had the largest RMR: 44% (95% CI 34.8–51.2). In contrast the women who had been screened the most, i.e. those aged 60–69 years and who had been invited to participate in the screening program (approximately 60% BreastScreen participation) had the smallest RMR: 19% (95% CI 10.5–26.9). On the basis of these findings, we recommended terminating BreastScreen, except for women at higher risk because of their family history of breast cancer [17].

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Our 2020 publication [13] built on this work when incidence trends in breast cancer stages at diagnosis became available for the State of Victoria from the Victorian Cancer Registry (VCR) for 2006-2013 The Cancer in Victoria 2013 report [18], showed that the incidence of advanced breast cancer stages 3 and 4 increased between 2006 and 2013. The data from the more recent report Cancer in Victoria 2018 [19] show a trend of increasing incidence of advanced breast cancer stages 3 and 4 for the decade 2008-2018. Thus, the incidence of late/advanced breast cancer has continued to increase. Cancer in Victoria 2018 reports that stages 1 and 2 EBC totalled 80%, stages 3 and 4 advanced breast cancer totalled 11% and that 9% were of unknown stage [19]. However, for the first time, the VCR has provided five-year survival data by stage and these reveal that the 9% unknown cancer stage at diagnosis had a 5-year

survival between those of stage 3 (78%) and stage 4 (13%) of 63% [19]. Therefore, the crude incidence of advanced/late stages 3 and 4 breast cancer 28.6 per 100,000 (20% of 143 per 100,000) was double what it was in 1986 In 2006 it was about one third larger than in 1995 [13].

What of the future for screening mammography and other imaging technologies to detect EBC, for example magnetic resonance imaging (MRI)?

The top priority is to measure breast cancer stages at diagnosis over a decade or more in female populations undergoing screening mammography to determine whether screening results in downstaging the disease. Without this critical information the balance between benefits and harms of screening cannot be validly determined. For example, this was not done for any regional UK NHS screening mammography program, so the UK Government report of "*The benefits and harms of breast cancer screening: an independent review*" [20] is uninterpretable. This has been highlighted in a 2013 analysis by Michael Baum [21]. In this paper, he also succinctly summarizes harms of screening mammography, particularly overdiagnosis of *in situ* and small breast cancers that would never progress to cause women any harm in their lifetimes [21, 22]. Overdiagnosis almost always leads to overtreatment, with the inevitable harms associated with external beam radiotherapy used in conjunction with breast sparing surgery [21]. These have been quantified by the IMPACT RCT [23], which compared single dose targeted intra-operative radiotherapy (IORT) to fractionated daily EBRT after curative surgery. Overall breast cancer mortality was similar between the two groups after 5 years of follow-up, but there were significantly fewer non-breast cancer deaths with IORT (1·4% [0·8–2·5] vs 3·5% [2·3–5·2]; p=0·0086), i.e. fewer deaths attributable to cardiovascular causes and other cancers.

CONCLUSION

It is appropriate to quote Bernard Fisher here [1]: "*The twentieth century must, indeed, be viewed as a period of unprecedented progress relative to the understanding, treatment and prevention of breast cancer*".

The most important immediate challenges are to determine whether screening mammography or breast MRI can result in downstaging breast cancer at diagnosis. It is also important to improve molecular and genetic analysis of circulating and primary breast cancer cells, in order to determine whether the breast cancer has, or will, develop the capacity to metastasize to distant organs, which is the cause of death in the great majority of women who die of this disease.

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Finally, the ongoing improvements in the biological, endocrine and chemotherapy of breast cancer to prevent, downstage (neoadjuvant therapy) and cure this disease will continue to reduce — and may have already abolished — the impact of screening for this malignant disease in many populations.

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