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RESEARCH ARTICLE

Mandatory TNM Staging of Breast Cancer and Harms of mammographic Screening

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ABSTRACT

In Australia and many other high and middle-income countries diagnosis of the most curable stages of breast cancer, early breast cancer (EBC), in women by population based mammographic screening began after 1990. In many of these same and other high and middle-income countries administering adjuvant endocrine and chemotherapy after surgical complete resection of EBC (adjuvant therapy) also began in the 1990s. Some populations then underwent declines in breast cancer mortality that were recorded in population-based Cancer Registries that were attributed to either mammographic screening and/or adjuvant therapy. In only a few populations, for example, in the State of Victoria Australia from 1986-2019 long term trends in the incidence of breast cancer stages at diagnosis have been recorded by the population-based Victorian Cancer registry (VCR). These long-term stage trends have shown that advanced stages of breast cancer have increased or remained stable in those populations, so mammographic screening could not have directly caused the recorded declines in breast cancer mortality in their population-based Cancer Registries. In contrast in Victoria Australia adjuvant therapy use can explain all the recorded mortality decline.

Editorial Objectives

This editorial aims to examine why monitoring trends in biological stages of breast cancer from early potentially curable to advanced more fatal stages at diagnosis and then analysing the impact on those diagnostic stages on long term trends in breast cancer mortality should be mandatory whenever mammographic screening of populations of women is practised and to examine whether biological/endocrine/ chemotherapy given as adjuvant treatment after diagnosis of early breast cancer reduces or nullifies the impact of this screening.

Introduction: History of breast cancer screening

In order to directly reduce breast cancer mortality by mammographic screening, it must detect early mainly curable breast cancers (EBC) in asymptomatic women[1], so that effective treatment can reduce the incidence of late/advanced more lethal breast cancers[2]. The first randomised controlled trial (RCT) of screening mammography for breast cancer began in the US in 1963 with a combination of screening mammography and clinical breast examination (CBE) versus usual care[3], and by 1990 a total of 10 RCT of screening mammography with or without CBE versus observation or CBE alone in women between 40-74 years had finished recruiting[4]. By 1990, it had been reported that mammographic screening of women aged 50-69 years could significantly reduce breast cancer mortality; for example, an Australian systematic review and meta-analysis in 1990 of three RCT that had reported on breast cancer mortality outcomes 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 lead to the initiation of population and opportunistic mammographic screening programs in many countries world-wide from the late 1980s onwards[4]

An 11th RCT in women 40-49 years of age in the United Kingdom (UK) was completed in the 1990s, when 160,921 women were randomly assigned 1:2 to screening mammography or usual care[6], based on previous smaller RCT testing mammographic screening in this age group that had not either individually or when meta-analysed as a group produced a statistically significant reduction in breast cancer mortality in screened women. Likewise, this RCT did not show a statistically significant reduction in breast cancer mortality in women randomised to screening after a decade of follow-up: relative risk 0·83 (95% CI 0·66–1·04), p=0·11[6]. In 2016 the IARC in its second of its breast cancer screening monographs[7] found that two of these 11 RCT produced a statistically significant reduction in breast cancer mortality in the women randomised to mammographic screening: for women aged 50-69 years in the Kopperberg component of the Two Counties RCT[4] and for women aged 45-49 years in the combined Malmo I and II RCT, which randomised women aged 45-69 years[7]. Meta-analyses of the five Swedish RCT of screening mammography versus observation for women aged 50-69 years by the World Health Organizations (WHO) International Agency for Research on Cancer (IARC) produced a statistically significant 25% reduction in breast cancer mortality ($p<0.05$)[4,7]. There were no other age groups of women meta-analysed for which screening mammography +/- CBE resulted in a statistically significant reduction in breast cancer mortality, so the impact of screening mammography on breast cancer mortality in women aged 50-69 years is small. If there were methodological faults in these RCT they could well nullify even this small benefit.

The systematic review and meta-analyses of nine of these RCT published in Lancet in 1990, from two principals of what was to become the Nordic Cochrane Centre, found many faults both with individual RCT and meta-analyses of groups of them[8]. Of particular relevance was the method used to randomise women participating in a particular RCT. Gøtzsche and Olsen reported that only 3 of the RCT, all of which randomized women individually, met their predefined quality standards and that there was no significant breast cancer mortality outcome between the 66013 randomised to screening and 66105 control women who were not screened: 183 breast cancer deaths in screened women and 177 in the control women[8]. Nystrom and colleagues systematically reviewed long term follow-up the Swedish breast cancer screening RCT, with the exception of the Kopperberg county of the Two Counties RCT for which this data was not available and critically examined the randomisation techniques used in those five RCT[9]. They reported that the two Malmo RCT had used individual randomisation and the other three cluster randomisation, but meta-analyses had all assumed individual randomisation[9]. They noted that cluster randomisation widened the confidence intervals, so RCT that produced $p<0.05$ levels of statistical significance with individual randomisation might not do so when cluster randomised. Gøtzsche and Olsen also noted that the cluster randomised Kopparberg and Östergötland components of the Two County RCT had been analysed as though women were individually randomised[8]. This is important, because cluster randomised RCT require a different analytic technique, where interactions between individuals randomised by group, for example by residential area or medical facility, must be taken into account; a technique the author has used[10].

History of monitoring of stages in screening for breast cancer

The IARC 2016 second systematic review of breast cancer screening recommended mandatory

monitoring of stages in mammographic screening in its monograph on Breast Cancer Prevention in 2016[7]: "the rates of advanced-stage disease are still a very direct measure of the impact of early detection by screening, as several studies have reported. To estimate the potential beneficial effect, not simply the proportion of cases with advanced-stage disease but also the reduction in the absolute rate of advanced-stage disease should be reported". This results in EBC being diagnosed 4-6 years before a woman would have presented to health care professionals with late/advanced stage breast cancer[7]. The Tumour Node Metastasis (TNM) system, the first international cancer staging system, was developed in the 1940s by Dr Pierre Denoix at the Institute Gustave-Roussy, France. Subsequently, the Union Internationale Contra Cancer (UICC- International Union against Cancer) established a Committee on Clinical Stage Classification under his leadership and continued to develop the TNM Classification. In 1982 the UICC published the 3rd edition of the TNM Classification and the American Joint Committee for Cancer (AJCC) began publishing separate definitions of TNM categories, in particular for breast cancer; the two systems were unified in 1987. The TNM staging currently used internationally for breast cancer is based on AJCC TNM staging 7th edition[11]. The AJCC defines EBC as stages 1 and 2 breast cancer confined to the breast +/- mobile apical axillary lymph nodes containing metastatic breast cancer[11]. Late/advanced mainly incurable breast cancer is AJCC stage 3 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 and AJCC stage 4 breast cancer has haematogenous metastases to organs and tissues distant to the breast[11].

This TNM is now the staging system used worldwide[11], however the USA Surveillance, Epidemiology, and End Results (SEER) Program with its localised/regional/distant metastatic staging system is also used in some populations[1]. Only the AJCC stage 4 and the SEER distant disease stages are identical: metastasis via the bloodstream to distant organs and tissues[1,11]. This allows comparison of the impact of screening mammography on breast cancer mortality in all countries collecting staging data, where the incidence of the metastatic stage of breast cancer must remain stable or decline over time as breast cancer incidence increases if screening is to have had a direct beneficial impact on mortality: downstaging [1,7]. The SEER regional stage is a conglomerate of the AJCC stages 1 and 2[1], so changes in SEER regional disease do not simply directly impact on downstaging.

Surprisingly, to date monitoring of stages at diagnosis has rarely been done with mammographic screening of populations worldwide. The IARC 2016 systematic review of breast cancer screening[7] reported that for 72 countries, where more than half all the world's women reside, screening mammography was available to some or all populations of women. However, breast cancer stages trend data over decades were not reported for any country in that review[7], so the effectiveness of mammographic screening in those countries cannot be evaluated from that report. Analyses of long-term advanced stage breast cancer incidence trends from population Cancer Registries over decades are available for populations screened by mammography in the States of Victoria and New South Wales (NSW) Australia[12-14], the USA[1], Norway[15] and the Netherlands[16]. In all these populations advanced breast cancer incidence either remained stable[1,12-14] or increased[15,16] over the decades since mammographic screening began, so downstaging to EBC was not detected.
The details of the methods used in Victoria to reach this conclusion have been published[12] and are illustrated by Figure 1 below.

Breast cancer crude mortality (Figure 1-Vic crude mortality), which peaked in 1994 had fallen by 33% to 2019 since that peak and Victorian age standardised mortality to 2001 (Figure 1-Vic ASM) had fallen by 43% to 2017[13]. In contrast the crude incidence of advanced breast cancer stages 3 and 4 (Figure1-Stages 3&4 Crude Incidence) had tripled since 1986[12,13], ruling out a direct impact of mammographic screening on breast cancer mortality.

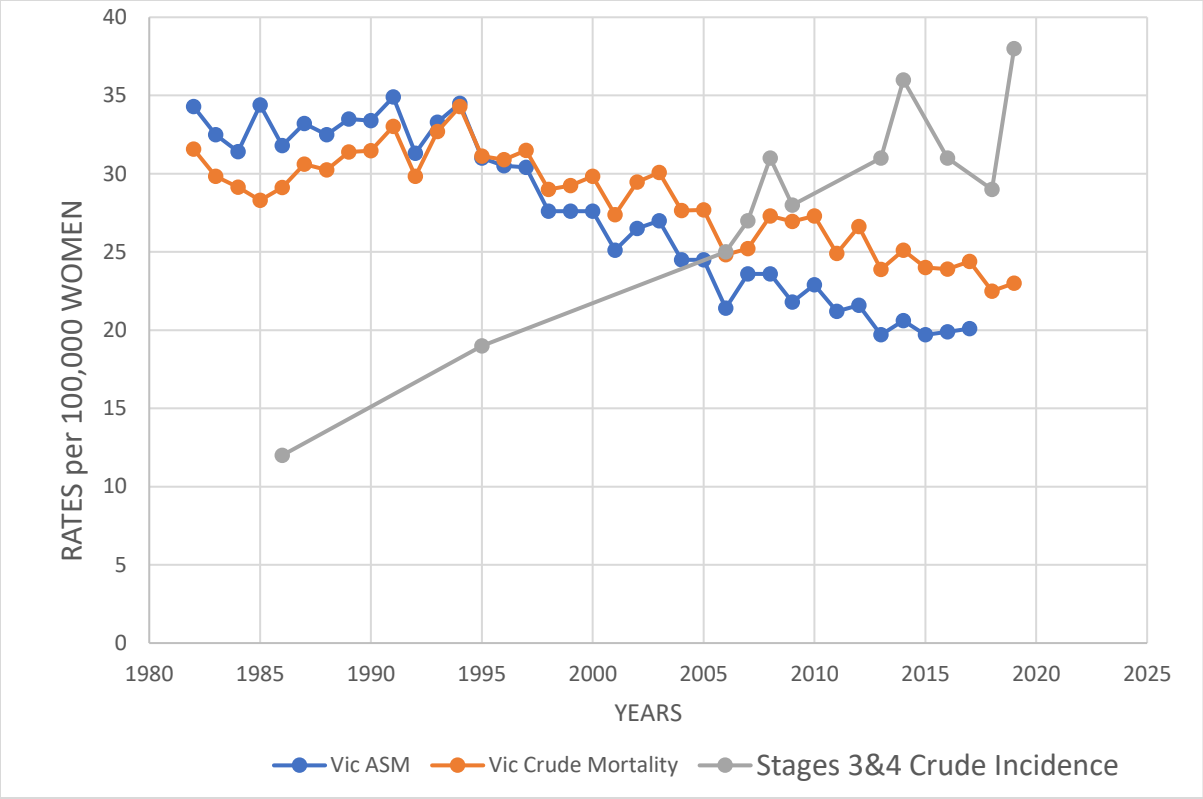

Figure 1. Mammographic screening does not downstage breast cancer mortality in Victoria Australia.

I considered whether diagnosis via BreastScreen in Victoria could have had an indirect impact on breast cancer mortality by resulting in greater access to adjuvant therapy, which subsequently reduced breast cancer mortality, but could find no published evidence of this[13].

Adjuvant therapy of breast cancer

The modern era of adjuvant breast cancer treatment began in the 1970s with the USA (US) National Surgical Adjuvant Breast and Bowel Project (NSABP) randomised controlled trials (RCT) of anti-cancer chemotherapy given as adjuvant therapy after surgical removal from the chest wall and adjacent axilla of all detectable breast cancer; early breast cancer (EBC)[2]. The watershed RCT for adjuvant chemotherapy was the 1976 Italian RCT that reported a statistically significant reduction in breast cancer mortality for a combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMP) adjuvant chemotherapy versus observation in women with EBC[17]. Subsequently, adjuvant therapy introduction to the routine management of EBC began, particularly in high income countries[2].

Diagnosis of breast cancer at an early stage where curative treatment is possible (EBC) has been a priority in breast cancer management for more than half a century[2]. 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 screening asymptomatic women[12]. The Early Breast Cancer Triallist Collaborative Group (EBCTCG) based in Oxford in the UK have 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 and the fifth EBCTCG review was published in 2005[18]. The review reported that breast cancer specific mortality in women with EBC would be approximately halved throughout the next 15 years by 6 months of anthracycline-based chemotherapy followed by 5 years of adjuvant tamoxifen, and that for middle-aged women with oestrogen receptor positive (ER+) breast cancer administering this adjuvant chemotherapy to premenopausal women for more than one year and adjuvant tamoxifen to all women for more than two years would significantly reduce their cumulative breast

cancer mortality[18]. Therefore, the impact of competent adjuvant therapy on breast cancer mortality should be apparent within two years in a population of these women receiving appropriate therapy. Adjuvant therapy for EBC has been progressively initiated in high/middle income countries since the 1990s and new pharmaceutical drugs have been included.

Harms of treatments for early breast cancer

Breast conserving surgery is now the norm in high income countries worldwide[19] and segmental mastectomy/lumpectomy followed by megavoltage external beam radiotherapy (EBRT) to the affected breast with a boost to the tumour site is the preferred management[19]. Morbidity and mortality from breast EBRT resulting in cardiac damage and intrathoracic cancers have been known for decades, and were discussed in our 2020 JAMA Network publication[12]. All-cause mortality, in particular cardiovascular mortality, is not collected by population-based Cancer Registries[7]. These harms have been discounted in the past as the outcomes of outdated radiotherapy techniques and/or as findings from only observational studies[12]. However, recent findings from an International RCT to which Australia contributed on the harms of contemporary EBRT, have proven that this therapy carries a significant risk of death from cardiovascular injury and initiation of other cancers[20]. EBRT for EBC treated by surgery and lumpectomy in this RCT injured the heart and other thoracic organs and caused additional cancers resulting in a statistically significant ($p<0.005$) doubling of non-breast cancer mortality after 12 years, as compared to single dose per-operative breast TARGIT radiotherapy.

Conclusion

This editorial emphasizes that continuous measurement of breast cancer stages at diagnosis, all-cause and breast cancer–specific mortality, and adjuvant therapy uptake should be mandatory in monitoring and evaluating mammographic screening programs and that alternatives to EBRT should be considered in all patients in whom postoperative radiotherapy is a consideration.

Conflicts of Interest. The author has no conflicts of interest to declare.

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