

Research Article

Open Access

Strong Beliefs and Soft Evidence Underlying Mammography Surveillance Recommendations in Breast Cancer Survivors: A Study in Reflexive Science and Decision-Making

Humaid O. Al-Shamsi^{1,4}, Sadir Alrawi^{1,2}, Ahmed S. Abdulsamad⁵, Ibrahim Abu-Gheida^{1,2,4}, Faryal Iqbal^{1,2} and Nuhad K. Ibrahim⁶

¹Department of Oncology – Burjeel Cancer Institute – Burjeel Medical City, Abu Dhabi, United Arab Emirates

²Innovation and Research Center – Burjeel Cancer Institute – Burjeel Medical City, Abu Dhabi, United Arab Emirates

³College of Medicine, University of Sharjah, Sharjah, United Arab Emirates

⁴Emirates Oncology Society, Dubai, United Arab Emirates

⁵Alzahra Hospital – Dubai, United Arab Emirates and Department of Medicine

⁶Department of Breast Medical Oncology; The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

ABSTRACT

Breast cancer is the most common cancer in women worldwide and more recently it has overtaken lung cancer as the world's mostly commonly-diagnosed cancer, according to statistics released by the International Agency for Research on Cancer (IARC) in December 2020 Mammograph screening has been widely used as screening modality and been shown in reduce mortality. Although, benefit of screening mammography in healthy woman cannot be denied, extrapolating this evidence from screening experience in healthy individuals may be unrepresentative and erroneous. Continued mammographic surveillance of breast cancer survivors (BCSS) as of now continued to be standard of care even though still an unsettled issue in survivorship care due to the absence of high-level evidence supporting this current practice. Besides the fact that data regarding efficacy of mammography in BCSS is unclear, there are other concerns regarding its use. Considering, mammography is associated with false positive results requiring additional evaluations, overdiagnosis leading to needless treatment, psychological distress, physical discomfort and significant health-care expenditure, understanding the risk-benefit ratio of mammography in BCSS is crucial. Appropriate studies evaluating mammographic surveillance in BCSS are necessary to assess survival outcomes, cost-benefit ratios and to identify subgroups that derive significant benefit. This holds the key to avoiding unwanted harm to our patients as well as unnecessary financial burden on health-care services.

*Corresponding author

Humaid O. Al-Shamsi, MD, MRCP (UK), FRCP(C), FACP, Associate professor, University of Sharjah, Sharjah, United Arab Emirates, Tel No: +971506315388, E-mail: Humaid.Al-Shamsi@medportal.ca.

Received: April 18, 2021; **Accepted:** April 26, 2021; **Published:** April 29, 2021

Keywords: Mammogram, Mammography, Breast Cancer, Cancer Survivors, Surveillance

Introduction

Breast cancer is the most common cancer diagnosed in women in the United States (276,480 new cancer cases as per 2020 estimates) and accounts for 15.3% of all new cancer cases in the US [1]. Based on 2013-2015 data, approximately 12.9 percent of women will be diagnosed with female breast cancer at some point during their lifetime [1]. Rates for new female breast cancer cases have been rising on average 0.3% each year over the last 10 years [1]. The median age at diagnosis is 61 [2].

An estimated 42,170 deaths in 2020 attributable to breast cancer makes it the third most common cause of cancer related mortality in women in the United States following lung and colorectal cancers [1]. Death rates have been falling on average 1.8% each

year over 2006-2017 due to early diagnosis and improved adjuvant therapy [1]. This decline in breast cancer mortality has resulted in an ever expanding pool of breast cancer survivors (BCSS) in the population, which is expected to grow further in coming years [2].

Consequently, ongoing health-care needs of BCSS have become an active area of survivorship health-services planning and research. Furthermore, the steady increase in expenditure related to care of BCSS and its potential of presenting a significant financial burden in the future has necessitated research to assess efficacy of survivorship care and utilization of resources for this populace. As per the National Cancer Institute (NCI) Progress Report, the US expenditure estimate for female breast cancer for FY2006 was \$13.8 billion [3,4]. A notable part of this monetary load is accounted for by continued surveillance of BCSS. Evidence has taught us that, more is not necessarily better, when it comes to post-therapy follow-up of breast cancer patients [5].

Intensive approach to surveillance when compared to minimalistic strategy, although counter-intuitive, has not resulted in any survival or quality of life benefit [5]. Economic analysis revealed that direct cost associated with intensive follow-up is about 3 to 5 times that of basic follow-up and adoption of minimum follow-up regimen would result in significant economic savings [6]. Accordingly, expert guidelines from both American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend surveillance with regular history/physical examination and annual mammography only [7,8,9]. This resulted in a 35-45% decrease in mean social security expenditure per patient per year [9].

Continued mammographic surveillance of BCSS as of now, is still an unsettled issue in survivorship care. Although, mammography has emerged as an effective tool for breast cancer screening in healthy populations, its utility in BCSS is unknown, since BCSS are typically excluded from screening trials [10,11]. No prospective randomized-controlled trials (RCTs) have been performed to assess the efficacy of mammography in routine care of BCSS [12]. The studies published thus far have been retrospective and have shown mixed results [12-18]. Thus, the controversy over the role of mammographic surveillance of BCSS remains unresolved to date, owing to indisputable lack of randomized data. Additionally, no data whatsoever exists with regards to cost-benefit analysis of mammography in BCSS.

Despite the paucity of compelling empirical evidence, recommendations from both ASCO and NCCN maintain annual mammography as a part of routine surveillance in all BCSS [7,8]. In the face of absent high-level evidence supporting this current practice, the case sustaining these recommendations has been built on three propositions. Firstly, in patients with primary breast cancers (PBCs), risk of recurrence persists for years after treatment [19]. Secondly, patients with PBCs are at higher risk of second primary breast tumors [20].

Lastly, mammography results in early detection of recurrence and second primaries which in turn improves mortality outcomes [15]. However, this hypothesis has never been subjected to the rigorous appraisal of a RCT. The possibility of designing such a trial with randomization to mammography and no mammography is currently arguable, due to a widespread and established belief in mammographic surveillance among both patients and providers. Conducting such a study may be plagued by ethical issues and the acceptability of denying a "standard of care" to one cohort of patients.

Probing these rationales raises important concerns about strength of recommendations supporting mammography in BCSS. Firstly, Most breast cancer recurrences (77%) were patient-detected, 12% were detected by imaging, and 11% were clinician-detected. While the majority of recurrences were patient-detected, these were detected later and at a more advanced clinical stage. Secondly, 41% of all second primary cancers diagnosed among U.S. women occur among breast cancer survivors and approximately 10% of breast cancer survivors will develop a second primary cancer. The four most common sites of second primary cancer, breast, lung, colon and endometrium, account for 70% of these second primaries [21].

Moreover, this risk is age dependent [risk with PBC < 40 yr = 3 X (risk with PBC > 40 yr)] and is modifiable with adjuvant hormonal therapy. As such, it is reasonable to state that the benefit of screening for second primary breast cancer is not uniform in all

BCSS. Lastly; early detection of recurrence or second primaries does not always translate into a survival benefit, since screening outcomes are confounded by lead-time bias, overdiagnosis and length-biased sampling [21,22]. Mammography screening, even in healthy population, where it has been studied exhaustively is not an unassailable strategy. The degree to which observed reductions in breast cancer mortality is attributable to screening mammography has become increasingly controversial.

A comparison of eight countries in Europe and North America does not demonstrate a correlation between the penetration of national screening and either the chronology or magnitude of national breast cancer mortality reduction. In the United States, the magnitude of the mortality decline is greater in the unscreened, younger women than in the screened population and regional variation in the rate of breast cancer mortality reduction is not correlated with screening penetrance, either as self-reported or by the magnitude of screening-induced increase in early-stage disease [23].

Notably, although the reduction in breast cancer mortality has been significant; Advances in treatment and changes in risk factors e.g. hormone replacement therapy (HRT) are responsible for a major part in the reduction of breast cancer mortality [24]. Meta-analysis of the 8 RCTs that have evaluated effectiveness of screening mammography in healthy population estimates the number needed to invite (NNI) to prevent 1 breast cancer death as 1904, 1339 and 377 for age groups 39-49, 50-59 and 60-69 years respectively. The NNI for age group > 70 was not estimable [24].

Although there is a mortality reduction seen in trials from screening, the magnitude of this effect is unclear especially in relation to potential harms. The chance that a woman will benefit from attending screening is small [24]. With a 29% relative reduction in breast cancer mortality (as seen in the Swedish trials) the absolute reduction in breast cancer mortality is 0.1% after 10 years. [24,25] This corresponds to a 2 day life extension per woman per 10 years of screening notwithstanding the time needed to attend these screenings and the potential harms attendant to screening [24].

Although Mammography screening efficacy has been demonstrated in randomized controlled trials (RCTs). There are no RCTs evaluating survival outcomes from mammographic surveillance in BCSS to date [7,12]. Keeping in mind the above stated data, it is reasonable to question the survival impact of any such strategy.

Four noteworthy retrospective studies have been performed to assess the impact of mammography in BCSS [18]. performed a case-control study (1351 breast cancer deaths (cases) and 5,262 controls) and showed that women with a mammogram during a one or two-year time interval were less likely to die from breast cancer than women who did not have any mammograms during this time period (within 1-yr OR: 0.83, 95% CI: 0.72-0.95; within 2-yr OR: 0.80, 95% CI: 0.70-0.92) [18]. However, this observational study also showed a decreased risk of all-cause mortality due to mammograms. in 266 patients with local recurrence after breast conserving surgery demonstrated that recurrences were diagnosed by mammography alone in 25% of cases and were significantly smaller than those by physical examination [15].

Since distant metastasis free survival was better for patients with a lower T stage, they concluded that early detection may improve treatment outcomes; however no survival outcomes were reported [15]. Lash et al. conducted a retrospective review of 1,846 stage

I and II breast cancer patients who were at least 65 years old and concluded that surveillance mammography lead to 0.69-fold decrease in breast cancer mortality in BCSS [13]. However, there were unanswered questions regarding the differential protective association of mammography with stage (Stage I disease had greater reduction in odds of breast cancer diagnosis or mortality compared to stage II disease), type of surgery (OR lower with mastectomy vs. breast conserving surgery) and age (effect increased with increasing age).

Compared accuracy and outcomes of mammography in women with and without a personal history of breast cancer (PHBC & non-PHBC) [14]. The study showed that mammography detects more early-stage second breast cancers, ductal carcinoma in-situ (DCIS) and favorable stage interval cancers. Nonetheless, mammography had lower sensitivity (65.4% vs. 76.5%) in BCSS than healthy individuals [14]. Also, PHBC screens were more frequently associated with additional imaging (18.1% vs. 8.3%), recommendation for fine-needle aspiration, biopsy, or surgical consultation after assessment (2.2% vs. 1.4%) [14]. Although these retrospective analyses lend support for surveillance recommendations, they are highly heterogeneous in methodology, surveillance regimens and patient populations in addition to suffering from the inevitable bias and errors inherent to all retrospective studies.

Overdiagnosis refers to disease that is detected by screening but would have otherwise caused no significant morbidity or mortality, exposing patients to needless therapy and side-effects. Overdiagnosis confounds survival outcomes and is a valid concern with mammographic surveillance. a systematic review of methods estimated of overdiagnosis attributed to population mammography screening ranges in 10-22% [26].

The most recent and comprehensive meta-analyses of the RCTs has been reported by Nelson and colleagues [27,28] by age-strata to inform the US Preventive Services Task Force recommendations on breast screening. It showed that screening conferred significant reductions in the relative risk of BC death in women aged 50–59 years (RR 0.86; 95% CI 0.68–0.97) and 60-69 years (RR 0.67; 95% CI 0.54–0.831); however screening did not significantly reduce the risk of BC death in women aged 40–49 years (RR 0.92; 95% CI 0.75–1.02) or in those aged 70–74 years (RR 0.80; 95% CI 0.51–1.28) although trial data were relatively sparse for the estimated effect in the 70–74 years age-group [27].

In absolute terms, these pooled estimates translate to prevention of 2.9 (40–49 years), 7.7 (50–59 years), 21.3 (60–69 years), and 12.5 (70–74 years) BC deaths, per 10,000 women screened for 10 years [30,31] [27,28]. The meta-analysis from Nelson also reported that screening reduced the risk of advanced-stage BC in women aged ≥50 years (RR 0.62; 95%CI 0.46–0.83), but not in those aged 39–49 years (RR 0.86; 95%CI 0.68–0.97) based on a subgroup of the screening RCTs [27,28].

The precept of competing comorbidities is also central to survivorship care. The odds of death from other causes relative to breast cancer death increase with increasing age. With increasing age in BCSS, benefits resulting from early detection may be diminished due to competing comorbidities. Besides the fact that data regarding efficacy of mammography in BCSS is unclear, there are other concerns regarding its use. Sensitivity and specificity as seen in healthy population range from 75-88% and 83-98% respectively [29,30]. Prior breast surgery and radiation can affect screening accuracy by altering these parameters and results in

lower sensitivity and specificity in BCSS [14,28]

False positive rate of mammography can be as high as 23.8% with an estimated 10-yr cumulative risk of a 49.1% [29]. Recall rates can be as high as 43.3% and the positive predictive value ranges from 3-9% [30, 31]. These figures can be inflated in BCSS due to architectural distortion in breast anatomy resulting from surgery and/or radiation changes and tendency of radiologists to have a low threshold for calling a mammogram positive due to known previous history of breast cancer [32]. The recommendations for additional tests and procedures in women who do not have cancer have critical clinical and fiscal implications.

The experience of having a false-positive screening mammogram can cause breast cancer-specific psychological distress that may endure for up to 3 years, and reduce the likelihood that women will return for their next round of mammography screening. Women with false-positive results have higher than normal levels of distress and anxiety about breast cancer than those with normal results [33,34]. Recall after mammography among women with a false-positive mammogram was associated with transiently increased anxiety and a slight increase in depression. However, the level of anxiety was similar to and the level of depression was lower than in the general female Norwegian population.

Remarkably subsequent use of health care services (breast-related & non-breast-related) increase in the years after false-positive mammograms [35]. Also, pain and/or discomfort are reported by a majority (47%) of women undergoing mammography [36]. Although, no formal analysis of subsequent health-care expenditure resulting from surveillance mammography has been done in BCSS, a cost analysis review by Eddy et al. published in 1989 in healthy women indicates a potential large financial burden resulting from screening mammography [37].

Data from screening trials also show that false positive tests in 2400 women over 10 years can lead to 870 outpatient appointments, 539 diagnostic mammograms, 186 ultrasound examinations, 188 biopsies and 1 hospitalization [29]. Among women who do not have breast cancer, mammography can lead to a biopsy in 18.6% women after 10 examinations [29]. Screening resulted in a 33% added expenditure from evaluation of false positive results [29]. A subgroup analysis of the Stockholm trial (n = 352) showed that follow-up costs of false positive screening results after 2 rounds was £334,000 [38].

Conclusion

The mammographic surveillance is routinely recommended in BCSS without compelling data. Although, benefit of screening mammography in healthy woman cannot be denied, extrapolating this evidence from screening experience in healthy individuals may be unrepresentative and erroneous. Considering, mammography is associated with false positive results requiring additional evaluations, overdiagnosis leading to needless treatment, psychological distress, physical discomfort and significant health-care expenditure, understanding the risk-benefit ratio of mammography in BCSS is crucial. Appropriate studies evaluating mammographic surveillance in BCSS are necessary to assess survival outcomes, cost-benefit ratios and to identify subgroups that derive significant benefit. This holds the key to avoiding unwanted harm to our patients as well as unnecessary financial burden on health-care services.

Consent for Publication: All authored approved and agreed to submit to publication

Funding: Khalifa Bin Zayed Al Nahyan Foundation, Abu Dhabi, United Arab Emirates. Khalifa Bin Zayed Al Nahyan Foundation had no role in the design and conduct of the study; review, or approval of the manuscript; and decision to submit the manuscript for publication. Khalifa Bin Zayed Al Nahyan Foundation provided funding for open-access publication.

Conflict of Interest: None by all authors

Acknowledgements: None

References

1. https://www.breastcancer.org/symptoms/understand_bc/statistics. Accessed April 18th 2021
2. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, et al. (2012) Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 62: 220-241.
3. NCI Cancer Trends Progress Report [<https://progressreport.cancer.gov/doc>].
4. NCI Office of Science Planning & Assessment (OSPA) [<http://planning.cancer.gov/library>]
5. Rojas M P, Telaro E, Russo A, Fossati R, Confalonieri C, et al. (2000) Follow-up strategies for women treated for early breast cancer. *Cochrane Database Syst Rev* 4: CD001768.
6. Mapelli V, Dirindin N, Grilli R (1995) Economic evaluation of diagnostic follow-up after primary treatment for breast cancer. Results of the Working Group on Economic-Organizational Aspects of Follow-up. *Ann Oncol* 2: 61-64.
7. Khatcheressian J L, Wolff A C, Smith T J, Grunfeld E, Muss H B, et al. (2006) American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 24: 5091-5097.
8. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. In 2012.
9. Mille D, Roy T, Carrere MO, Ray I, Ferdjaoui N, et al. (2000) Economic impact of harmonizing medical practices: compliance with clinical practice guidelines in the follow-up of breast cancer in a French Comprehensive Cancer Center. *J Clin Oncol* 18: 1718-1724.
10. Nelson H D, Tyne K, Naik A, Bougatsos C, Chan BK, et al. (2009) Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 151: 727-737.
11. Bucchi L (2011) Should breast cancer survivors be excluded from, or invited to, organised mammography screening programmes? *BMC Health Serv Res* 11: 249.
12. Grunfeld E, Noorani H, McGahan L, Paszat L, Coyle D, et al. (2002) Surveillance mammography after treatment of primary breast cancer: a systematic review. *Breast* 11: 228-235.
13. Lash T L, Fox M P, Buist D S, Wei F, Field T S, et al. (2007) Mammography surveillance and mortality in older breast cancer survivors. *J Clin Oncol* 25: 3001-3006.
14. Houssami N, Abraham L A, Miglioretti D L, Sickles E A, Kerlikowske K, et al. (2011) Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. *JAMA* 305: 790-799.
15. Voogd A C, van Tienhoven G, Peterse H L, Crommelin M A, Rutgers E J, et al. (1999) Local recurrence after breast conservation therapy for early stage breast carcinoma: detection, treatment, and outcome in 266 patients. Dutch Study Group on Local Recurrence after Breast Conservation (BORST). *Cancer* 85: 437-446.
16. Orel S G, Fowble B L, Solin L J, Schultz D J, Conant E F, et al. (1993) Breast cancer recurrence after lumpectomy and radiation therapy for early-stage disease: prognostic significance of detection method. *Radiology* 188: 189-194.
17. Joseph E, Hyacinthe M, Lyman G H, Busch C, Demps L, et al. (1998) Evaluation of an intensive strategy for follow-up and surveillance of primary breast cancer. *Ann Surg Oncol* 5: 522-528.
18. Schootman M, Jeffe D B, Lian M, Aft R, Gillanders W E (2008) Surveillance mammography and the risk of death among elderly breast cancer patients. *Breast Cancer Res Treat* 111: 489-496.
19. Saphner T, Tormey D C, Gray R (1996) Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol* 14: 2738-2746.
20. Chaudary M A, Millis R R, Hoskins E O, Halder M, Bulbrook R D, et al. (1984) Bilateral primary breast cancer: a prospective study of disease incidence. *Br J Surg* 71: 711-714.
21. Rosselli Del Turco M, Palli D, Cariddi A, Ciatto S, Pacini P, et al. (1994) Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. *JAMA* 271: 1593-1597.
22. Allgood P C, Duffy S W, Kearins O, O'Sullivan E, Tappenden N, et al. (2011) Explaining the difference in prognosis between screen-detected and symptomatic breast cancers. *Br J Cancer* 104: 1680-1685.
23. Nystrom L, Rutqvist L E, Wall S, Lindgren A, Lindqvist M, et al. (1993) Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet* 341: 973-978.
24. Jorgensen K J, Zahl P H, Gotzsche P C (2010) Breast cancer mortality in organised mammography screening in Denmark: comparative study. *BMJ* 340: 1241.
25. Gotzsche P C, Nielsen M (2011) Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 1: CD001877.
26. Elmore J G, Barton M B, Mocerri V M, Polk S, Arena P J, et al. (1998) Ten-year risk of false positive screening mammograms and clinical breast examinations. *N Engl J Med* 338: 1089-1096.
27. Smith-Bindman R, Chu P W, Miglioretti D L, Sickles E A, Blanks R, et al. (2003) Comparison of screening mammography in the United States and the United Kingdom. *JAMA* 290: 2129-2137.
28. Kerlikowske K, Grady D, Barclay J, Sickles E A, Eaton A, et al. (1993) Positive predictive value of screening mammography by age and family history of breast cancer. *JAMA* 270: 2444-2450.
29. Shapiro S, Strax P, Venet L (1966) Evaluation of periodic breast cancer screening with mammography. Methodology and early observations. *JAMA* 195: 731-738.
30. Miller A B, To T, Baines C J, Wall C (2002) The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med* 137: 305-312.
31. Banks E, Reeves G, Beral V, Bull D, Crossley B, et al. (2004) Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. *BMJ* 329: 477.
32. Wapnir I L, Alden-Corbett S, Zicherman B, Greco R S (1993) Mammographic changes following biopsy and lumpectomy-breast irradiation. *N J Med* 90: 55-59.
33. Brewer N T, Salz T, Lillie S E (2007) Systematic review: the long-term effects of false-positive mammograms. *Ann Intern Med* 146: 502-510.
34. Lerman C, Trock B, Rimer B K, Boyce A, Jepson C, et al. (1991) Psychological and behavioral implications of abnormal

- mammograms. *Ann Intern Med* 114: 657-661.
35. Barton M B, Moore S, Polk S, Shtatland E, Elmore J G, et al. (2001) Increased patient concern after false-positive mammograms: clinician documentation and subsequent ambulatory visits. *J Gen Intern Med* 16: 150-156.
36. Nielsen B B, Miaskowski C, Dibble S L, Beber B, Altman N, et al. (1991) Pain and discomfort associated with film-screen mammography. *J Natl Cancer Inst* 83: 1754-1756.
37. Eddy DM (1989) Screening for breast cancer. *Ann Intern Med* 111: 389-399.
38. Lidbrink E, Elfving J, Frisell J, Jonsson E (1996) Neglected aspects of false positive findings of mammography in breast cancer screening: analysis of false positive cases from the Stockholm trial. *BMJ* 312: 273-276.

Copyright: ©2021 Humaid O. Al-Shamsi, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.