Journal of Oncology Research and Therapy
Ofri A, et al. J Oncol Res Ther 7: 10126.
www.doi.org/10.29011/2574-710X.10126
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Research Article

# Older Breast Cancer in Australia: Tumour Characteristics of Screened Versus Symptomatic Breast Cancers

**Dr Adam Ofri[1,2*], BMed MS FRACS, Nazim Bhimani[3], MBiostat, Bsc (Adv Sc)(Hons), Dr Sanjay Warrier[4,5], BSc (Med), MBBS MS FRACS**

[1]Department of General Surgery, St Vincent's Hospital, Darlinghurst, Australia

[2]St Vincent's Clinical School, University of New South Wales, Sydney, Australia

[3]Department of Upper Gastrointestinal Surgery, Royal North Shore Hospital, Sydney, Australia

[4]Department of Surgery, Chris O'Brien Lifehouse, 119-143 Missenden Rd, Camperdown Australia

[5]Royal Prince Alfred Hospital Institute of Academic Surgery, Camperdown, Australia

[*]**Corresponding Author:** Adam Ofri, St Vincent's Private Hospital, Darlinghurst NSW 2010, Australia. Email: adamofri@gmail.com

**Citation:** Ofri A, Bhimani N, Warrier S (2022) Older Breast Cancer in Australia: Tumour Characteristics of Screened Versus Symptomatic Breast Cancers. J Oncol Res Ther 7: 10126. DOI: 10.29011/2574-710X.10126

**Received Date:** 08 March, 2022**; Accepted Date:** 11 March, 2022**; Published Date:** 14 March, 2022

## Abstract

**Background:** Breast cancer is the most common non-skin cancer in Australia, affecting 1 in 7 women by the age of 85. The Australian 2020 projected incidence of breast cancer in the older population, 70 years or greater, is over 6500. This is almost a third of the entire projected incidence of over 20,000. BreastScreen Australia invites women aged 50-74 years of age for biennial screening; however, a significant proportion of Australian women continue screening well beyond this. We have evaluated the tumour characteristics of older breast cancer patients - comparing symptomatic to screen detected patients. **Methods:** This was a retrospective study of data from the BreastSurgANZ Quality Audit (BQA) between 1 January 2001 and 31 December 2019. Female patients aged ≥ 70 at diagnosis were included only. Exclusion occurred for incompletely recorded cases. Patients were then divided based on means of detection - either screen detected (Group A) or symptomatic (Group B). **Results:** From 1 January 2001 to 31 December 2019, 34,258 patients were appropriately reported in the BQA. There were 11,021 in Group A and 23,237 in Group B. DCIS was more prevalent in Group A (16.83% versus 6.49%, p = <.001). T stage distribution was statistically different, with higher T stages for Group B, p = <.001. IDC sub-type distribution varied between the two groups, p = <.001. IDC Grade 3 and lymphovascular invasion were more common in Group B (p = <.001). Hormonal status was statistically different, with Group B having greater rates of TNBC and HER2+ cancers compared to Group A (12.99% versus 7.10%, p = <.001 and 4.45% versus 2.55%; respectively, p = <.001). **Conclusion:** This is the first BQA review of older breast cancer tumour characteristics, comparing screen to symptomatic patients. As hypothesized, screen detected cancers were smaller and earlier stage, compared to symptomatic patients. Tumour biology was statistically less favourable in Group B being higher grade, and greater rates of lymphovascular invasion, TNBC and HER2+ cancers.

**Keywords:** Older breast cancer; Screen; Symptomatic; Axillary surgery

## Introduction

Breast cancer is the most common non-skin cancer in Australia, affecting 1 in 7 women by the age of 85. The Australian 2020 projected incidence of breast cancer in the older population, 70 years or greater, is over 6500: almost a third of the entire projected incidence of over 20,000. This mirrors international data that 30% of new breast cancer diagnosis occurs in the older population [1,2]. In Australia, the average life expectancy was 83.5 years in 2020. Landmark studies have encouraged a more selective

approach to Older Breast Cancer (OBC) management [3-5]. The Society of Surgical Oncology (SSO) and the American College of Surgeons have made recommendations regarding reducing rates of Sentinel Lymph Node Biopsy (SLNB) and Radiotherapy (RT) in the older population, respectively. However, this has been perceived as unreasonable by some [6].

The current Australian screening program extends from 50-74 years of age for those with a normal risk of breast cancer patients. Patients over the age of 74 years are eligible for ongoing BreastScreen attendance however are not contacted biennially with reminder letters. Some patients are recommended by their surgeons to have yearly extended screening times due to previous breast cancer diagnosis. Others privately fund their own yearly screening due to their concern of breast cancer, coupled with their high quality of life. There is limited data to date showing the current rates of screening for OBC patients in Australia. There is no published Australian data comparing OBC patients who are symptomatic, versus those who were detected on screening.

Breast cancer in older patients have a higher expression of positive prognostic biological factors [7,8]. This is concordant with the clinical observation of less aggressive tumours in the elderly compared to the young [9]. Studies have shown screen-detected breast cancers are more biologically favourable, compared to symptomatic patients [10,11]. Key areas of difference include tumour size, histological grade, and hormonal status. In these studies, older patients are typically under-represented. The overall opinion that OBC is less aggressive has failed to assess the differences in the tumour biology of screen-detected cancers versus symptomatic. We performed a retrospective review of the BreastSurgANZ Quality Audit (BQA) to review the tumour biology of OBC patients, comparing screen-detected to symptomatic.

## Patients and Methods

The BQA was formerly known as the National Breast Cancer Audit. Initially voluntary, it is now a mandatory aspect of BreastSurgANZ membership to ensure a quality assurance service for surgeons who treat breast cancers. The audit collects data on the surgical care of early and locally advanced breast cancer and ductal carcinoma in situ. The BQA database currently contains over 175,000 episodes of breast cancer (capturing 90% of breast cancer cases in Australia and New Zealand), with over 300 surgeons contributing data each year. The Register records de-identified data of patient demographics, means of diagnosis, surgeries performed, pathology data and adjuvant therapies.

The BQA was reviewed to identify all older patients (aged ≥ 70 years) diagnosed with Ductal Carcinoma In-Situ (DCIS) or invasive breast cancer from 1st January 2001 to 31st December 2019. Prospectively collected data on all older patients, including methods of diagnosis and cancer characteristics were retrospectively reviewed. Breast cancer characteristics were reviewed based on the American Joint Committee on Cancer (AJCC) T-stage. Male patients and those with incompletely recorded data were excluded from the study. Comparison was made between screen-detected breast cancer patients (Group A) and symptomatic patients (Group B).

Statistical analysis was performed using Stata (Version 17; College Station, TX), including Z (normal) test for group comparisons, and the Chi-square test for independence to compare distributions between the groups and Z (normal) test for two.

## Results

From 1 January 2001 to 31 December 2019, 34258 patients were appropriately reported in the BQA. There were 11021 (32.17%) screen-detected patients (Group A) and 23237 (67.83%) symptomatic presentations (Group B). The age of patients differed between the two groups; Group A patients were on average younger (74.04 ± 3.92 years) compared to Group B patients (78.53 ± 6.01 years).

DCIS was more prevalent in Group A (16.83% versus 6.49%, p = <.001). This was expected, given the working hypothesis that screening detects early parenchymal changes, especially in the older population. Associatively, T stage distribution was statistically different, with higher T stage more frequent for Group B, p = <.001. Further differences were encountered as shown in Table 1. Breast cancer sub-type distribution was varied between the two groups, p = <.001. Histological Grade 3 and LVI were more prevalent in Group B (p = <.001). Hormonal status was statistically different, with Group B having greater rates of Triple Negative Breast Cancer (TNBC) and HER2+ cancers compared to Group A (12.99% versus 7.10%, p = <.001 and 4.45% versus 2.55%; respectively, p = <.001) Table 1.

| | Screen detected (Group A) | Symptomatic (Group B) | P value |
|---|---|---|---|
| No of patients | 11 021 (32.17%) | 23 237 (67.83%) | N/A |
| Mean age, SD | 74.04, 3.92 | 78.53, 6.01 | N/A |
| T stage | | | |
| DCIS | 1855 (16.83%) | 1508 (6.49%) | |
| T1 | 6969 (63.23%) | 9875 (42.50%) | < 0.001 |
| T2 | 1868 (16.95%) | 9346 (40.22%) | |
| T3 | 237 (2.15%) | 1769 (7.61%) | |
| T4 | 92 (0.83%) | 655 (2.82%) | |
| Cancer Subtypes | | | < 0.001 |
| IDC of NST | 6639 (73.22%) | 15431 (72.96%) | |
| ILC | 1325 (14.61%) | 2996 (14.16%) | |
| Mucinous | 284 (3.13%) | 800 (3.78%) | 0.003 |
| Other invasive of mixed type | 260 (2.87%) | 690 (3.26%) | 0.036 |
| Other neoplasm | 212 (2.34%) | 659 (3.12%) | < 0.001 |
| Unknown | 94 (1.04%) | 217 (1.03%) | |
| Tubular | 207 (2.28%) | 158 (0.75%) | < 0.001 |
| Basal-like | 32 (0.35%) | 152 (0.72%) | < 0.001 |
| Medullary | 14 (0.15%) | 48 (0.23%) | < 0.001 |
| Grade | | | |
| 1 | 2650 (28.91%) | 3414 (15.77%) | |
| 2 | 4603 (50.22%) | 10133 (46.81%) | < 0.001 |
| 3 | 1671 (18.23%) | 7118 (32.89%) | |
| Unknown | 242 (2.64%) | 980 (4.53%) | |
| LVI | | | |
| Present | 1336 (14.58%) | 6029 (27.85%) | < 0.001 |
| Absent | 7360 (80.30%) | 13842 (63.95%) | |
| Unknown | 470 (5.13%) | 1774 (8.20%) | |
| Hormonal status | | | |
| ER/PR+, HER2- | 6627 (80.15%) | 13260 (70.65%) | |
| ER+, PR/HER2- | 810 (9.80%) | 2147 (11.44%) | < 0.001 |
| PR+, ER/HER2- | 33 (0.40%) | 88 (0.47%) | |
| HER2+ | 211 (2.55%) | 836 (4.45%) | |
| TNBC | 587 (7.10%) | 2438 (12.99%) | |

SD: Standard Deviation; DCIS: Ductal Carcinoma In-Situ; LVI: Lymphovascular Invasion; IDC: Invasive Ductal Carcinoma; NST: No specific type; ILC: Invasive Lobular Carcinoma; ER: Oestrogen receptor; PR: Progesterone Receptor; TNBC: Triple Negative Breast Cancer.

**Table 1:** Tumour characteristics of Older Breast Cancer patients diagnosed with Breast Cancer.

## Discussion

As patients age, comorbidities can develop, increasing the complexity in managing the health care of patients. The term frailty has been used to describe the generalised diminished physiological reserve and increased stress-related vulnerability affected the elderly [12]. Patient frailty strongly correlates to morbidity and mortality associated with surgical pathology management [13]. Given the variability in the health status of older patients, they become under-represented in clinical trials. This only leads to further difficulties with treatment decision-making due to the lack of appropriate evidence. The recent suggestion of de-escalation of treatment in older patients is understandable, given that some patients have a hypothesised short life expectancy. However, prior to determining whether we should offer or withhold a treatment, we should ensure that we have thoroughly evaluated OBC patients and their tumour biology.

Histological tumour grade is related to the degree of tumour tissue differentiation and is calculated by the Nottingham Grading System (NGS). The NGS is recommended by multiple international bodies and is derived from the evaluation of three morphological features - nuclear pleomorphism, mitotic count and degree of tubule or gland formation [14]. The prognostic impact of histological grade has been well studied, with evidence that grade is as important a prognostic factor as lymph node stage [15,16]. It is no surprise that the 8$^{th}$ edition of the AJCC has now included histological grade, impacting upon a patients defined stage of breast cancer [17]. Histological grade has been shown to provide significant prognostic information on chemotherapy benefit as well as patterns of survival, including BCSS, DFS and OS [15,18]. Stage II Grade 1 cancers have been shown to have a < 10% event risk at 10 years; however, Stage II Grade 2 or 3 cancers have a > 10% risk of event in 5-10 years [19]. Grade 3 cancers are more likely to recur, with metastasis occurring within 8 years [15]. Our study has shown that symptomatic patients have a statistically higher rate of histological Grade 3 breast cancers, compared to those that were screen detected. Almost 80% of symptomatic patients present with either Grade 2 or 3 cancers, a far less favourable tumour biology than Grade 1.

Lymphovascular invasion is defined as the presence of malignant tumour cells in lymphatic or blood vessels. Initial reports discounted the relevance of LVI in breast cancer, thought to be associated with lymphangiogenesis or immune response. Recent evidence is suggestive of a highly proliferative cancer [20]. As an independent factor, LVI is indicated to negatively impact local recurrence rates, distant relapse, and overall survival [21,22]. Recent studies have also drawn attention to LVI's impact on survival after neoadjuvant chemotherapy - a potential prognosticator superior to pathological complete response [23-25]. In our study, the presence of LVI was statistically higher in symptomatic patients (27.85% versus 14.58%); comparable to previously reported rates of LVI presence of 23-24.3% [9,22]. This indicates a protective-effect of screen-detected cancers, when compared to symptomatic tumours.

IDC no specific type (NST) is the most common type of IDC, accounting for 40-75% of all mammary invasive carcinomas [26]. Invasive Lobular Carcinoma (ILC) is the second major sub-type of invasive mammary carcinoma, constituting approximately 5-15% of invasive carcinomas. Tubular and medullary carcinomas are rare, well-differentiated breast carcinomas most common in older women. Nodal involvement is similar, occurring in approximately 10-20% of cases [27]. Both are associated with a good prognosis; however, prognosis is significantly worse in the context of mixed tumours. Our subtype distribution is in keeping with the literature; with elevated mucinous rates and depressed medullary rates, as expected in an older population [28].

Receptor status has significant impact in differing clinical outcome for all breast cancer patients [29]. When comparing older patients to younger patients, there are greater rates of over-expression of ER and PR, with under expression of HER2. This receptor expression difference correlates with a comparative reduction in the level of tumour biology aggressiveness. Our distribution rate of HER2 cancers (Group A 2.55%, Group B 4.45%) were significantly lower than in the literature, 14-15% [22,30]. Group B's rate of TNBC of 12.99% was comparable to reported rates of ~ 12% [22,31]. Screen detected breast cancers in older patients have a significantly elevated frequency of ER ± PR positivity (over 90%), resulting in a more favourable tumour biology when compared to older symptomatic cancers; and therefore, even greater favourability when compared to their younger cohort.

## Conclusion

In the current international stance of de-escalating treatment of breast cancer in the elderly, it is pivotal to ensure we are not providing sub-standard care for patients. It is reasonable to recommend a reduction in an intervention when the time to efficacy is greater than the patient's likely survival. However not all OBC patients are equal. There are significant risk differences, starting with their means of diagnosis. We have shown that symptomatic patients have statistically significant different tumour biology compared to screen-detected patients. These differences should be further assessed, and mode of diagnosis should be considered prior to determining de-escalation of OBC management.

### Weakness

An obvious shortcoming of our study is the inability to review these tumour characteristics with recurrence and survival. However, there is significant literature available reporting these rates, as discussed above. The BQA is a surgeon-reported audit,

thus the onus of updating patient recurrence and mortality is on the surgeon. Fortunately, for patients, mortality from breast cancer in Australia is low; from a database perspective however, this results in an inability to update patient mortality from other causes. In Australia, a patient's death in a hospital or nursing home, reported to their general practitioner, not to their affiliate surgeon. Therefore, a proposed direction for the BQA would be the incorporation of the National Death Index (NDI), a Commonwealth database recording deaths and their causes.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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