Original Study

Extending Screening in "Elderly" Patients: Should We Consider a Selective Approach?

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Abstract

In response to The Ministry of Health in New Zealand's population modeling proposal of extending breast cancer screening to the older population, The Auckland Breast Cancer Register was reviewed for outcomes of women aged 45 to 69 years and over 70 years. Although bias can be difficult to accommodate in studies reviewing the benefit of population screening programs, it was found that screening of patients aged over 70 years continues to identify early breast cancer and facilitate improved outcomes. A "selective approach" to extending screening services to appropriate "elderly patients" may facilitate patient outcomes.

Background: Breast cancer screening has been shown to reduce breast cancer-associated mortality. However, screening is limited to the targeted age group of 45 to 69 years in New Zealand despite the recognized increased risk with age. This study aims to compare the outcomes of women aged over 70 years with screen-detected and clinically detected cancers. **Patients and Methods:** A retrospective review was performed of prospectively collected data from June 2000 to May 2013 by the Auckland Breast Cancer Register. Demographic and tumor characteristics of women with invasive cancer and ductal carcinoma in situ diagnosis aged 70 years and over were compared between those screened and clinically detected. Five-year disease-free and overall survival outcomes were reviewed. **Results:** A total of 2128 women aged 70 years and over were diagnosed with breast cancer (median, 77 years; interquartile range [IQR], 74-84 years). Of these, 416 (19.5%) were diagnosed through mammography screening, with a median age of 74 years (IQR, 71-77 years) compared with 79 years (IQR, 74-85 years) for those with clinical detected cancer diagnosis. Screen-detected cancers accounted for a significantly higher proportion of diagnoses in those aged 70 to 74 years compared with older patients ($P < .001$). Screen-detected cancers were of lower T and N stages. Disease-specific survival was significantly longer in screen-detected cancers versus other cancers (5-year survival, 93.7% vs. 81.9%; $P < .001$), as was overall survival (5-year survival, 84.7% vs. 57.4%; $P < .001$). **Conclusion:** Screening in those aged 70 years and over continues to identify breast cancer at early stages and with improved survival. Although aware of the potential for lead-time bias and the healthy volunteer effect, there should still be consideration to extend breast cancer screening to patients aged to up 74 years after appropriate assessment of comorbidities and functional status.

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Introduction

Population screening has been adopted internationally in the management of breast cancer. With a reported reduction in breast cancer-associated mortality of up to 20% to 39%, the benefit of mammographic screening for breast cancer has been confirmed for women aged between 50 and 69 years.[1,2]

Successful implementation of a screening program requires careful consideration and balance of the benefits of detecting early cancers that are amenable to treatment with the potential harms of physical and psychological burden resulting from lead-time bias and over-diagnosis. Over-diagnosis rates are reported between 1% and 10%,[3] subjecting women to biopsy and treatment interventions that would not have been of benefit to them.

The impact of age, which is a well-recognized risk factor for breast cancer, is a particularly pertinent consideration in the older population. Although increased age is a known risk factor for breast cancer development, with peak incidence in the eighth decade,[4] older patients may have competing mortality risks from overall

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Table 1 The Characteristics and Outcomes of Women Aged 70 years and Over Diagnosed With Breast Cancer in Auckland

	Screen-detected, n (%)	Clinically Detected, n (%)	Total, n (%)	*P* Value
No. patients	416 (19.5)	1712 (80.5)	2128 (100)	N/A
Median age, y (IQR)	74 (71-77)	79 (74-85)	77 (73-84)	N/A
T stage				.116
Unknown	7 (1.7)	49 (2.9)	56 (2.6)	< .001
Tis (DCIS)	84 (20.2)	82 (4.8)	166 (7.8)	
T1	268 (64.4)	577 (33.7)	845 (39.7)	
T2	50 (12.0)	786 (45.9)	836 (39.3)	
T3	7 (1.7)	148 (8.6)	155 (7.3)	
T4	0 (0.0)	70 (4.1)	70 (3.3)	
N stage				.516
Unknown/not done	110 (26.4)	452 (26.4)	562 (26.4)	< .001
N0	252 (60.6)	721 (42.1)	973 (45.7)	
N1	40 (9.6)	333 (19.5)	373 (17.5)	
N2	10 (2.4)	119 (7.0)	129 (6.1)	
N3	4 (1.0)	87 (5.1)	91 (4.3)	
Outcome				< .001
Deceased: breast cancer	26 (6.3)	280 (16.4)	306 (14.4)	
Deceased: other cause	56 (13.5)	481 (28.1)	537 (25.2)	
Alive	334 (80.3)	926 (54.1)	1260 (59.2)	
Unknown	0 (0.0)	25 (1.5)	25 (1.2)	N/A

Abbreviations: DCIS = Ductal carcinoma in situ; IQR = interquartile range; N/A = not applicable.

poor health that may subject them to alternative causes of mortality. The benefit of early cancer detection may also be negated if their poor health excludes treatment options. Accordingly, the upper age limits of screening programs vary internationally. Currently, the program in New Zealand screens women up to 69 years of age, whereas the United Kingdom, Australia, and the Netherlands screen women up to 70, 74, and 75 years, respectively.

Since implementation in 1998 to target women aged 45 to 69 years, the New Zealand program has successfully reduced breast cancer mortality in those aged 50 to 64 years by 3% per annum. However, despite a rising life expectancy rate in women, to 83 years,[5] an indirect marker of reduced competing mortality factors in the seventh decade, the upper limit of the target screening age group has not been extended. Rather, women aged 70 years and over may individually "volunteer" to continue breast cancer screening if health-conscious or in good health. This is despite 80% of patients diagnosed with breast cancer actually surviving 10 years or more with current management regimes.[6]

The purpose of this study was to compare the outcomes of screen-detected and clinically detected breast cancers in those aged 70 years and over in New Zealand. It aimed to address whether extended population screening may be of benefit owing to the increased life expectancy rates since the 1990s.

Patients and Methods

The Auckland Breast Cancer Registry was reviewed to identify all screen-detected and clinically detected ductal carcinoma in situ (DCIS) and breast cancers from June 2000 to May 2013. The Auckland Breast Cancer Register captured all breast cancer cases in the Greater Auckland Region since its establishment on June 1, 2000, with mandatory reporting of breast cancer and DCIS in New Zealand.

Prospectively collected data on all patients aged 70 years and over, including demographics, DCIS and cancer characteristics, treatment, and long-term outcomes, were retrospectively reviewed. Breast cancer characteristics were reviewed based on the American Joint Committee on Cancer TMN eighth edition staging system. Follow-up occurred until November 23, 2017 when calculating outcomes, recurrences, and survival. Disease-specific and overall survival rates were defined as time from diagnosis to last follow-up or date of death. Male patients and patients with unknown presentations were excluded from the study.

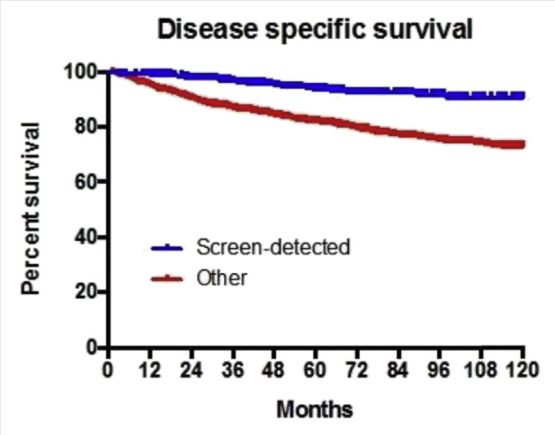
Statistical analyses were performed using GraphPad Prism (Version 6.0; La Jolla, CA), including the χ^2 test for categorical comparison, Kaplan-Meier curves for 5-year survival rates, and univariate Cox regression analysis with R Studio used to determine prognostic impact of tumor and age on survival.

Results

From June 2000 to May 2013, a total of 2128 patients aged 70 years and over (median, 77 years; interquartile range [IQR], 73-84 years) were diagnosed with breast cancer in Auckland. Of these, 416 (19.5%) patients were diagnosed via breast screening, whereas the remaining 1712 (80.5%) were diagnosed after clinical assessment. Clinical symptomatology included a palpable mass in 72.7% (n = 1554), whereas 6.3% (n = 134) reported pain, skin changes, or nipple discharge. Incidental diagnosis was made in 1% (n = 22) of patients.

Patients with screen-detected cancers were younger than those with clinical symptomatology, with a median age of 74 years (IQR,

Figure 1 Disease-specific Survival in Women Aged 70 Years and Over With Screen-detected and Clinically Detected Breast Cancers

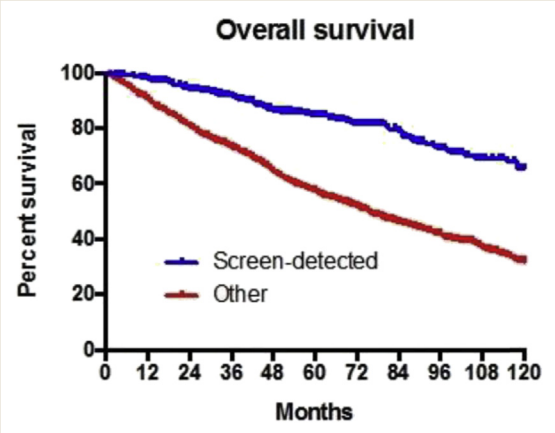


71-77 years) compared with 79 years (IQR, 74-85 years) for the latter. Accordingly, when reviewing the detection of breast cancer at the different age groups, there was a higher proportion of screen-detected cancers in those aged 70 to 74 years when compared with those aged 75 years and over (33.8% vs. 12.7%; $P < .001$).

Reflecting the established notion that screening may allow earlier detection of change within the breast, the stage of disease was significantly lower in patients who had presented with screen-detected cancer in both the T and N stages, as seen in Table 1. Accordingly, there was a higher rate of nonoperative management in the clinically detected group (11.5% vs. 1.9%; $P < .001$).

Owing to the older median age of diagnosis between screen- and clinically detected breast lesions, the median follow-up period was longer for those who were screen-detected (62.5 vs. 50.7 months). At last follow-up, a higher proportion of the screen-detected patients had no evidence of disease when compared with those who were

Figure 2 Overall Survival in Women Aged 70 Years and Over With Screen-detected and Clinically Detected breast Cancers



clinically detected (356 [85.6%] vs. 1118 [65.3%] patients; $P < .001$). Disease status was unknown in 100 patients at last follow-up owing to the retrospective nature of this register review, encompassing 14 (3.4%) screen-detected and 86 (5.0%) clinically detected patients.

Recurrent disease patterns were not significantly different between the 2 groups, with similar proportions of locoregional relapse and distant metastases. Two (5.3%) screen-detected patients compared with 14 (4.5%) clinically detected patients experienced locoregional recurrence, and 36 (94.7%) screen-detected patients compared with 297 (95.5%) clinically detected patients experienced distant metastases ($P = .689$). Five-year disease-specific survival was, however, significantly better in the screen-detected group when compared with the clinically detected group (93.7% vs. 81.9%; $P < .001$) as seen in Figure 1. Overall survival was similarly better in the screen-detected group (84.7% vs. 57.4%; $P < .001$), as seen in Figure 2.

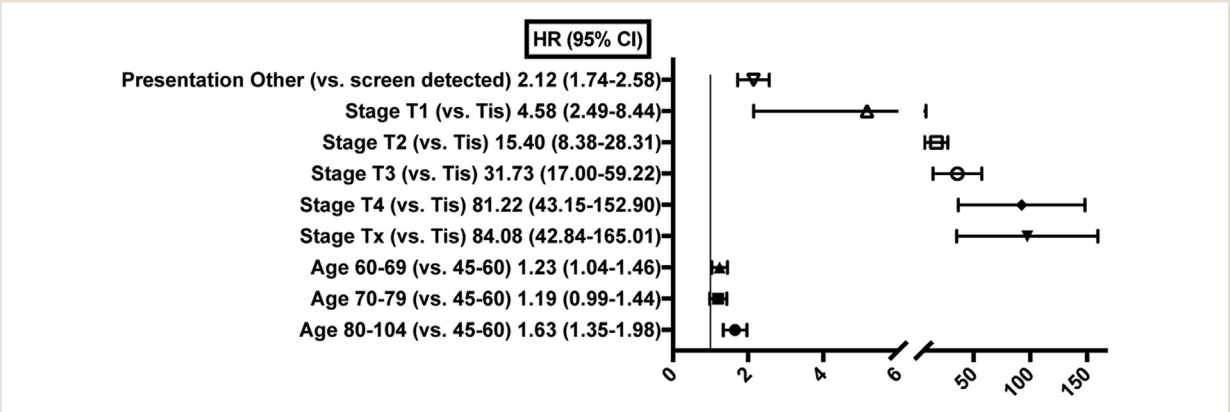
Reviewing mortality after allowing for tumor stage, each increase of 1 year in age increased the risk of mortality by 23% and 63% for those aged between 60 and 69 years and 80% to 104%, respectively, when compared with those aged 45 to 60 years. Although there was a non-significant trend of increased mortality in those aged between 70 and 79 years, the effect of tumor stage on mortality was that those with higher stage of disease had greater mortality when compared with those of lower stage presentation. Allowing for age and stage of presentation, those with clinically detected breast cancer had 2.12 times increased mortality with any Tis (DCIS) diagnosis compared with those who presented following screening as seen in Figure 3.

Discussion

The incidence of breast cancer in females in New Zealand has increased with time, from 88.8 per 100,000 in 1998 to 94.4 per 100,000 in 2013. Breast cancer-associated mortality has declined owing to the introduction of breast cancer screening in 1998, from 25.2 per 100,000 to 17.7 per 100,000.[7,8] Without disputing its success in reducing overall breast cancer-associated mortality, the guidelines for breast cancer screening have not evolved since its introduction, despite rising life expectancy and presumed decreased competing mortality factors for women in New Zealand. The previous lack of extended screening may be owing to conflicting evidence about the benefits in the older population (ages 70 to 74 years), with some studies concluding insufficient evidence, whereas others report up to 15% reduction in late-stage presentations if adequate participation occurs.[9] A recent impact analysis through population modeling by the National Screening Unit postulates that extended screening to 74 years may reduce breast cancer mortality by one-third.[8]

However, clinicians may be biased with the notion of an "elderly patient," as they are stereotypically attached to a notion that those aged over 65 years, as per the World Health Organization, may be medically frail and unable to undergo available treatment options.[10] Studies have reported varying treatment regimens offered by clinicians despite the National Institute of Clinical Excellence guidelines stating that, irrespective of age, early and locally invasive breast cancer should be treated with surgery and appropriate systemic therapy rather than endocrine therapy alone.[11] Radiotherapy

Figure 3 Cox Regression Analysis of Mortality Risk Associated With Diagnosis



Abbreviations: CI = confidence interval; HR = hazard ratio.

recommendations were particularly tenuous, with clinicians biased towards treatments they provide. The inclination for altered management and possible clinician bias based on actual rather than physiological age[10,12] was reflected by our study results, which showed a higher proportion of under-treated older patients with clinically detected breast cancer who underwent nonoperative or primary endocrine therapy.

It is difficult to ascertain the most appropriate treatment regimen for a specific age category of patients, as individuals differ in their overall health and functional status. However, under-treatment with deviation from established guidelines likely underpins the lower reported relative 5- and 10-year survival rates of breast cancer in the "elderly" population. The results of under-treatment with a high rate of nonoperative management in review of the registry's older population has likely contributed to the higher rate of disease at last follow-up, and poorer disease-specific 5-year and overall survival.

In an attempt to improve breast cancer survival, earlier detection prior to clinical symptomatology is a critical consideration and assumption to the population modeling of extended screening to 74 years by the Ministry of Health's analysis.[8] Akin to the ideology behind population-based breast screening for those aged 50 to 69 years, our study reflected their results in that those aged 70 years and over with screen-detected cancers had significantly lower American Joint Committee on Cancer T and N stages compared with those who presented with clinical symptoms. Screening identified 20.2% DCIS and 64.4% T1 lesions, compared with 4.8% and 33.7%, respectively, in the clinically detected group. These results reflect other international studies that have demonstrated that screening in the older population will reduce late-stage presentations and reduced breast cancer mortality, even if the magnitude of the effect was small.[1-15]

The implication of earlier cancer detection is increasingly justified in the past decade, with substantial advances made in the surgical, local, and systemic management options for breast cancer. Given the evolving treatment options that may be possible in the older patient, our study demonstrated that extending the upper age limit of screening should be considered in New Zealand. The majority of screen-detected cancers were found in those aged 70 to 74 years, reflective of the recent Impact Analysis by the National Screening Unit.[8] Moreover, our study found that there was a marked decrease in the proportion identified in those aged over 75 years; hence, those aged over 75 years are less likely to benefit from screening.

Despite the postulated benefits, however, equitable resource allocation of health care professionals and financial and physical infrastructure remains a concern to ensure appropriate distribution among the population. Rather than extended screening to 74 years in the entire population, potential means of selective identification of women between 70 to 74 years who would benefit from ongoing screening may be achieved by completion of a comprehensive geriatric or functional performance assessment. If not time feasible at BreastScreen Aotearoa clinics, this may be completed in conjunction with general practitioners who are the primary carers for a woman's overall health assessment. Using an assessment to identify those who are still healthy would identify those that would continue to benefit from screening, without the added burden of including those who would not benefit or be able to undertake systemic therapy and surgery owing to competing morbidity factors.[16] Incorporating this selective approach would reflect current United States guidelines that recommend ongoing breast cancer screening for healthy elderly women with an expected life expectancy of 10 years.[17] Currently, although women aged between 70 and 74 years with average risk may obtain mammogram imaging at the public hospital on their own accord, the removal of their invitation to screening may cause women to inaccurately interpret their risk as minimal and forgo subsequent imaging.

It is unclear what the optimum means are of assessing the patient's medical and functional performance status is to establish if they are "frail" and justify the benefit of ongoing breast cancer screening.[18] Although a comprehensive geriatrics assessment tool exists[17] that thoroughly reviews somatic, functional, and psychosocial factors to improve treatment compliance, quality of life, and overall survival, it is a time-demanding tool that may be difficult to incorporate into a busy surgical clinic. Other screening tools that may guide cognitive and functional assessments to reduce clinician influence and bias include the abbreviated comprehensive geriatrics assessment, Vulnerable Elders Survey, and the Charlson Comorbidity Index Scoring System.[18]

The results of our study have been viewed as an adjunct to consideration in the means of health care screening and provision to women in New Zealand. We recognize that this is a single-city database with a retrospective review of prospectively collected data. There may be selection bias in women who choose to attend screening in the post-targeted age group, where health consciousness and the healthy volunteer effect may translate to treatment compliance and better outcomes. Other barriers to access may include patient choice, financial limitations, and lack of practical ability to attend adjuvant therapies such as radiotherapy or chemotherapy in isolated rural areas. Identification of what is considered over-diagnosis and treatment of slow-growing cancers that may have otherwise not impacted survival remains a difficult task and important consideration in allocation of assessment, treatment, and support services. Although benefits would ideally be demonstrated by randomized trial evidence, no randomized control trial data currently exists for reviewing the benefits of mammographic screening in elderly women. Uncompromised trial data is difficult to achieve without health care access inequity, given mammograms may still currently be provided to a selective population who are considered "healthy enough" to reap the benefits of a screening service. Ongoing research to account for tumor biology and natural progression remains an important component.

In conclusion, reflective of the recent population modeling proposal by the BreastScreen Aotearoa, extended breast cancer surveillance in the "elderly" population should be considered in New Zealand. With the traditional implications of being "elderly" and "frail" changing owing to improvements in overall health and life expectancy, the patient's physiological rather than chronological age should be considered when they reach the upper targeted age for breast cancer screening. Rather than discontinuing their invited access to screening at 69 years, incorporating performance or functional assessment tools may help to identify those who may benefit from early cancer detection and personalized surgical and adjuvant treatment regimens without significant burden to the public health care system. This may provide an intermediate step to the government's proposed extended population-wide screening to 74 years, by balancing attempts to reduce breast cancer-associated mortality with the public health service provision. Functional assessment tools may identify those who would truly benefit from extended screening and bridge equity gaps to ensure appropriate health care service provision for all sectors in New Zealand.

Clinical Practice Points

- Population screening will reduce breast cancer mortality by up to 20% to 39%. Effective screening, however, needs to consider whether extending screening to the older population will improve breast cancer-associated outcomes owing to competing mortality interests. Judicious resource allocation must be considered to allow equitable health care provision with meaningful outcomes.
- As there is currently limited evidence on the optimal age to cease screening, this article reviewed a large breast cancer register in New Zealand to determine if there were outcome differences in the targeted screening population (45 to 69 years) and those older than the targeted age (70 years and over). It found that patients aged 70 years and over with screen-detected disease had lower stage disease (T and N stage) and longer disease-specific and overall survival than patients who presented with self-detected lesions. This suggests that there may be some benefit of ongoing screening for patients who are "elderly" but physiologically fit to allow for earlier disease detection and treatment.
- As a result, this article proposes that a more selective approach could be employed to the "elderly population," rather than merely raising the upper age limit for breast cancer screening. It should be considered that employing strategies, such as functional studies or health assessment tools, within the screening practice or in conjunction with local practitioners, may allow assessment of the woman's physiological age. This may facilitate for a more practical and considered approach to continued screening of women who will benefit from earlier cancer detection and treatment.

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Disclosure

The authors have stated that they have no conflicts of interest.

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