Incidence of Invasive Breast Cancer and Ductal Carcinoma *In situ* in a Screening Program by Age: Should Older Women Continue Screening?

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Abstract

Objective: The evidence for the effectiveness of screening is strongest for women ages 50 to 69 years; however, there is variation in the target age group for screening programs between different countries. In particular, there is uncertainty over whether women should continue screening once they reach age 70. We therefore investigated incidence rates for invasive and *in situ* breast cancer by age as well as prognostic features of tumors within a screening program. **Methods:** We studied 474,808 women who attended BreastScreen Victoria from January 1, 1993 to December 31, 2000. Of these women, 5,301 were diagnosed with invasive cancer and 1,127 were diagnosed with ductal carcinoma *in situ*. We used generalized additive models to model age-incidence rates for invasive cancers and ductal carcinoma *in situ* separately by users and nonusers of hormone replacement therapy at most recent screen. Nonparametric trends for ordered groups and regression methods were used to investigate trends in size, grade, and nodal involvement for invasive tumors by type of attendance and time since previous negative screen for age group. **Results:** The incidence of ductal carcinoma *in situ* among women with a previous negative screen clearly declined after age 70 irrespective of hormone replacement therapy use. At subsequent screen, the age-incidence curve for invasive breast cancer flattened at ages 60 to 75 years and then increased only for women taking hormone replacement therapy. Tumor size at diagnosis declined with age at both first round ($P = 0.15$) and subsequent round ($P = 0.08$). The proportion of poorly differentiated tumors also decreased with age, with the smallest proportion of grade III tumors diagnosed in women ages ≥ 75 years ($P = 0.09$ for first screen and $P = 0.05$ for subsequent screen). The presence of positive nodes at diagnosis declined with age ($P < 0.001$) for both first and subsequent screening rounds. **Conclusion:** Older age is associated with more favorable prognostic tumor features and a lower incidence of ductal carcinoma *in situ* among subsequent attenders of screening. When making decisions regarding continuing screening, older women and their physicians should also consider the presence of other comorbid conditions that may mitigate any impact of screening on mortality. (Cancer Epidemiol Biomarkers Prev 2004;13(10):1569–73)

Introduction

The evidence regarding the effectiveness of mammographic screening from randomized controlled trials is strongest for women ages 50 to 69 years; thus, most screening programs emphasize this age range (1). However, recommendations for screening women ages >70 and <50 years vary widely between screening programs and countries. In the United Kingdom, women ages 50 to 64 years are invited for screening every 3 years; however, the age range for invitation will be extended to age 70 by 2004 (2). The Dutch program provides biennial screening for women ages 50 to 75 years and the United

States adopts a series of recommendations with no defined upper age limit and no organized screening program (3). In Australia, BreastScreen Victoria, a population-based screening program, invites women ages 50 to 74 years for biennial mammographic screening. Once women turn age 75, they are no longer invited but may attend if they choose to do so. There is no upper age limit for access to the program.

For women ages <50 and >70 years, there is far less evidence regarding the effectiveness of screening. There has been much debate regarding the screening of women ages 40 to 49 years as data from randomized trials have failed to show a substantial benefit of screening in this age group (4-6). The reduced benefit of screening in this age group may be due to reduced sensitivity of mammography due to increased breast density and the greater likelihood of faster-growing tumors in younger women that occur within the screening interval. There is little evidence from randomized trials to support screening of women ages >69 years as most trials included women ages 45 to 64 years. Of the prospective randomized trials of mammography, only the Swedish

Two-County Trial included women ages ≥70 years (2) and reported a 40% reduction in mortality in the 50- to 74-year age group for women with a screening interval of ~3 years but did not present results specifically for women ages >75 years due to insufficient numbers.

The presence of comorbid conditions and the detection of clinically insignificant lesions are potentially a greater problem in older women and may impact on the effectiveness of screening in this age group. Women who commenced screening at ages 50 to 69 years face the dilemma of whether to continue screening biennially after reaching age 70. To contribute to the debate on whether older women should continue screening after turning 70, we investigated the relationship between age and incidence of invasive breast cancer and ductal carcinoma in situ (DCIS) in women attending a screening program. We also examined the association between known prognostic factors: tumor size, histologic grade, and nodal involvement by age, and evaluated whether these associations varied by screening interval. We focused on women attending for a second or subsequent screen to provide data relevant to women already attending screening and to adjust for screening history.

Materials and Methods

We analysed routinely collected de-identified data on a large cohort of women who attended BreastScreen Victoria from January 1, 1993 to December 31, 2000. BreastScreen Victoria provided mammographic screening to 474,808 women during this time with 330,846 of these women attending for a second or subsequent screen. The participation rate in 2000 was 92% for women ages 40 to 49 years, 60.2% for women ages 50 to 69 years, and 33.0% for women ages 70 to 79 years. A subsequent attendee is defined as a woman with at least one prior negative screen within the program. During this time period, 5,301 invasive cancers and 1,127 cases of DCIS (49% comedo-type) were diagnosed by BreastScreen Victoria. Among subsequent attendees of the program, 2,739 invasive cancers and 537 DCIS were screen detected. In addition, 924 invasive breast cancers were diagnosed in women in the 24-month interval after a negative screen. For these interval cancers, information was available on tumor size (mm) for 820 (88.7%) and tumor grade for 788 (85.3%). Nodal status (81.4%) is defined as no positive nodes (include those where no axillary dissection was done) and one or more positive nodes identified.

For the 2,739 women diagnosed with invasive cancer at a subsequent screen, information was available on size (mm) for 2,700 (98.7%), tumor grade for 2,735 (99.8%), and nodal status for 2,735 (99.8%) women (no positive nodes include those women where no axillary dissection was done). At attendance, basic demographic and personal information: current use of hormone replacement therapy (HRT) and duration of use, and presence of symptoms (current bloodstained or watery nipple discharge, current lump present for <12 months not seen by a doctor and other symptoms) were collected. The study was approved by the BreastScreen Victoria Research and Evaluation Committee.

Generalized additive models were used to describe the relationship between age and incidence of screen-detected invasive breast cancer and DCIS. Generalized additive models fit a nonparametric smooth curve to age, defined as age at diagnosis, and the incidence rate per 1,000 women screened. To discern this underlying relationship, the generalized additive models were fitted separately by HRT use at the most recent screen. The age-incidence curves are presented as a cubic smoothing spline (7) on a partial residual scale adjusting for significant covariates with corresponding 95% confidence intervals.

We applied nonparametric tests for trend across ordered groups to investigate patterns in invasive tumor size, histologic grade, and nodal involvement and length of time between diagnosis and prior negative screen by age groups. The specific age groups evaluated were 40 to 49, 50 to 69, 70 to 74, and ≥75 years. This test, developed by Cuzick (8), is an extension of the Wilcoxon rank sum test. All statistical analyses were done using both SPLUS (9) and StataCorp (10). A $P < 0.05$ was considered to be statistically significant.

Results

Table 1 shows the crude detection rates for invasive breast cancer and DCIS by age group and attendance round. The age-incidence rates for invasive breast cancer and DCIS diagnosed at subsequent screen and stratified by HRT use are presented in Figs. 1 and 2. The nonlinear age-incidence curve for invasive breast cancer differed by HRT use. For women not using HRT, the incidence of invasive breast cancer clearly decreased for women ages >70 years who had a previous negative screen. In contrast, for women using HRT, the curvilinear age-incidence pattern increased for those in the target age group (50-69 years), flattened at ages 60 to 75 years, and then increased for women ages >75 years.

Inclusion of women diagnosed with interval cancers did not alter the shape of the curves (data not shown). The age-incidence curves for DCIS were similar for HRT users and nonusers, with a decline in incidence for women ages >70 years.

Size, proportion of poorly differentiated tumors (grade III), and nodal status for invasive and interval cancers by age and screening round are displayed on Table 2. For all ages, mean size (mm) of invasive tumors was larger at first screen compared with subsequent screen. Tumor size declined with age and older women had the smallest tumors at diagnosis at both first round ($P = 0.15$) and subsequent round ($P = 0.08$), although this did not reach statistical significance. Overall, the proportion of poorly differentiated tumors decreased with age, with the smallest proportion of grade III tumors in women ages >75 years and the highest proportion in women ages <50 years. This result was similar for first attendance ($P = 0.09$) and subsequent attendance ($P = 0.05$). Positive nodal status at diagnosis also declined with age and was similar across rounds.

Age-related trends were less apparent for interval cancers in this screening cohort. There were no differences in tumor size for women diagnosed with an interval cancer by age, but the proportion of grade III tumors and positive nodal status at diagnosis declined with age ($P = 0.06$ and $P < 0.001$, respectively).

Table 1. Rate of diagnosis of breast cancer per 1,000 women screened by age group and first/subsequent screening attendance

Type of attendance	Age group				
	40-49	50-69	70-74	≥75	Total
First attenders	93,402	312,139	29,895	18,340	453,776
Invasive breast cancer					
n	254	1,753	294	254	2,555
Rate per 1,000 women screened	2.7	5.62	9.83	13.85	
DCIS					
n	86	414	62	28	590
Rate per 1,000 women screened	0.92	1.33	2.07	1.53	
Subsequent attenders	27,661	506,117	87,545	24,699	646,022
Invasive breast cancer					
n	69	2062	478	127	2,736
Rate per 1,000 women screened	2.49	4.07	5.46	5.14	
DCIS					
n	23	414	76	24	537
Rate per 1,000 women screened	0.83	0.82	0.87	0.97	
Total	121,063	818,256	117,440	43,039	

Trends for invasive tumor size and time since previous negative screen by age are displayed in Table 3. For each age group, mean tumor size significantly increased with longer screening interval, with the exception of the youngest women for which tumor size remains relatively constant ($P = 0.7$).

Discussion

In this large statewide screening program, we observed differences in the age-incidence curves for women diagnosed at subsequent screen by HRT use. For women on HRT who were subsequent attenders, the incidence of invasive breast cancer plateaued around age 65. A further increase in incidence was observed at around age 75. In contrast, the incidence of invasive breast cancer decreased after age 70 for women not on HRT. DCIS incidence at subsequent screen declined after age 70 irrespective of HRT use. Older women were more likely to be diagnosed with smaller tumors that were better differentiated and less likely to be node positive at diagnosis. As expected, tumor size increased with longer screening interval for all age groups, although this result was less apparent in women ages <50 years.

There are several strengths to our study. We analyzed a large comprehensive database of women of all age groups participating in a statewide mammographic screening program. Women ages <50 and >75 years are not routinely invited to attend; however, we had many women in these age groups available for analysis. Although we cannot exclude the possibility of selection bias among the older women choosing to attend the
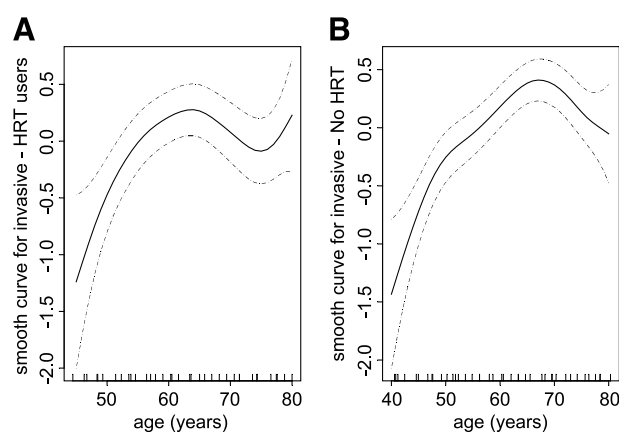

Figure 1. Age-incidence rates per 1,000 women screens for invasive breast cancer diagnosed at a subsequent screen within BreastScreen Victoria separately for (**A**) women on HRT and (**B**) women not on HRT at most recent screen. *Fitted curve,* cubic smoothing spline fit on the partial residual scale (*y*-axis); *dashed lines,* point-wise 95% confidence intervals.

Figure 2. Age-incidence rates per 1,000 women screens for DCIS diagnosed at a subsequent screen within BreastScreen Victoria separately for (**A**) women on HRT and (**B**) women not on HRT at most recent screen. *Fitted curve,* cubic smoothing spline fit on the partial residual scale (*y*-axis); *dashed lines,* point-wise 95% confidence intervals.
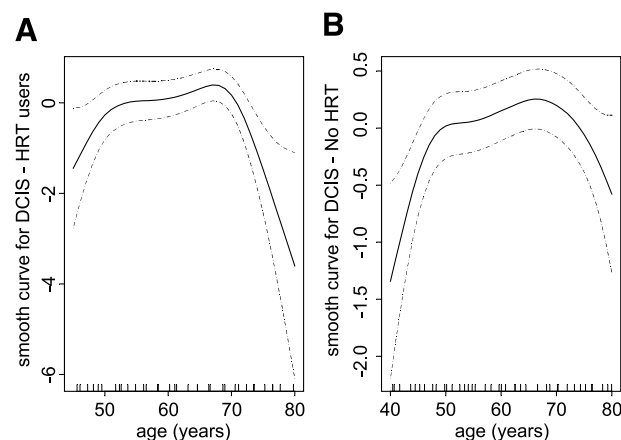
Table 2. Size (mm), proportion of grade III cancers, and nodal status by age and screening round for screen detected and interval invasive breast cancer

Type of attendance	Age group				
	40-49	50-69	70-74	≥75	P*
Invasive cancer					
First screen					
Cancers (n)	245	1,711	290	242	
Mean size (mm)	18.09	16.10	16.27	15.74	0.15
Grade (n)	254	1752	294	253	
Grade III (%)	20.87	16.67	16.67	13.83	0.09
Nodal status (n)	254	1,753	294	254	
Node negative (%)	69.29	74.22	76.19	83.46	
Node positive (%)	30.71	25.78	23.81	16.54	<0.001
Subsequent screen					
Cancers (n)	66	2,040	469	125	
Mean size (mm)	17.2	13.88	13.40	13.66	0.08
Grade (n)	69	2,061	478	127	
Grade III (%)	20.29	18.10	15.06	13.39	0.05
Nodal status (n)	69	2,061	478	127	
Node negative (%)	71.01	80.49	84.73	90.55	
Node positive (%)	28.99	19.51	15.27	9.45	<0.001
Interval cancer					
Cancers (n)	112	625	59	24	
Mean size (mm)	20.64	21.39	18.61	20.75	0.52
Grade (n)	106	605	55	22	
Grade III (%)	49.06	38.18	30.91	45.45	0.06
Nodal status (n)	126	705	66	27	
Node negative (%)	24.60	15.74	28.79	40.74	
Node positive (%)	75.40	84.26	71.21	59.26	<0.001

*Two-sided P's from a nonparametric test for trend. n, nonmissing size, nonmissing grade, and nonmissing nodes.

program, it is more likely that women at higher risk continue within the program; therefore, selection bias is an unlikely explanation for the decline in incidence observed for DCIS and invasive cancer.

Fewer axillary dissections are done with increasing age, and as the node negatives include unknown dissections, this could contribute to the decline. Factors such as period effects (year of screen) and length of time (months) since

the previous negative screen and diagnostic screen may mask the true age-incidence relationship. The statistical methods used for estimating the age-incidence curve in this study adjusted for these factors.

The differences in age incidence by HRT use would be predicted on the basis of extensive data confirming that HRT users are at modestly increased risk of breast cancer (11-13). However, the decline in incidence of

Table 3. Size (mm) of invasive cancers diagnosed within BreastScreen Victoria characterized by age and time since previous negative screen

Time since previous negative screen (mo)	Age group				
	40-49	50-69	70-74	≥75	Total
<27					
No. screened	6,245	204,092	41,745	16,580	
Invasive cancers					
Cancers (n)	26	1,751	414	82	2,273
Mean size	16.97	13.66	13.35	12.71	
27-36					
No. screened	4,124	24,897	4,165	3,000	
Invasive cancers					
Cancers (n)	24	173	36	17	250
Mean size	17.25	14.17	13.08	12.41	
≥37					
No. screened	4,493	15,503	1,541	1,986	
Invasive cancers					
Cancers (n)	16	116	19	26	177
Mean size	17.51	16.91	15.21	17.46	
P*	0.7	0.005	0.6	0.08	

*Two-sided P's from a regression of log size and time since previous negative screen for each age group.

invasive breast cancer at subsequent screen for women ages >70 years among non-HRT users was unexpected. Previously published age-adjusted incidence rates show an increase in incidence of invasive cancer with age but have included prevalent cancers and have not distinguished by HRT use (14, 15). Further confirmation of these findings in other populations is warranted.

Overdiagnosis of DCIS in older women has been cited as a potential drawback of screening older women (16), but our data show that this is not the case among repeat attenders of the program. Our data suggest that the incidence of DCIS actually declines after age 70. This observation may reflect a true decline in incidence with age or it may be a function of changes in mammographic detection of DCIS with age. Paradoxically, it might be predicted that DCIS may be more readily detected in older women as mammographic density declines substantially with age, thus making the detection of subtle lesions easier. On the other hand, a greater prevalence of microcalcification in younger women has been reported, possibly making DCIS easier to detect (17). Because breast epithelium regresses substantially in postmenopausal women (18), fewer DCIS lesions may arise due to the reduced number of cells at risk of neoplastic transformation (19).

Our findings are consistent with those of a recent study (20) showing an increasing trend in the frequent detection of DCIS or microinvasive cancers for women ages 40 to 69 years and not for women ages >70 years. Another study using mammographic screening data on initial and subsequent screens (21) also showed no increasing trend of *in situ* cancers by age similar to that observed by invasive cancers. In contrast, two separate studies reported an increased rate of DCIS by age for screened women (22, 23).

If screening is to be beneficial, tumors must be detected at an earlier stage than in the absence of screening. As expected, we observed that tumor size increased with longer screening interval for women ages >50 years, but this was less apparent for women ages <50 years. We hypothesize that this may be due to young women having more aggressive tumors that are more likely to present with symptoms within the first 12 months after a previous screen, reflected by the high interval cancer rate in younger women. Thus, mean tumor size following a longer screening interval may reflect a depletion of larger tumors in younger women.

The sensitivity of mammography increases with age, which is partly due to decreased breast density but may also be due to older women having slower-growing, less aggressive tumors that tend to be detected at screening. This is consistent with our finding that the invasive cancers detected in older women are predominantly made up of better-differentiated tumors. Early detection of these more prognostically favorable tumors may not have a substantial impact on mortality. Older women and their physicians need to make informed decisions regarding continuing mammographic screening based on the presence of other comorbid conditions, as these may mitigate any impact of screening on mortality.

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