



Opting into breast screening over the age of 70 years: seeking evidence to support informed choice



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ARTICLE INFORMATION

Article history:

Received 25 October 2020

Accepted 26 January 2022

AIM: To provide evidence specific to the Scottish population regarding the risk–benefit balance of women >70 years opting into continued breast screening, which may be used as a basis for patient information documentation.

MATERIALS AND METHODS: The present study consisted of a parallel, retrospective data analysis of breast cancer mortality data for breast cancer cases diagnosed between 2009 and 2013 ($n=22,013$) followed up to 31/12/18, and breast screening programme data from 2010 and 2015 ($n=47,235$). Screening outcome measures included recall for assessment, oncome of assessment, and tumour features. Tumours were classified as high, intermediate, or low risk according to grade and presence of invasion. Mortality data were linked to age at diagnosis and cause of death was recorded.

RESULTS: The proportion of all deaths due breast cancer is inversely related to age at diagnosis. From 77 years, women are more likely to die with breast cancer, than directly due to breast cancer. Mammographic screening accurately identifies breast cancer in older women; however, many of the cancers detected were considered intermediate or low risk.

CONCLUSIONS: Harms may outweigh the benefits of continued breast screening in older women. This information should be available to all older women.

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Introduction

Since the inception of national breast screening programmes there has been increased concern regarding negative effects of screening, including the psychological impact of a false-positive screen and the over-diagnosis and over-treatment of indolent cancers and ductal carcinoma in situ (DCIS). Although it is largely accepted that there is a sufficient benefit to justify national screening programmes for women between the ages of 50 and 70 years,¹ the

risk–benefit ratio of screening women >70 years of age is unclear. At present, the Scottish Breast Screening Programme invites all women triennially for mammographic screening between the ages of 50 and 70 years. The upper age limit has been extended to 73 as part of the AgeX trial (<http://www.agex.uk>) in some regions of England. Following this, women can opt into continued triennial screening with no upper age limit; however, no tailored information is provided for older women to allow them to make an informed choice about whether to attend. This is particularly relevant,

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<https://doi.org/10.1016/j.crad.2022.01.057>

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as it has been demonstrated that the most important factor influencing older women's decisions to attend screening is a doctor's recommendation.²

Evidence on the benefits and harms of screening women >70 years is limited. The incidence of breast cancer increases with age, as does mammographic sensitivity alongside decreasing breast density.³ However, over-diagnosis and the associated harms also increase with age due to a combination of more indolent cancers and shorter remaining life expectancy.⁴ In other words, older women are more like to die with, rather than of, breast cancer than their younger counterparts.⁵

The AgeX trial should ultimately provide evidence for women to the age of 73 years when it concludes in 2026. No preliminary results have been reported and a recent analysis has been highly critical of the study design, challenging the validity of the final results.⁶ As there is no randomised controlled trial data for screening in women aged >75 years, attempts to quantify the effects of continued screening have been made using data modelling. Gunsoy *et al.*⁷ estimate a breast cancer mortality reduction and over-diagnosis of 18.1% and 5.6% for a UK triennially screened population between 47–73 years, this represents a reduction of five breast cancer deaths and an increase of 14 cases of over-diagnosis, per 10000 women screened compared to triennial screening from age 47–70 years. Unfortunately, the effects of extending at the extremities of screening age were not considered separately, and it is likely that the extension of the upper age limit contributed more to over-diagnosis than mortality reduction. Further modelling studies are based on data from the United States and are not directly transferable to the Scottish screening programme.^{8–10} Based on review of existing evidence and expert opinion, recent European guidelines suggest screening could continue until 74 years, although the authors state this should be guided by life expectancy.¹¹

The clinical impression in Scotland is an ever-increasing number of older women opting into continued screening without a targeted evidence base. It places both the individual woman and the screening service staff in a difficult position when the inevitable question “should I continue to attend screening?” is raised. This retrospective study seeks to provide evidence specific to the Scottish population, which may be used as a basis for patient information documentation. Breast cancer mortality data for symptomatically diagnosed patients provided an indication of outcome for those not opting into continued screening, and screening data provides evidence of the relative likelihood of screening outcomes.

Materials and methods

The most recent aggregate national screening data were retrieved from the KC62 Scottish Breast Screening Programme returns database for the period of 01/04/2010 to 31/03/2015. This was matched with comparable mortality data from the Cancer Registry.

The screening data for women aged >70 years was interrogated and the following information retrieved: total

number of women attending screening, number recalled to assessment, and number of cancers diagnosed. Biopsy rates, including benign biopsy rates (as an indication of ‘harm’), were extrapolated and cancer detection rates calculated. The following tumour information was extracted and recorded: cancer grade, size, and lymph node status. It was possible to obtain data distinctly for women aged 50–70 years and those aged >70 years.

Aggregate mortality data were acquired through Information Services Division (ISD) of NHS Scotland. It was not possible to retrieve patient level data. To provide contemporaneous data in sufficient numbers, breast cancer incidence was identified from the Cancer Registry for the period of 01/01/2009 to 31/12/2013, according to age at diagnosis, in 5-year age bands. This was linked to death records, which were interrogated until 31/12/18, resulting in a follow-up period of between 5–10 years according to date of diagnosis. Cause of death was categorised initially as a “death directly attributed to breast cancer” if this was the primary cause of death listed on the death certificate, and “death indirectly attributed to breast cancer” where breast cancer was listed but not as the primary cause, and “unrelated death” when breast cancer was not recorded on the death certificate. Unfortunately, it was not possible to ascertain what proportion of indirect breast cancer death was related to the disease process (e.g., pulmonary embolus) versus treatment of the cancer (e.g., neutropenic sepsis). Therefore, subsequent analysis concentrated on death directly attributed to breast cancer. The “diagnostic route” was extracted from the cancer registry and categorised into “screening”, “symptomatic” (clinical presentation and interval cancer), and “other” (incidental finding, incidental finding at autopsy, other and unknown). The “other” category was excluded from subset analysis due to small numbers and its heterogeneous nature. The outcomes for women diagnosed through the symptomatic service act as surrogate markers of outcomes for those women over 70 years of age who do not opt into continued screening.

Statistical analysis of categorical tumour-specific data was performed using the chi-square test for trend. Mortality data were analysed using a logistic regression model. Statistical analysis was performed using R statistical software, available at https://github.com/bartongroup/Breast_cancer_over_70.

Results

Between 2009 and 2013, 22,013 women were diagnosed with breast cancer in Scotland. In the period to 31/12/18, there were 6,697 deaths within this group. The majority of deaths (3,957) were in women aged >70 at diagnosis: 2,058 were aged 50–70 years, and 682 were <50 years. Overall mortality is displayed in Fig 1 and Table 1. Mortality rates for breast cancer patients were generally low; 17% in younger patients aged <50 years at diagnosis and 18% for those of screening age; however, there was a sharp increase in the overall mortality in the older population; 61% in those aged >70 years at diagnosis. The cause of death varied with age,

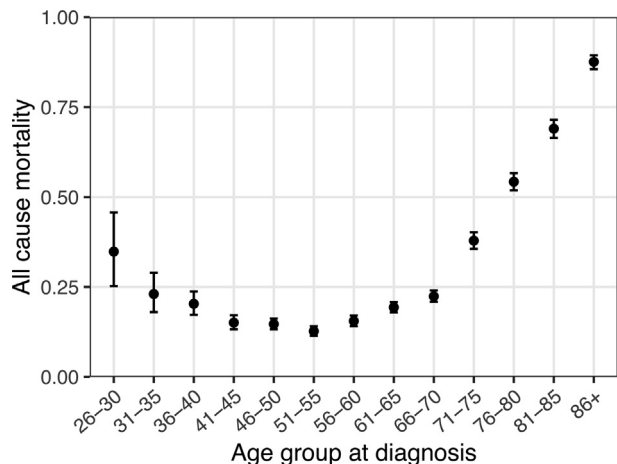


Figure 1 All-cause mortality according to age at diagnosis. Mortality is defined as the proportion of all women in each age group at diagnosis who died of any cause within the follow-up period. The error bars represent 95% confidence intervals of a proportion. See Table 1 for detailed mortality data.

and although the absolute numbers of deaths due directly to breast cancer increased with age, the proportion significantly decreased, for both screened patients and those diagnosed symptomatically. The logistic regression model showed that the percentage of deaths directly attributable to breast cancer decreased at a rate of ~1% per year (see Fig 2) in patients >40 years.

As a proportion of all deaths in the whole population, the death of 89% (659 of 737) of those aged <50 years at diagnosis was directly attributable to breast cancer, as opposed to 60% (1,136 of 1,900) of those aged 50–70 and 44% (1,535 of 3,530) of those aged >70 years at diagnosis. The proportion of deaths directly attributable to breast cancer also reduced with age in the screen-detected cohort (from 74% in those <50 years to 29% in those aged >70 years at diagnosis) and symptomatic cohort (from 90% to 44%, respectively). When all outcomes were considered, all cause survival in addition to breast cancer survival is higher in the screen-detected group.

In the 5-year period from 2010–2015, a total of 47,235 women >70 years were screened, (25,923 aged 71–74 years

and 21,312 aged ≥ 75 years). A total of 2,327 women (5%) were referred for further assessment following their screening mammogram. Outcome data were available for 2,280 women (see Table 2). Of those who attended assessment, 70% were ultimately discharged. Of the 971 (43%) women who underwent biopsy, 678 had cancer and 293 had a benign or inconclusive biopsy. The cancer detection rate was 14/1,000, and the invasive cancer detection rate was 12/1,000. Tumour factors are illustrated in Table 3. The distribution of tumour factors, including tumour size and grade, was similar between women aged 50–70 years and those aged >70 years ($p > 0.5$).

Discussion

The principles of screening were first introduced by Wilson & Jugner in 1968¹² and were subsequently updated by Andermann in 2008.¹³ Key criteria include scientific evidence of effectiveness, informed choice, and that overall benefits should outweigh the harm. At present, although these criteria are largely met for those women within the standard screening population (50–70 years), they are lacking for older women.

It is vitally important that if women are given the option of continued screening that they are aware of the possible outcomes, and the relative probability of these. This study of almost 50,000 women aged >70 years aims to provide these data for the Scottish population.

Over a contemporary 5-year period in Scotland, almost 50,000 women aged >70 years attended screening. For every 1,000 women screened, 47 were recalled for further assessment. Of these, 70% (763 of 1,091) were considered normal after further assessment and were discharged, resulting in a positive predictive value (PPV) of 30% and false-positive rate of 3.6%. This is consistent with previously published UK data, which demonstrated an increasing PPV with age.¹⁴ In contrast, the rates of false-positive mammograms are substantially lower in the present series than the reported rates of 11–20% amongst older screened American women,^{15,16} further highlighting the fact that US data cannot be applied directly to the UK population. Although the false-positive rates are lower than amongst younger screened women, it remains an important proportion of women attending screening. Not only are such recalls associated with increased short-time anxiety,^{17,18} but in the 14% of cases requiring a biopsy procedure to prove benignity, anxiety may persist at 3 years.¹⁹

Several key definitions must be considered when analysing cancer detection rates within a screening setting.²⁰ Lead-time bias is the apparent increase in survival rates due to time from diagnosis at the asymptomatic screen-detected stage and the onset of clinical symptoms. In other words, early diagnosis may not lead to longer overall lifespan for an individual, just a longer period with the known diagnosis. Length-time bias describes the fact that screening tests disproportionately detect slower-growing cancer. Over-diagnosis is an extreme form of length-time bias: the cancer is sufficiently indolent that it does not alter remaining lifespan and the individual will die of other

Table 1
Mortality data.

Age	Group size	Survivals	Deaths of any causes	Deaths directly due to breast cancer (% of all death)
26–30	89	58	31	28 (90.3)
31–35	243	187	56	51 (91.1)
36–40	620	494	126	122 (96.8)
41–45	1,346	1,143	203	174 (85.7)
46–50	2,187	1,866	321	284 (88.5)
51–55	2,433	2,124	309	247 (79.9)
56–60	2,427	2,050	377	245 (65.0)
61–65	3,099	2,500	599	369 (61.6)
66–70	2,746	2,131	615	275 (44.7)
71–75	1,745	1,084	661	345 (52.2)
76–80	1,701	778	923	409 (44.3)
81–85	1,314	407	907	389 (42.8)
86+	1,186	147	1,039	392 (37.7)

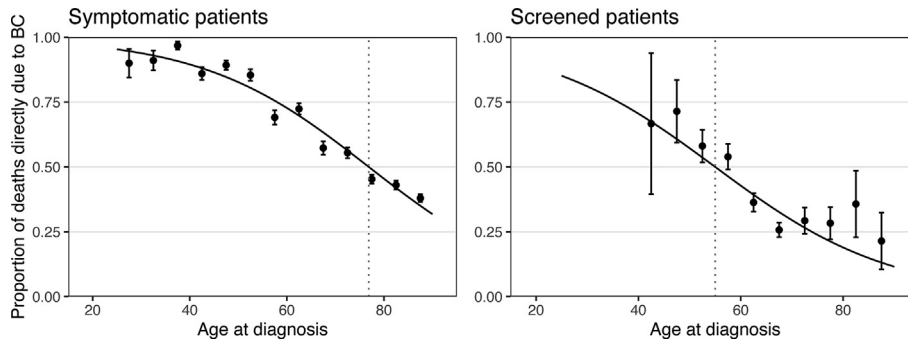


Figure 2 Proportion of all deaths that was directly attributed to breast cancer, according to age at diagnosis. The error bars represent 95% confidence intervals of a proportion. The solid line shows a logistic regression model, where the predictors are age at diagnosis and diagnostic route (symptomatic or screening). The effect of each predictor is significant ($p < 10^{-16}$), that is the probability of dying directly due to breast cancer depends significantly both on age and diagnostic route. The dashed vertical line shows the age at which half of the deaths are directly attributed to breast cancer.

causes. Over-diagnosis typically leads to over-treatment with the associated morbidity. Even if over-treatment does not occur, the psychological and potential financial consequences remain, such as insurance and credit scores. Over-diagnosis is estimated to be 10% within the screening age population.^{5,21} To increase the accessibility and understanding for the target population, malignant lesions were classified as low-risk, intermediate-risk, and high-risk based on the likelihood of harm during a woman’s remaining lifespan. Low/intermediate grade DCIS and grade 1 invasive disease are considered low risk, i.e., very unlikely to cause harm within the patients remaining life-time; high-grade DCIS and grade 2 invasive disease are considered intermediate risk, and grade 3 cancers are considered high risk, i.e., likely to become symptomatic in the patients’ life-span with risk of associated mortality. The explanation for these classifications is detailed below.

The natural history of malignant breast lesions was considered in the context of life expectancy. The average life expectancy for a 71-year-old Scottish woman is 15 years, dropping to 10 years at age 78.²² Follow-up studies of patients with untreated predominately low-grade DCIS reported a rate of transition to invasive cancer as 18–53% with an average time to invasive cancer as between 38 months and 13 years.^{23–27} As the grade of DCIS increases, the rate of transition to invasive cancer increases, ranging from 48% for high-grade DCIS to 32% and 18% for intermediate and low-grade DCIS, respectively. Conversely, the median time to develop invasive cancer is shorter for high-grade DCIS at 38 months than for both intermediate grade (60 months) and

low-grade DCIS (51 months). Young age is a risk factor for progression to invasive cancer, suggesting older age may be protective.²⁷

With respect to invasive cancer, Tabar *et al.*²⁸ demonstrated that screening in women aged up to 74 years prevented a substantial number of deaths from grade 3 cancer, but no significant reduction in mortality was seen with grade 1 cancers. They report that more deaths were prevented from grade 3 cancers than grades 1 and 2 combined. Historical data of untreated invasive breast cancer demonstrate that the survival decreases with histological grade: 47, 39, and 22 months for grade 1, 2, and 3 tumours, respectively.²⁹ Time to emergence of distant metastases is also inversely related to grade, with average times of 64, 44, and 21 months for grades 1, 2, and 3 cancers, respectively.³⁰ In one long-term follow-up series (median 127 months) of grade 1 breast cancers, 29.4% of ductal cancers developed metastases with 9% cancer-specific deaths, only 12.7% of tubular carcinomas developed recurrent disease with no

Table 2
Outcome of assessment for women aged >70 years.

	N	%
Total assessed	2,280	100
Biopsy	971	42.6
Benign ^a	293	12.9
Cancer	678	29.3
Invasive cancer	575	25.2
Discharged	1,600	70.2

^a Including no result/inadequate sample.

Table 3
Tumour features of screen-detected cancers.

Feature	50–70 years		>70 years		p-Value
	n	%	n	%	
Grade					0.18
Low/intermediate-grade DCIS	318	4.7	27	4.1	
High-grade DCIS	806	11.9	68	10.3	
Grade 1 invasive	1,363	20.2	116	17.5	
Grade 2 invasive	3,117	46.2	328	49.6	
Grade 3 invasive	1,145	17.0	122	18.5	
Total	6,749		661		
Size					0.76
<10 mm	1,629	28.8	157	27.9	
10 < 15 mm	1,665	29.4	167	29.7	
15 < 20 mm	1,108	19.6	107	19.0	
20 < 50 mm	1,157	20.5	123	21.8	
≥50 mm	96	1.7	9		
Size unknown	109		12		
Total known	5,655		563		
Nodal involvement					
Positive nodes	1,094	19.5	109	19.5	
Patient with nodes sampled	5,611		558		

DCIS, ductal carcinoma in situ.

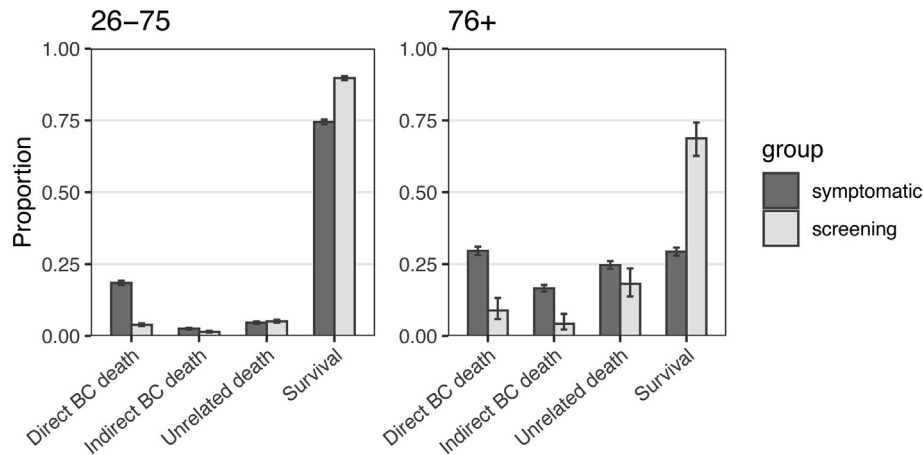


Figure 3 Outcome for breast cancer patients according to age at diagnosis and route of diagnosis. Error bars represent 95% confidence intervals of a proportion.

cancer specific deaths.³¹ Age-specific lead time estimates also increase with age, from 12 months for women aged 40–49 years to 53 months for those aged 70–79 years.³² It is reasonable to assume a substantially longer lead time for grade 1 cancers.

Even for women with a life expectancy >10 years, although a small proportion of low/intermediate-grade DCIS may become symptomatic or invasive within their lifetime, earlier diagnosis is unlikely to have a mortality benefit. With respect to high-grade DCIS, the evidence suggests that almost half would become invasive and potentially symptomatic within 5 years. Whether early diagnosis confers a mortality benefit, however, remains unclear. Regarding invasive disease, although grade 1 invasive tumours may not represent true over-diagnosis, there is no evidence that early screen detection will improve survival outcome. In contrast, the early diagnosis of grade 3 cancer may improve survival even in the older population, due to the rapidity of nodal and distant metastatic spread.

Tumour characteristics are displayed in Table 3. Regarding the grade of cancer detected, 19% of all screen-detected cancers were grade 3 invasive tumours. Half were grade 2 invasive cancers, and the remainder were grade 1 invasive or DCIS. Regarding malignant potential, 22% were considered low risk, 60% were considered intermediate risk, and 19% were considered high risk. Just over half of screen-detected cancers were small (≤ 15 mm). Approximately 20% of women had lymph node involvement.

For every woman aged >70 years diagnosed with a high-risk cancer, 2.4 women had a benign biopsy, 1.2 were diagnosed with a low-risk cancer, and 3.2 with an intermediate risk cancer (see Fig 4).

The mortality data for the symptomatic cohort provides an indication of outcomes of invasive breast cancers not diagnosed early through screening. The effect of age on breast-cancer specific mortality is highly significant with the proportion of breast-cancer specific deaths decreasing at a rate of $\sim 1\%$ per year, for women aged >40 years (see Fig 2).

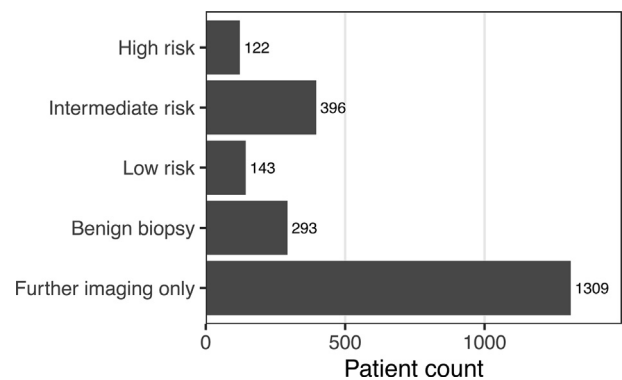


Figure 4 Outcome of screening assessment for women aged >70 years.

According to the logistic model, women >77 years diagnosed with a symptomatic breast cancer are more likely to die from other causes than to die of breast cancer. This finding is likely to be due primarily to the increased burden of co-morbid disease in older women.

It must be noted, however, that overall survival is higher in screen-detected group, including those >70 years. Interestingly the non-breast-cancer-related survival is also higher, suggesting that this cohort may have fewer comorbidities. Furthermore, breast cancer survival is expected to be higher in a screened population due lead-time bias. Unfortunately, due to the aggregate nature of the data, it is not possible to correct for this.

The present data suggest that diagnosing cancer earlier through a screening programme is unlikely to have a survival benefit for older women, especially those with co-morbidities, and any benefit will decrease with age. In addition, it may result in unnecessary morbidity from treatment of a pre-symptomatic tumour. This finding is supported by a large longitudinal observational study of breast cancer patients aged 40–84 years, which found patients with three or more comorbid conditions had a 20-fold higher rate of mortality from other causes and fourfold higher rate of all-cause mortality compared to patients with no comorbid conditions. Similar to the present findings, for women aged 75–84 years,

cause of death was breast cancer in <50%. They concluded that early diagnosis in women with severe comorbid conditions of any age conferred no survival advantage.³³

One possible limitation of the present study is that both screening and mortality data are collected as aggregate population data, meaning patient level data cannot be retrieved. This limits the analysis that can be performed. Mortality data are derived from death certification, and therefore, may not be entirely accurate; however, in an autopsy study of breast cancer patients, Parham *et al.*³⁴ found that death was clinically attributed to breast cancer too readily, with an alternative cause of death identified at autopsy in 22% of cases. Therefore, if inaccurate, it is more likely that the data underestimate the proportion of older symptomatic breast cancer patients dying from other causes, and the true trend would be even more marked.

Direct comparison of mortality data for screened and unscreened breast cancer patients is not possible within the present dataset. Although breast cancer mortality is lower within the screen-detected group, an unquantifiable proportion of this will be due to lead-time and length-time bias. The symptomatic group cannot include the small indolent, non-palpable screen-detected cancers. Should the cancer be detected through screening, lead-time would result in the patient appearing to survive for additional years, even without treatment. As the present cohort were followed for 5–10 years, a lead time of 5 years would be sufficient for a patient to appear as a “survivor” in the screening cohort as opposed to a “death directly attributable to breast cancer” in the symptomatic cohort even without treatment. Furthermore, if improved survival within the screening group was due solely to the earlier detection and treatment of breast cancer, a slight compensatory increase in unrelated deaths would be expected in the screen-detected cohort. Although this is true for those women ≤ 70 years, for those women aged >70 years at diagnosis there is a higher proportion of death from unrelated causes (vs all outcomes) within the symptomatic population (see Fig 3). This suggests that the improved survival for screened patients is not simply a result of the early detection and treatment of breast cancer. It is likely partly a result of the population attending screening representing is a self-selecting cohort of people with greater health awareness and thus fewer co-morbidities.

It would be interesting to compare the surgical outcomes for screening and symptomatic patients as an indication of morbidity. Unfortunately, this information is not available for this cohort of patients.

In conclusion, to the authors' knowledge, this is the first study providing outcomes evidence for British women aged >70 years deciding whether to opt into continued screening. The present study demonstrated that 5% of all older women screened will be recalled for assessment, but only 0.25% will be diagnosed with a high-risk grade 3 cancer. Twice as many women will have a benign biopsy as will be diagnosed with a high-risk grade 3 cancer. There is a highly significant inverse relationship between age and proportion of death directly attributable to breast cancer in symptomatic breast cancer patients. For older patients, especially those aged >77 years

or with co-morbidities the benefits of screening may not outweigh the harms. It is vitally important that women and their healthcare providers are provided with this information prior to decision making.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors acknowledge John Quinn from NHS National Services Scotland for his support with data gathering and analysis.

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