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Short Communication

Effective biennial mammographic screening in women aged 40–49

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ABSTRACT

Background: The United Kingdom is currently moving the age limit for invitation in its national breast screening programme downwards from 50 to 47. In contrast, the US Preventive Services Task Force concluded that, because of borderline statistical significance on effectiveness of mammographic screening, the current evidence is insufficient to advise screening in women aged 40–49.

Material and methods: We designed a case-referent study to investigate the effect of biennial mammographic screening on breast cancer mortality for women in their forties. In Nijmegen, the Netherlands, screening started in 1975. A total of 272 breast cancer deaths were identified, and 1360 referents aged 40–69 were sampled from the population invited for screening. Effectiveness was estimated by calculating the odds ratio (OR) indicating the breast cancer death rate in screened versus unscreened women.

Results: In women aged 40–49, the effect of screening was OR = 0.50 (95% confidence interval (CI) = 0.30–0.82). This result is similar to those aged 50–59 (OR = 0.54; 95% CI = 0.35–0.85) and 60–69 (OR = 0.65; 95% CI = 0.38–1.13).

Conclusion: Our results add convincing evidence about the effectiveness of biennial mammographic screening in women aged 40–49.

1. Introduction

In 2009, the US Preventive Services Task Force recommended against routine mammographic screening in women aged 40–49. They concluded that current evidence is insufficient to advise screening under age 50, largely because of inconclusive statistical outcomes.[1] In contrast to the United States, the United Kingdom is currently moving the age limit for invitation in the National Health Services Breast Screening Programme downwards from 50 to 47.[2]

Present discussions on screening under the age of 50 mostly concern annual screening and/or at least one exam additional to starting at age 50.[3] We investigated the effectiveness of biennial mammographic screening by age, with a particular focus on women aged 40–49.

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2. Material and methods

We designed our study based on the population of women invited to the screening programme in Nijmegen, the Netherlands.[4] In 1975, this programme started inviting women aged 35 years and over for a biennial mammographic screening examination. In 1990, at the start of the national screening programme, the age of invitation was adapted to that of the national policy (50–69 years until 1997 and 50–74 years thereafter). The lack of overlap in the age groups over calendar time prompted us to restrict the study population to women aged 40–69 at invitation between 1975 and 1990.

Our registry holds information on all patients with breast cancer in Nijmegen. Vital status was obtained from the Municipal Personal Records Data Base (GBA) up to and including 2008. Assessments of causes of death were made by a committee of physicians comprising a pathologist, medical oncologist and a radiologist.

We applied a case-referent design[5] to evaluate the effect of mammographic screening on breast cancer mortality by age at invitation. Women who died from breast cancer and who were invited for screening between 1975 and 1990 were selected as case subjects. By means of incidence density sampling[6,7] risk sets of referents were constructed, and from all sets five referents were randomly sampled for each case. Referents had to be eligible for screening, and living in Nijmegen at the time of death of the case.

Screening can only be effective if the examination is performed in the period when the cancer is potentially detectable before symptoms appear; the detectable preclinical period.[8,9] The duration of the detectable preclinical period is unknown at the individual level; based on estimates of lead time for breast cancer,[9,10] we have set the opportunity to screening for both the case and its referents at a 2-year period before diagnosis of the case. In a biennial screening programme this is the most recent invitation preceding the diagnosis, i.e. the index-invitation.[8] Thus each case and its referents had been given the same index-invitation for screening; accordingly both cases and referents have had a similar opportunity to participate in the screening examination following their index-invitation.

To estimate the effect of screening on breast cancer mortality, we calculated the odds ratio (OR), using logistic regression techniques. The OR is the odds of being screened versus not screened following the index-invitation in the case series of breast cancer deaths, compared with the reference group from which the cases theoretically originate. As such, the OR is the breast cancer mortality in screened women divided by the breast cancer mortality in unscreened women.[6]

We adjusted for differences in age at index-invitation between the comparison groups by stratification. Thereafter, we added the combination of screening and age as an interaction term to the logistic model to assess the effect of screening by age. Age was first added as 10-year age categories and after that as a continuous variable.

3. Results

We identified 272 cases, and we randomly sampled 1360 referents from the population invited for screening. The median age at index-invitation in the case group was 55 years (interquartile range 49–62) and 49 years (interquartile range 44–54) in the reference group.

Women aged 40–49 at index-invitation had a 50% lower breast cancer mortality compared with unscreened women (OR = 0.50; 95% confidence interval (CI) = 0.30–0.82; Table 1). Amongst women aged 50–59 and 60–69, screening prevented 46% (OR = 0.54; 95% CI 0.35–0.85) and 35% (OR = 0.65; 95% CI = 0.38–1.13) of the otherwise prevailing breast cancer deaths, respectively. The screening effect by age at invitation is displayed in Fig. 1; *p*-value for the interaction term was 0.67.

4. Discussion

Our data demonstrate an effective biennial screening for women aged 40–49, which is similar to the screening effect in those aged 50–59 and 60–69.

Evaluations from regions within Sweden and Canada, using a 12, 18 and 20 month screening interval, respectively,[11–13] also found an effect of screening on breast cancer mortality in women aged 40–49 that was similar to the effect in those aged above 50. These studies showed reductions in breast cancer mortality of 37–48% in women screened between age 40 and 49. Our findings indicate that a 2-year screening interval performs just as well as a shorter one.

The UK Age Trial,[14] specifically designed to address the question of starting at age 40, showed after 10.7 years of follow-up a 17% breast cancer mortality reduction in women invited for screening (relative risk (RR) = 0.83; 95% CI = 0.66–1.04). The full effect of the UK Age Trial is not expected to have emerged yet, so a further follow-up is awaited.

Our results represent screening practice from 1975 to 1990. We believe that improvements over time in mammographic detection techniques and treatment modalities are likely to result in an even greater beneficial effect on the prevention of breast cancer death. Since the start of screening programmes the complete chain, from technical aspects of mammography to training and experience of radiographers and radiologists has improved.[15–17] In addition, since the 1980s there has been a growing use of adjuvant therapy.[18]

Declining trends in breast cancer mortality represent the advancements made in screening and treatment. Recently, Autier and colleagues[19] reported that the strongest reduction is observed in women under age 50, usually not invited for

Table 1 – The effectiveness of mammographic screening on breast cancer mortality expressed by odds ratios, according to age at index-invitation.

Age at index-invitation	Cases	Referents	Odds ratio (95% CI)
	Screened (unscreened)	Screened (unscreened)	
40–49	50 (26)	596 (154)	0.50 (0.30–0.82)
50–59	69 (39)	350 (107)	0.54 (0.35–0.85)
60–69	53 (35)	107 (46)	0.65 (0.38–1.13)

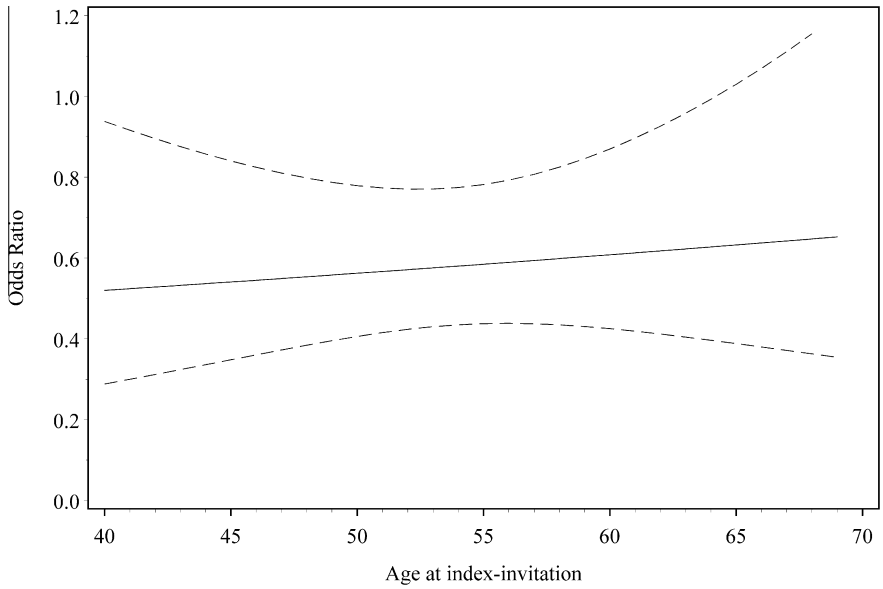

Fig. 1 – The odds ratio of breast cancer death in screened versus not screened women from 40 to 69 years of age. The line represents the OR along the continuum of age at index-invitation; the dotted lines represent the 95% CI.

screening. However, previous research has emphasised the importance of the synergy between early detection and treatment.[20] The combination of screening and adjuvant treatment for early stage breast cancer in women under age 50 might therefore result in an even more substantial reduction in breast cancer mortality.

The analysis of association in our study included participation of cases and referents following the index-invitation. An additional analysis including the invitation prior to the index-invitation, resulted in a small change in the mortality reduction, for instance the OR in women aged 40–49 changed from 0.50 to 0.57 (95% CI = 0.42–0.79). This indicates that a possible underestimation of the preclinical detectable period had no relevant impact in our study.

Confounding- and self-selection bias may have had an influence on our results. We will discuss these two biases consecutively.

First, a notable candidate for producing confounding bias is mammographic density, i.e. the composition of glandular tissue and stroma, which is an important risk factor for breast cancer.[21] By stratifying on age we indirectly corrected for mammographic density, because of the high correlation between age and mammographic density.[22] Other risk factors for breast cancer like obesity, socio-economic group, nulliparity, late age at menopause, early age at menarche, and family history show a 1.5–4-fold relative risk of breast cancer at the most.[23] Sensitivity analysis[24] confirmed that, under realistic circumstances, a correction for residual confounding caused by these factors would not bring about a major shift in our estimated OR. For instance, if a risk factor or risk profile with a relative risk of 4 is present in 10% of the screened women compared to 20% in the unscreened women, then our apparent OR of 0.50 would be adjusted to 0.62. Our effect estimate will only weaken in an extreme situation where a combination of strong risk factors is much less present amongst screened women compared to unscreened women.

Second, mammographic screening may seem more efficacious than it in fact is if women who participate in screening programmes have a lower background risk of dying from breast cancer. To obtain a fair estimate of the amount of self-selection, the ratio of the breast cancer death rate amongst not-invited women and non-participants in the screening programme has to be calculated.[25] In our study we were not able to calculate an estimate for self-selection, since we did not have an uninvited group for the main part of the study period. Nevertheless we have two reasons for believing that the influence of self-selection bias in our results was only minor. First, a geographical comparison, during the early years of the screening programme, on breast cancer incidence rates found no evidence of self-selection bias.[26] Second, we[27] recently quantified the extent of self-selection bias for a region close to Nijmegen. The resulting correction factor of 0.84 (95% CI = 0.58–1.21) indicates a lower background risk in women who do not attend screening. When we applied this factor to the formula described by Duffy and colleagues,[25] our OR of 0.50 changed to 0.40, which indicates a 60% reduction in breast cancer mortality.

The results of our study support lowering the starting age in breast cancer screening. A decision about the optimal age to commence screening should, however, also take into account cost effectiveness and the burden of breast cancer in younger women. In the Netherlands, the current breast cancer incidence at age 45–49 is similar to the incidence measured in women aged 50–59 at the start of the national screening programme two decades ago, whilst the incidence has only slightly increased in women aged 40–44.[22] Breast cancer has thus become an important health problem in the age group 45–49. An additional economic evaluation is needed to underpin a possible decision to start screening at age 45.

In conclusion, our study adds convincing evidence on the effectiveness of biennial mammographic screening in women aged 40–49.

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Conflict of interest statement

None declared.

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