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A modelling study to evaluate the costs and effects of lowering the starting age of population breast cancer screening

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ABSTRACT

Background: Because the incidence of breast cancer increases between 45 and 50 years of age, a reconsideration is required of the current starting age (typically 50 years) for routine mammography. Our aim was to evaluate the quantitative benefits, harms, and cost-effectiveness of lowering the starting age of breast cancer screening in the Dutch general population.

Methods: Economic modelling with a lifelong perspective compared biennial screening for women aged 48–74 years and for women aged 46–74 years with the current Dutch screening programme, which screen women between the ages of 50 and 74 years. Tumour deaths prevented, years of life saved (YOLS), false-positive rates, radiation-induced tumours, costs and incremental cost-effectiveness ratios (ICERs) were evaluated.

Results: Starting the screening at 48 instead of 50 years of age led to increases in: the number of small tumours detected (4.0%), tumour deaths prevented (5.6%), false positives (9.2%), YOLS (5.6%), radiation-induced tumours (14.7%), and costs (4.1%). Starting the screening at 46 instead of 48 years of age increased the number of small tumours detected (3.3%), tumour deaths prevented (4.2%), false positives (8.8%), YOLS (3.7%), radiation-induced tumours (15.2%), and costs (4.0%). The ICER was €5600/YOLS for the 48–74 scenario and €5600/YOLS for the 46–74 scenario.

Conclusions: Women could benefit from lowering the starting age of screening as more breast cancer deaths would be averted. Starting regular breast cancer screening earlier is also cost-effective. As the number of additional expected harms is relatively small in both the scenarios examined, and the difference in ICERs is not large, introducing two additional screening rounds is justifiable.

1. Introduction

Breast cancer screening has been implemented in many European countries to detect breast cancer at an early stage and decrease breast cancer mortality. In these programmes, usually the age of 50 is considered optimal for starting regular screening due to the increasing incidence of the disease afterwards [1]. There are, however, some countries (United Kingdom, Czech Republic) and regions (e.g. in Sweden and Italy) that invite women younger than 50 years to be screened despite the controversy in the benefit-harm balance [1,2].

Arguments in favour of lowering the starting age of screening are based on the potential breast cancer specific mortality decrease for

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women as there is evidence of an increased incidence of breast cancer above the age of 40 and more prominently between 45 and 50 years, and there is a great potential number of years of life gained for deaths averted [3]. Results from the United Kingdom Age Trial [4] suggest that regular mammographic screening in the age group 40–49 could reduce the risk of dying from breast cancer (relative risk (RR) 0.88 (95% confidence interval (CI) 0.74–1.04), although the reduction was less pronounced as compared to results from meta-analyses for older age groups [5,6]. On the other hand, there are also studies showing that potential harms as overdiagnosed breast cancers [7], radiation-induced breast cancer deaths [8,9], false positive test results [10–15], unnecessary biopsies [11,12], and costs of false positive biopsies [16] accompany regular screening, though their estimated numbers varied largely. Such potential harms have been considered to outweigh the benefits of regular screening for women 40–49 years old and thus regular breast cancer screening in this age group is generally not recommended [17].

There are a number of recent modelling studies [7,8,10–15,18] which tried to balance the expected benefits and harms of breast cancer screening but these evaluations were partial, i.e. focused only on mortality reduction, radiation-induced tumours and tumour deaths, or overdiagnosis and only three of them analysed the Dutch setting [7,8,18]. The most recent study focused on the cost-effectiveness of digital mammography screening before the age of 50 in the Netherlands and concluded that additional screening between age 40 and 49 was cost-effective, however, their model only considered age as a risk factor for breast cancer and did not incorporate other factors as breast density which is important in younger age groups [18].

Therefore, in the current analysis we performed a comprehensive evaluation regarding the proper balance of harms and benefits of regular breast cancer screening starting from a younger age, including breast density variation as a function of age. The aim of our study was to evaluate the quantitative benefits, harms, and cost-effectiveness of lowering the starting age of breast cancer screening in the Dutch general population given the already available biennial screening among women aged 50–74. The following outcomes were considered: tumour deaths prevented, years of life saved (YOLS), number of false positives, radiation-induced tumours, costs and cost-effectiveness. Qualitative outcomes (such as quality of life) were not included.

2. Methods

This study was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [19]. We applied the Simulation Model on Radiation Risk and breast cancer Screening (SiMRiSc) in the current analysis. The model was previously published and externally validated in women with BRCA mutations [20–22]. For the purpose of this analysis, the SiMRiSc model was extended by including a breast density parameter (Table 1) and externally validated (Table 2) for the general population of women by comparing the outcomes to empirical data from the Dutch national screening programme. As this model was restricted to invasive breast cancer only, ductal carcinoma in situ (DCIS) was not included.

The current breast cancer screening scheme in the Netherlands was included: biennial population screening in women aged 50–74 years as a reference scenario. Scenarios were developed for two alternative screening regimens with earlier starting ages: biennial screening from 48 to 74 years and from 46 to 74 years. The outcomes of the model consisted of potential benefits: tumour deaths prevented, YOLS; and potential harms of screening: number of false positives and radiation-induced tumours.

2.1. Description of the model and its components

SiMRiSc is a micro-simulation Markov model (Fig. 1). An extensive description of the model can be found in previous publications [20–23]. Women were simulated during their lifetime taking into account their life expectancy, chance of developing a tumour, tumour growth and survival from breast cancer, breast density and mammographic sensitivity and specificity, and risk of tumour induction due to diagnostic radiation. If a tumour was present at the screening moment, the chance of detection was dependent on the mammographic sensitivity. If the tumour was found, either by screening or self-detection, the woman was removed from the simulation and the breast cancer specific death age of the woman was calculated based on the life expectancy after breast cancer diagnosis depending on the tumour size at clinical detection.

The model parameters are presented in Table 1. In the simulation, every woman was given a predetermined natural death age which was sampled from the life expectancy in the Netherlands [20]. The breast cancer incidence rate was sampled to assign an individual probability to develop breast cancer during the lifetime of the women and the age at which the tumour would be clinically detected [24]. A systematic literature search was performed to estimate the parameters in the tumour growth model and the tumour size at clinical (self-) detection. The history of the tumour was calculated by applying an exponential growth model with an age-dependent tumour volume doubling time sampled from a population log-normal distribution. The preclinical period of the tumour was defined as the time from which the tumour size was larger than the minimal detection threshold for mammography (5 mm) until the time of clinical detection without screening [25]. The specificity of mammography was based on a single RCT which was considered the best source for mammographic specificity for the current analysis since the screened women were in the age group 45–69 years [26].

Finally, a systematic error was introduced which referred to a fraction of breast cancer cases that could not be detected by mammography mainly due to lobular carcinomas, dense breast tissue and tumours located close to the thorax wall. Based on expert opinion (RMP), we assumed this fraction to be 10%, that is, 10% of all cases that should be detected based on tumour volume would not be detected due to their characteristics.

2.2. Modelling the effect of breast density

In the model the chance of tumour detection at screening was modelled to be dependent on the mammographic sensitivity given the breast density of the woman at certain age. Systematic literature searches were performed to find estimates for the distribution of breast density in the population and the relation between breast density and mammographic sensitivity [27–29]. A meta-analysis based on calculating the weighted average value from the reported sample sizes [27–29] was performed to estimate the baseline values and the 95% CI for breast density. The same method of meta-analysis was applied for estimating the sensitivity of mammography as a function of breast density and age, based on the resulting literature [30–38].

2.3. Screening scenarios

Two alternative screening scenarios in which women were subjected to systematic mammographic screening were simulated according to different starting ages, i.e. 46 and 48 years of age. The screening interval was biennial and the end age was set at 74 years. The current population breast cancer screening programme, i.e. biennial screening in the age group 50–74 years, was set as a reference scenario and was compared to the alternative scenarios.

2.4. Expected benefits and harms of regular breast cancer screening

The results from the model simulations were reported in terms of potential benefits: tumour deaths prevented, YOLS; and potential harms of screening: number of false positives and radiation-induced tumours. Tumour deaths prevented, YOLS and radiation-induced tumours were