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LETTER TO THE EDITOR

Impact of assumptions – the example of the Welch-analysis of mammography screening effectiveness

Elsebeth Lynge, Anna-Belle Beau and Søren Lophaven

Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Introduction

Based on analysis of SEER data from 1975 to 2012, Welch et al. [1] concluded that in screening, women were more likely to have breast cancer detected 'that was overdiagnosed than to have earlier detection of a tumor that was destined to become large', and that 'the reduction in breast cancer mortality after the implementation of screening was predominantly the result of improved systemic therapy.'

Welch assumptions

The Welch et al. analysis builds on a number of assumptions that might not be unproblematic.

First, it was assumed 'that the underlying probability that clinically meaningful breast cancer would develop was stable' over time given no screening. This assumption was based on the observed, very low and stable incidence of metastatic breast cancer. As the breast cancer incidence data analyzed by Welch et al. started in 1975 and screening in the USA disseminated shortly thereafter, limited data were available from a prescreening period. However, long-term breast cancer incidence data from Rochester, Minnesota [2], from Kaiser Permanente, Portland [3], and from the Connecticut Tumor Registry [4], showed prescreening, cohort-related increases in the breast cancer incidence. Based on long-term prescreening breast cancer incidence data from other countries (for instance Denmark, see section below), it seems likely that the US prescreening cohort trends would have continued also after the start of screening.

Second, screening implies a change in time of diagnosis and therefore a change in the incidence pattern. At the start of screening, a prevalence peak is observed, during screening an artificial aging, and when the women have exited screening a compensatory dip will be seen in the incidence [5]. If it takes 2 years to carry out the prevalence screen, around a 100% increase in incidence will be observed during the period [6]. Screening started gradually in the USA, with 17% (aged 50+) in 1978 having had a mammogram to 74% in 1992 (aged 40+) [7]. This means that in the USA, the prevalence peak is spread out over a long time interval, and that very long time will pass before the compensatory dip becomes visible at the population level. It is therefore questionable when Welch et al. attribute the observed increase in breast cancer incidence to overdiagnosis. The use of

CONTACT Elsebeth Lynge elsebeth@sund.ku.dk Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, DK-1014 København K, Denmark

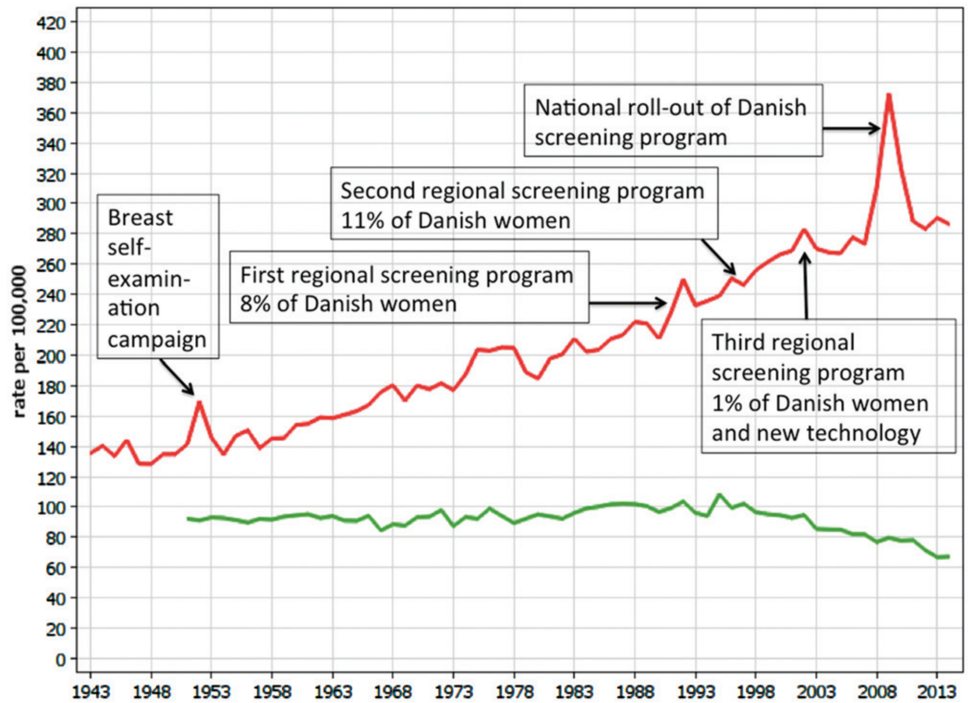

Figure 1. Age-standardized (2000 Nordic population) breast cancer incidence (red) and mortality (green) for women 40+ years in Denmark 1943–2014.

calendar-specific, age-standardized breast cancer incidence rates for all women aged 40+ is simple a too crude tool to identify the dynamic of the incidence rates during screening.

Third, Welch et al. estimated the impact of screening on breast cancer mortality by combining stage-specific incidence and case fatality rates, and concluded that 'improved treatment was responsible for at least two-third … of the reduction in breast cancer mortality'. However, this calculation is still based on the questionable assumption 'that the underlying probability that clinically meaningful breast cancer would develop was stable' over time given no screening.

Breast cancer incidence in Denmark

In Denmark, nationwide registration based on international coding schemes started for incident cancer cases in 1943, and for causes of death in 1951. The age-standardized (2000 Nordic population) breast cancer incidence for women age 40 years and above increased steadily over time, while the breast cancer mortality was stable up until the mid-1990, thereafter it decreased [8] (Figure 1).

In 1951–1952, a breast self-examination campaign took place in Denmark [9]. In modeling of lymph node status data from 1978 to 1994, the overall increase in breast cancer incidence derived from node-negative and moderately node-positive tumors, indicating increased breast cancer awareness [10]. Population-based screening was implemented step-wise in Denmark, though always targeting only women aged 50–69 years, and screening outside the organized programs was rare [11]. The first regional program started in Copenhagen in 1991 and targeted about 8% of women [12], the next regional programs started around 1994, targeting about 11% of women [13], and a very small regional program started in 2001. In 2001–2002, also high-frequency ultrasound devices and stereotactic breast biopsies were implemented which increased the screen-detection rate [14]. National roll-out of screening took place in 2008–2010 [15].

The breast self-examination campaign and the start of the screening programs left marks on the time trend in breast cancer incidence in Denmark. But in the long-time perspective, these marks appeared as irregularities on an underlying increasing trend. In the years before screening, the increase in incidence seems to have come primarily from node-negative and moderately node-positive tumors. As improved awareness – like screening – will move the time of diagnosis forward, it can have some temporary impact on the time trend in the incidence. Some may interpret an increase in node-negative tumors as an indicator of overdiagnosis of indolent tumors. But women will not harbor an inexhaustible pool of indolent tumors. Overdiagnosis is therefore unlikely to explain the doubling of the breast cancer incidence over the past 60 years in Denmark.

Conclusions

Welch et al. presented an interesting and novel approach to assess the effect of breast cancer screening. However, the opportunistic and gradual implementation of screening in the USA makes it very difficult to separate out a possible screening effect from the underlying time trends and improvement in treatment.

In this respect, data from countries with population-based, organized screening programs are more useful. This is especially the case, if the screening program has been implemented region-wise, because it is then possible to identify a comparison group not yet invited to screening. However, screening changes the age-specific incidence in cohorts of women offered screening. This includes a prevalence peak at first screen; an artificial aging at subsequent screens; and a compensatory dip after end of screening [5,6]. Therefore, studies of overdiagnosis require also that women can be followed for a sufficiently long period after end of screening for the compensatory dip to materialize. Such studies have been undertaken in for instance Florence Italy [16]; in Finland [17]; and in Denmark [18].

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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LETTER TO THE EDITOR

A case of isolated small cell carcinoma of the brain

C. Noonan[a] and M. James[a,b]

[a]Department of Oncology, Canterbury District Health Board, Christchurch, New Zealand; [b]Department of Medicine, University of Otago, Christchurch, New Zealand

Case description

Presentation

A 43-year-old Caucasian female presented to the emergency department with a four week history of decreased fluency of speech and headache. She had no significant previous medical history or regular medications, although was a current cigarette smoker with 20 pack-year history. On examination, she had expressive dysphasia, global right-sided hypoesthesia, hypertonicity and weakness of the right upper limb.

Investigation

Her initial MR brain revealed prominent rim-enhancing neoplasms to the left parietal (41 mm AP × 35mm T) and posteromedial temporal lobes (25 mm AP × 11 mm T) with associated mass effect (as shown in Figure 1). A provisional diagnosis of brain metastases from an unknown primary was made. Staging investigations (including CT, MR and FDG PET-CT modalities) showed no evidence of extra-cranial disease. Serum haematology, biochemistry and tumour markers

CONTACT Charles Noonan charlienoonan@gmail.com Oncology Department, Christchurch Hospital, Canterbury, New Zealand