Cancer Epidemiology 42 (2016) 147–153

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Extrapolation of pre-screening trends: Impact of assumptions on overdiagnosis estimates by mammographic screening

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ARTICLE INFO

Article history:
Received 17 December 2015
Received in revised form 22 March 2016
Accepted 25 April 2016
Available online xxx

Keywords:
Breast cancer
Excess incidence
Mammographic screening
Netherlands
Overdiagnosis
Pre-screening trend
Screening

ABSTRACT

Background: Overdiagnosis by mammographic screening is defined as the excess in breast cancer incidence in the presence of screening compared to the incidence in the absence of screening. The latter is often estimated by extrapolating the pre-screening incidence trend. The aim of this theoretical study is to investigate the impact of assumptions in extrapolating the pre-screening incidence trend of invasive breast cancer on the estimated percentage of overdiagnosis.
Methods: We extracted data on invasive breast cancer incidence and person-years by calendar year (1975–2009) and 5-year age groups (0–85 years) from Dutch databases. Different combinations of assumptions for extrapolating the pre-screening period were investigated, such as variations in the type of regression model, end of the pre-screening period, screened age range, post-screening age range and adjustment for a trend in women <45. This resulted in 69,120 estimates of the percentage of overdiagnosis, i.e. excess cancer incidence in the presence of screening as a proportion of the number of screen-detected and interval cancers.
Results: Most overdiagnosis percentages are overestimated because of inadequate adjustment for lead time. The overdiagnosis estimates range between −7.1% and 65.1%, with a median of 33.6%. The choice of pre-screening period has the largest influence on the estimated percentage of overdiagnosis: the median estimate is 17.1% for extrapolations using 1975–1986 as the pre-screening period and 44.7% for extrapolations using 1975–1988 as the pre-screening period.
Conclusion: The results of this theoretical study most likely cover the true overdiagnosis estimate, which is unknown, and may not necessarily represent the median overdiagnosis estimate. This study shows that overdiagnosis estimates heavily depend on the assumptions made in extrapolating the incidence in the pre-screening period, especially on the choice of the pre-screening period. These limitations should be acknowledged when adopting this approach to estimate overdiagnosis.

1. Introduction

Mammographic screening benefits some women and harms a number of others [1,2]. The major benefit of mammographic screening is the prevention of breast cancer deaths [1] by detecting breast cancers at an early stage with better treatment outcomes [3]. However, a major drawback of mammographic screening is the detection of cancers that would not be clinically detected during a woman's lifetime if screening had not occurred, i.e. overdiagnosed cancers.

There is much debate on the extent of overdiagnosis in mammographic screening, with estimates ranging from 0 to 57% [4,5]. According to Carter et al. [6], ecological and cohort studies are the most suitable method for estimating overdiagnosis. There is, however, a wide variability in the design of these studies, which are related to the methods used to adjust for lead time and the choice of the unscreened reference population [6]. The unscreened reference population is often obtained through extrapolating the incidence in the pre-screening period [5,7–10]. However, studies utilize different assumptions in order to estimate the pre-screening incidence trend [11]. Some studies apply linear regression to incidence rates, while others apply poisson regression to absolute numbers. Furthermore, studies differ in the age groups modeled, choice of pre-screening period and whether to adjust for a trend in non-screened ages.

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http://dx.doi.org/10.1016/j.canep.2016.04.015
1877-7821/

The Independent UK Panel on Breast Cancer Screening [11] estimated the absolute number of overdiagnosed cases in the UK National Health Service breast cancer screening program using several different assumptions. They showed that the estimated number of overdiagnosed cases depends on the specification of the model used for the estimation. Although this indicates that the choice of the model influences the estimated percentage of overdiagnosis, the panel only discussed the effects of a limited number of model assumptions. Furthermore, the percentage of overdiagnosis does not only depend on the estimated number of overdiagnosed cases, but also on the number of cancers in the denominator [12]. Therefore, this theoretical study investigates the influence of a large number of assumptions in extrapolating pre-screening incidence trends on the estimated percentage of overdiagnosis by mammographic screening in the Netherlands.

2. Methods

2.1. Setting

In 1989, a biennial mammographic screening program was gradually implemented in the Netherlands, inviting women aged 50–69 years. Nationwide full coverage was reached in 1997 and the upper age limit was gradually extended to age 75 in the period 1998–2001. Because women are invited per region and receive their first invitation in the year they turn 50, 51 or 52, women aged 49 can be screened. The attendance rates in the Dutch program have always been high, ranging from 72% in 1990 to about 80% from 1997 onwards [13]. Until 2014, initial screens consisted of two view mammography and subsequent screens of one view, an oblique view, unless a second cranio-caudal view was required. From 2014 onwards, two view mammography became the standard for subsequent screening. Mammograms are independently read by two radiologists who decide in consensus on recall. Digital mammography was introduced in 2004 and reached full coverage in 2010 [14].

Because the incidence of *ductal carcinoma in situ* (DCIS) was not registered before 1989, we limited our estimates of overdiagnosis to invasive breast cancer. Data on the number of invasive breast cancers were obtained from *Stichting Medische Registratie* for the period 1975–1988 (ages 0–85 years) and the website of the National Cancer Registry [15] in the Netherlands for the period 1989–2013 (ages 0–99 years). The number of screen-detected breast cancers and interval cancers were collected centrally from the screening organizations (1975–2009) [14] and the information on the number of women living in the Netherlands were obtained from Statistics Netherland (1975–2013) [16]. All data was provided by calendar year and 5-year age groups (0–85 years) (see supplement A). Fig. 1 presents the invasive breast cancer incidence rate per 100,000 women-years by calendar period and age group.

2.2. Percentage of overdiagnosis

The percentage of overdiagnosis was defined as '*the percentage of cancers detected during the screening period that would not present symptomatically during one's lifetime in the absence of screening*', in line with previous work [17]. The nominator is the absolute number of overdiagnosed cases estimated by subtracting the cumulative incidence in the absence of screening from the cumulative incidence in the presence of screening. In this study, the cumulative incidence in the presence of screening is the observed breast cancer incidence in the screened age group during the screening period. The cumulative incidence in the absence of screening could not be observed and was estimated by extrapolation of pre-screening incidence trends. This approach is called the cumulative incidence method or excess-incidence method [18,19]. The cumulative incidence approach needs to fulfill two conditions to adequately adjust for lead time: 1) the follow-up after screening cessation should include the maximum length of lead time, and 2) the excess incidence during screening and the compensatory drop after screening cessation should be estimated from women who had the same screening participation rates and experienced the

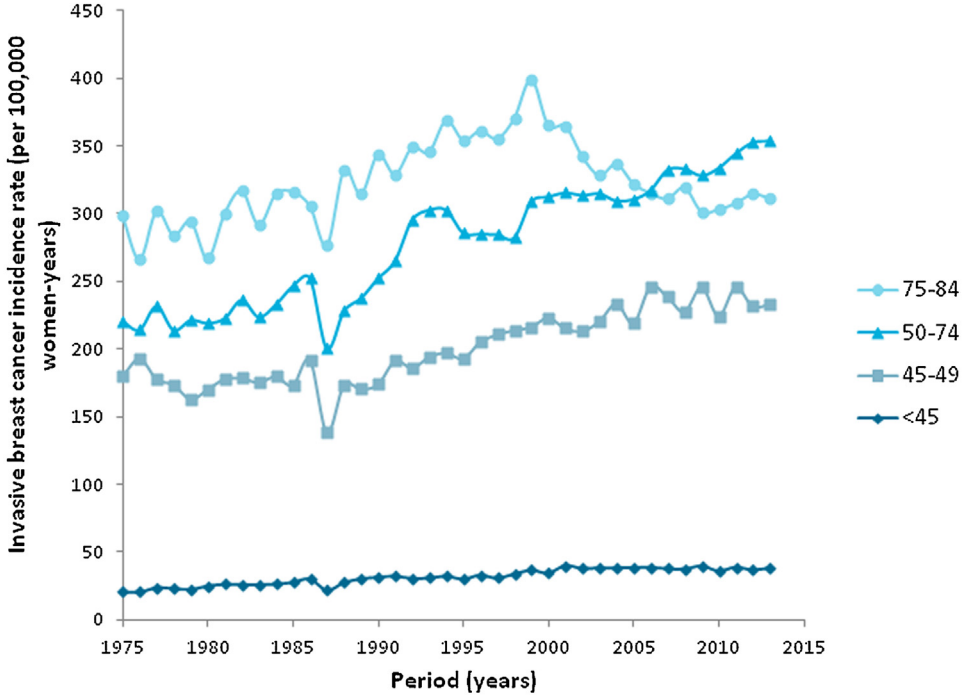

Fig. 1. Invasive breast cancer incidence rate per 100,000 women-years by calendar period.